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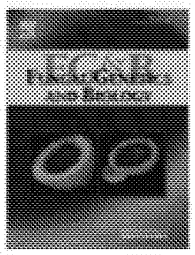
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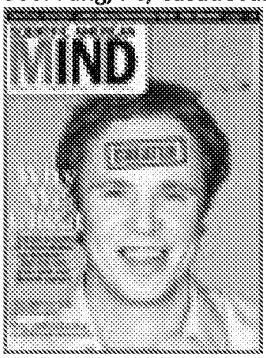
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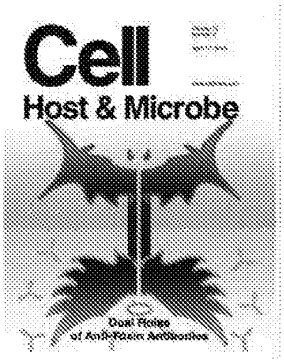
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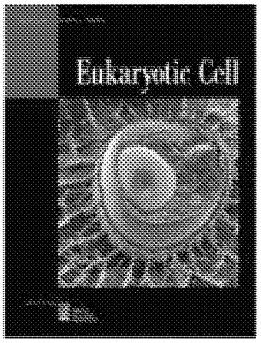
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Voice of America interview on science fraud and misconduct
http://www.voanews.com/audio/2969854.html

Inventions, Patents, Copyrights
US Patent 6,509,325. Nosanchuk Joshua D, Casadevall Arturo, Ovalle; Rafael. Method for inhibiting melanogenesis and uses thereof.
US Patent 6,545,130. Glatman-Freedman; Aharona, Casadevall; Arturo. Monoclonal antibodies to mycobacterium tuberculosis and a modified ELISA assay
US Patent 7,402,385 B2 E. Dadachova, J.D. Nosanchuk and A. Casadevall Radiolabeled antibodies and peptides for treatment of tumors.
US Patent 7,651,689 E. Dadachova, A. Casadevall and A. Nakouzi Methods of applying ionizing radiation for therapy of infections
US Patent 7,402,385 E. Dadachova, J.D. Nosanchuk and A. Casadevall Radiolabeled antibodies for treatment of tumors
Canadian Patent No. 2,606,022; European Patent No. 1868639 (validated in France, Germany, Italy, United Kingdom; Hong Kong Patent No. HK1117035; South African Patent No. 2007/08539) E. Dadachova, A. Casadevall and H. Goldstein. Methods of applying ionizing radiation for therapy of HIV infection.
US Patent 8,187,611 B2 N. Abboud and A. Casadevall. Anti-peptide antibodies that cross react with protective antigen *of Bacillus anthracis* and uses thereof.
US Patent 8,652,827 E. Dadachova, R. A. Bryan and A. Casadevall Radiosynthesis as an alternative energy utilization process in melanized organisms and uses thereof.
US Patent 8,586,090 E. Dadachova and A. Casadevall Melanin nanoshells for protection against radiation and electronic pulses.

Applications pending
J. Achkar, A. Casadevall, R. Rosales and A. Ziegenbalg Serologic test for the rapid diagnosis of tuberculosis.
E. Dadachova, A. Casadevall, H. Strickler and R.D. Burk Radioimmunotherapy and imaging of tumor cells that express viral antigens.
E. Dadachova, A. Casadevall, M.A. Sesay, H. Damania, P.E. Smariga Radiolabeled monoclonal antibodies, methods of preparation using TCEP and uses thereof.
E. Dadachova, A. Casadevall, M.A. Sesay, H. Damania, P.E. Smariga Disposable column system for purification of radiolabeled antibodies.
E. Dadachova and A. Casadevall Methods for increasing efficacy of radioimmuno-therapy of melanoma.
JM Friedman, AJ Friedman, G. Han, MS Navati, KP Davies, MT Tar, AA Alfieri, A Casadevall, E Dadachova, HC Eisenman, Jasmin and D Spray Versatile nanoparticulate biomaterial for controlled delivery and/or containment of therapeutic and diagnostic material.
E. Dadachova, C. Gravekamp, A. Casadevall. Radiobacteria for therapy of cancer.
E. Dadachova and A. Casadevall. Oral administration of melanin for protection against radiation.

TEACHING

Mentoring
Advisees (predoctoral PhD advisor)

1996	Yulin Wang	Ph.D.
1997	Sarah Franzot	Ph.D.
1998	Lin Chen	Ph.D.

1999	Wendy Cleare	Ph.D.
1999	Nikoletta Lendvai	Ph.D.
2000	Neely Mozaffarian	Ph.D.
2000	Angel Rosas	Ph.D.
2002	Johanna Rivera	Ph.D.
2002	Reid Schwebach	Ph.D.
2003	Judith Steenbergen	Ph.D.
2004	Javier Garcia-Rivera	Ph.D.
2006	Marcela Torres	Ph.D.
2006	Luis Martinez	Ph.D.
2007	Yong Luo	Ph.D.
2008	Mauricio Alvarez	Ph.D.
2009	Magdia DeJesus	Ph.D.
2009	Carolyn Saylor	Ph.D.
2010	Cara Chrisman	Ph.D.
2011	Patricia Andrade	Ph.D.
2011	Andres Nicola	Ph.D. (University of Brasilia)
2012	Radames Cordero	Ph.D.
2012	Alena Janda	Ph.D.
2013	Jacky Chow	Ph.D.
2013	Carolina Coelho	Ph.D. (University of Coimbra)
2014	Sabriya Stukes	Ph.D.
2015	Lisa Brown	Ph.D.
2016	Anthony Bowen	Ph.D.
2017	Carlos de Leon Rodriguez	Ph.D.
2017	Eric Jung	Ph.D.
2018	Joudeh Freiji	M.D.

Postdoctoral Fellows (Name, Years, Current Position)

Brian Currie, M.D., M.P.H. 1992-1993 Assist. Dean, Clinical Research, Montefiore Med. Center; Professor, Dept. Med., Dept. Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY

Sushovita Mukherjee, M.D. 1992-1996 Not Available

Jean Mukherjee, D.V.M., Ph.D. 1996-1997 Assist. Prof., Dept. Biomed. Sci. (Infectious Diseases), Cummings Sch. Vet Med., Tufts University, North Grafton, MA

Aharona Freedman, M.D. 1993-1998 Assist. Clinical Prof., Dept. Pediatrics (Infectious Diseases), Albert Einstein College of Medicine, Bronx, NY

Joshua Nosanchuk, M.D. 1996-1998 Prof., Dept. Med. (Infectious Diseases), Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Bettina Fries, M.D. 1997-1999 Prof., Dept. Med. (Infectious Diseases), Stony Brook University, NY

Marta Feldmesser, M.D. 1994-2001 Assoc. Prof., Dept. Med. (Infectious Diseases), Dept. Obstetrics & Gynecology and Women's Health, Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Carlos Taborda, Ph.D. 1999-2002 Assoc. Prof., Dept Microbio., Institute Biomed. Sci., University of Sao Paulo, Sao Paulo, Brazil

David Goldman, M.D. 1996-2003 Assoc. Prof., Dept. Med. (Infectious Diseases), Dept. Pediatrics, Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Stephanie Tucker, Ph.D. 1999-2003 Not Available

Oscar Zaragoza, Ph.D. 2001-2006 Principal Investigator, Dept. Microbio., Instituto de Salud Carlos III, Marid, Spain

Diane McFadden, Ph.D. 1999-2006 Assoc. Director, Northeast Biodefense Center, Columbia University, New York, NY
Marcela Torres, Ph.D. 2006-2007 Scientist, Regeneron Pharmaceuticals Inc., Tarrytown, NY
Helene Eisenman, Ph.D. 2003-2008 Assist. Prof., Dept. Microbio., Baruch College, New York, NY
Erin McClelland, Ph.D. 2003-2008 Assist. Prof., Dept. Basic Sci. (Microbio. & Immuno.), The Commonwealth Medical College, Scranton, PA
Susana Frases-Carvajal, Ph.D. 2004-2009 Scientist, Biotech. Lab., National Institute of Metroloy, Rio de Janeiro, Brazil
Yong Luo, M.D., Ph.D. 2007-2009 Residency, Long Island Jewish Medical Center, New Hyde Park, NY
Aviva Diamond, Ph.D. 2009-2010 Post-doc with Ian Willis, Albert Einstein College of Medicine, Bronx, NY
Emma Robertson, Ph.D. 2008-2011 Post-doc with Kirsten Nielsen, University of Minnesota, Minneapolis, MN
Andre Nicola, M.D., Ph.D. 2006-2011 Prof. and Researcher, Graduate Program in Genomic Sciences and Biotechnology, Catholic University of Brasilia, Brazil
Nareen Abboud, Ph.D. 2009-2011 Research Program Manager, Montefiore Medical Center, Bronx, NY
Monica Garcia-Solache, M.D., Ph.D. Postdoctoral fellow with Louis Rice, Brown University.
Rafael Prados, Ph.D. 2009-2014 Assist. Prof., Albert Einstein College of Medicine, New York, NY
Mary Pohl, Ph.D. 2011-2014 Senior Scientisit, Oncobiologics, Inc.
Julie Wolf, Ph.D. 2010-2015 ASM, Washington, DC
Radames Cordero, Ph.D. 2015-2017, Research Associate, Johns Hopkins University
Coelho, Carolina, Ph.D. 2015-2018, MRC Centre for Medical Mycology, University of Exeter
Maggie Wear, Ph.D. 2016-2019, Assistant Scientist, Johns Hopkins University

Awards for junior scientists in Dr. Casadevall laboratory

1995-2000	David Goldman MD	NIH Physician Scientist Award
1996-99	Rona Freedman MD	Aaron Diamond Scholarship
1999-2004	Rona Freedman MD	NIH Physician Scientist KO8 Award
1993	Wendy Cleare	American Heart Minority Scholarship
1994	Wendy Cleare	NIH Minority Award Supplement
1996-2001	Marta Feldmesser MD	NIH Physician Scientist KO8 Award
1995-97	Sarah Piancastelli Franzot (PhD student)	Fulbright Scholarship
1997-99	Joshua Nosanchuk MD	Mycology IDSA Award
1997-2002	Joshua Nosanchuk MD	NIH Physician Scientist KO8 Award
	Johanna Rivera	NIH Marc Graduate Student Fellowship.
1998-2000	Bettina Fries MD	Mycology IDSA Award (Declined due overlap)
1998-2001	Bettina Fries MD	Howard Hughes Postdoctoral Award
	Bettina Fries MD	NIH Physician Scientist KO8 Award
2001-03	Dianne McFadden PhD	Life Sciences Postdoctoral Fellowship Award
	Dianne McFadden PhD	NIH F32 Postdoctoral Award (Declined due to overlap)
	Javier Garcia	NIH Marc Graduate Student Fellowship
	Helene Eisenman PhD	NIH F32 Postdoctoral Award
	Erin McClelland PhD	Revson Fellowship
2007-12	Jacqueline Achkar MD	NIH K23 Award

Thesis committees

I have participated in dozens of PhD committees and defenses but did not keep track of these

Training grant participation

9/1/97-5/31/13 Molecular Pathogenesis of Infectious Diseases 5T32AI007506-09
NIH/NIADD
PI: Casadevall

Until 06 (training faculty) after 06 (PI)

9/1/94-6/30/21 The Molecular and Cellular Basis of Infectious Diseases (MCBID) Program
2T32AI007417-21A1
NIH/NIADD
PI: Casadevall

Teaching

Course Leader for **GRADUATE MICROBIAL PATHOGENESIS**; 6 credit graduate school course at the Albert Einstein College of Medicine Sue Golding Graduate Division which teaches the fundamentals of microbial pathogenesis. 1996 and 1999.

2000-present	Lecturer in Graduate Pathology Course - Albert Einstein College of Medicine
	Lecturer in Graduate Critical Reading Course- Albert Einstein College of Medicine
2001-present	Lecturer in Immunology Medical School Module - Albert Einstein College of Medicine
2000-2014	Lecturer in Graduate Immunology Course - Albert Einstein College of Medicine
2000-14	Lecturer in Infectious Disease Course - Albert Einstein College of Medicine
1999	Lecturer at Rockefeller Microbial Pathogenesis course
2000-14	Lecturer at NYU Microbial Pathogenesis course
2013-present	Lecturer at Columbia Ethics Course
2015	Lecturer in IBS course, Johns Hopkins Sch of Public Health
2015	Lecturer in Graduate Immunology Course, Johns Hopkins Sch of Public Health
2015	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2016	Lecturer in Graduate Immunology Course, Johns Hopkins Sch of Public Health
2016	Lecturer in Public Health Biology Course, Johns Hopkins Sch of Public Health
2016	Lecturer in Biomedical Sciences, Johns Hopkins Sch of Public Health
2017	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2017	Lecturer in Bacterial Pathogenesis course, Johns Hopkins Sch of Public Health
2017	Lecturer in Responsible Conduct of Research course, Columbia University
2017	Lecturer in Biophysics course, Johns Hopkins University
2017	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health
2017	Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2017	Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2017	Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2017	Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2017	Lecturer in Pediatric Ground Rounds, Johns Hopkins Sch of Medicine
2017	Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health
2018	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2018	Lecturer in Bacterial Pathogenesis course, Johns Hopkins Sch of Public Health
2018	Lecturer in Responsible Conduct of Research course, Columbia University
2018	Lecturer in Biophysics course, Johns Hopkins University
2018	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health
2018	Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2018	Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2018	Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2018	Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2018	Lecturer in Parasitology, Johns Hopkins Sch of Public HEalth
2018	Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health
2019	Lecturer in R3 Course, Johns Hopkins Sch of Public Health
2019	Lecturer in Responsible Conduct of Research course, Columbia University
2019	Lecturer in Biophysics course, Johns Hopkins University
2019	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health

2019	Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2019	Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2019	Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2019	Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2019	Lecturer in Parasitology, Johns Hopkins Sch of Public HEalth
2018	Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health

PART II
RESEARCH GRANT PARTICIPATION

Current Grants:

Period of Performance: 04/01/2015--01/31/2020
Title of Grant: Biology of Fungal Melanin
Grant Number: 5 R01 AI052733-13
Sponsoring Agency: NIH/NIAID
Direct Costs/yr: $131,898
PD/PI: Casadevall
Objective: The specific aims of this grant are to establish the mechanism by which melanin promotes the virulence of *C. neoformans in vivo*, to establish the protective efficacy of antibody to *Cryptococcus neoformans* melanin and laccase and the mechanism of antibody action, to investigate the molecular events of *C. neoformans* melanin biosynthesis.

Period of Performance: 08/01/2015--05/31/2020 (NCE)
Title of Grant: Synergy of Host Defense Mechanisms in the Lung
Grant Number: 5 R01 HL059842-17
Sponsoring Agency: NIH/NHLBI
Direct Costs/yr: $250,000
PD/PI: Casadevall
Objective:The goal of this project is to establish the relationship between macrophage damage and CN non-lytic exocytosis, to establish the mechanism by which host annexins contribute to CN non-lytic exocytosis, and to identify the fungal components that facilitates non-lytic exocytosis.

Period of Performance: 11/01/2016 – 10/31/2021
Title of Grant: Host inositol regulation of AIDS-Associated Cryptococcus brain infection
Grant Number: R01 AI123315
Sponsoring Agency: NIH
Direct Costs/yr: $60,000
PD/PI: Xue
Objective: Performing detailed GXM analysis using physical chemistry approaches, including using monoclonal antibody and light scattering; detection and isolation of different polysaccharide fractions under conditions with different carbon sources (inositol or glucose) for their role in BBB crossing in vitro; and potential development of protective antibody for inositol transporters.

ACADEMIC SERVICE

Institutional Administrative Appointments

1995-7	Member, Graduate Committee, Albert Einstein College of Medicine
1998-9	Member, Assistant Professor Promotion Committee, Albert Einstein College of Medicine
2005-6	Member, Search committee Dean, Albert Einstein College of Medicine
2012-3	Member, Search Committee Chair of Pediatrics, Albert Einstein College of Medicine
2013-4	Member, Search committee Chair of Medicine, Albert Einstein College of Medicine

2015 Member, Search Committee for Bloomberg Distinguished Professor, Johns Hopkins Sch Med
2015 Member, Committee Department of Biochemistry & Molecular Biology review site visit
2015 Member, Committee Sidney Kimmel Medical College of Thomas Jefferson University, Department of Microbiology & Immunology External Review

PRESENTATIONS

INVITED PRESENTATIONS (Partial List)

1992 Grand Rounds. Downstate Department of Medicine
Grand Rounds. New York University Department of Medicine
Dept of Pathology. Stony Brook University

1993 2nd International Conference on Cryptococcus and Cryptococcosis Milan, Italy

1994 Dept of Med. Grand Rounds. Newark School of Medicine
Systemic antifungals: discovery, development and applied therapeutics. New York City
Dept of Medicine. Mount Sinai School of Medicine
Dept of Medicine. Memorial Sloan-Kettering Hospital
Medical Mycology Society of the Americas, Las Vegas Meeting
New York University. Update on Fungal Infections Symposia, NY
Dept of Rheumatology. New York University, NY
Infectious Disease Society of America, Orlando, FL
International Congress of Mycology-Vancouver, Canada
2nd NIAID Workshop on Medical Mycology, Flagstaff, Az.
Dept of Medicine. Boston University.

1995 Dept of Structural Biology. Public Health Res. Institute, NYC
Dept of Medicine. Torrance-UCLA Med. Ctr., Los Angeles, CA
Dept of Medicine. Cincinnati School of Medicine. Cincinnati, OH
Dept of Microbiology. Georgetown School of Med., Georgetown, MD
Div. of Infectious Diseases. Memorial Sloan-Kettering Hospital, NYC
3rd NIAID Workshop on Medical Mycology. Big Ski, Montana
International Workshop on Molecular Pathogenesis of Fungal Infections. Wurzburg, Germany
Infectious Diseases, Duke University, Durham, NC
Dept of Chemistry, Queens College, CUNY

1996 Medical Mycology Society of the Americas, New Orleans
3rd International Conference on Cryptococcus and Cryptococcosis, Paris, France
Spanish Mycology Association, Valencia, Spain
Cuban Medical Convention, Miami Beach, Fla.
Dept of Biology, Hunter College, CUNY
ESATYBC Conference, Catskills, NY
Hunter College, NYC
NIH Workshop on The role of humoral immunity in the treatment and prevention of Infectious Diseases Washington, DC
Dept of Microbiology. Medical College of Ohio, Toledo
Merck Pharmaceuticals, Rahway, NJ
Medical Mycology Society of New York Lecture

1997	13th Congress of the International Society of Human and Medical Mycology, Parma Italy. Convener of symposium titled: Cell-mediated versus antibody mediated-protection mechanisms in fungal diseases: an ongoing dilemma. American Society of Microbiology General Meeting Symposium, Miami, Fla. FASEB conference, Colorado New York Academy of Sciences Lecture Rockefeller University IDSA Symposium on new therapeutic strategies for fungal infections Department of Microbiology, Oklahoma Health Sciences Center Mount Sinai School of Medicine-Molecular Medicine Seminar Series Woods Hole Mycology Course Lecturer NIAID Workshop: Bridging the gap for Underrepresented Minority Research Scientists
1998	Wistar Institute Grand Rounds Beth Israel Hospital Department of Microbiology, Medical College of Ohio Division of Infectious Diseases, Columbia University Society for Industrial Microbiology Annual Meeting, Denver, Co Department of Health, State of New York, Albany, NY Department of Microbiology, Stony Brook University, NY Anderson Lecture, Charlottesville, Va Woods Hole Mycology Course Lecturer
1999	ASM Division F Divisional Lecture Cold Spring Harbor Symposium on Microbial Pathogenesis and Host Response. 1999 Joint Committee Meeting of the US-Japan Cooperative Medical Science Program Nelson Lecture at the University of Montana in Bozeman Santa Fe symposia on Defense of the Brain International Meeting on Tuberculosis, Stockholm, Sweden ASM Symposium Millennial Challenges to Vaccines Trudeau Institute NHLBI Symposium on Pulmonary Immunobiology and Inflamation, NIH U.S.-Japan Cooperative Science Program Joint Committee, Bethesda, MD Woods Hole Mycology Course Lecture NIAID Workshop: Bridging the gap for underrepresented Minority Research Scientists
2000	Boston University 14th Congress of the International Society of Human and Medical Mycology, Buenos Aires, Argentina. Convener of symposium titled: Vaccines and Preventive Antibodies; Also speaker on symposium on Fungal Morphogenesis and Virulence 1st Japanese Mycology Forum, Tokyo, Japan, Keynote Speaker Foundation Lecture British Mycology Society Meeting, Stratford-upon-Avon, England Gordon Conference on Fungal Pathogenesis New York University - Division of Infectious Diseases 40th ICAAC. Toronto. Vaccines for the 21st Century: New disease Targets on Horizon. Ritterson Memorial Lecture, University of Rochester Medical Center Genome Therapeutics Corporation, Waltham, MA Immunology for nonviral infections, Trudeau Institute, Saranac Lake Yale University

2001	ASM Symposium Host defense against fungi: application toward therapeutics and vaccine development, Orlando, FL New York Medical College (Division of Infectious Disease) University of Minnesota (Department of Microbiology) Elli Lilly, Indianapolis, IN CSH Symposium on Microbial Pathogenesis and Host Response 22nd International Conference Chemotherapy (Amsterdam) Fungal Therapy, NJ Medical School Symposium Dept of Microbiology, University of Pennsylvania National Institute of Health Department of Microbiology, Charleston Newark School of Medicine
2002	Keystone Symposia on Molecular and Cellular Biology 5th Conference on Cryptococcus and Cryptococcosis, Adelaide Australia Gordon Conference on Fungal Pathogenesis IUMS Symposium, Paris ASM Symposium New Concepts in Physiology and Biochemistry of Pathogenic Fungi Salt Lake City, UT Woods Hole Mycology Course Lecture Dept of Microbiology, University of Michigan Dept of Microbiology, University of Wisconsin Dept of Microbiology, University of Louisiana Division of Infectious Diseases, Albany 2nd Conference on Vaccines, Instituto Superiore di Sanita, Rome Division of Infectious Diseases, Columbia University
2003	Dept of Genetic Medicine, Cornell University Dept of Immunology and Virology, U. Mass Medical School 9th Congress of the European Confederation of Medical Mycology, Amsterdam, Netherlands 15th Congress of the International Society of Human and Animal Mycology Duke University Medical School Participant, Banbury Conference. Toward a More Unified Understanding of Infectious Disease CSH Symposium on Microbial Pathogenesis and Host Response 15th Congress of the International Society of Human and Medical Mycology, San Antonio. Convener of symposium titled: Protective Antibodies; Also speaker on symposium on Fungal Morphogenesis and Virulence Keynote Speaker, Mount Sinai Medical Resident Forum NABI Pharmaceuticals, Rockville, MD South Dakota Health Research Foundation ACS Glycobiology Symposium, ACS Meeting, New York. Washington University School of Medicine Miami University, Oxford Ohio New York University Division of Infectious Diseases Grand Rounds Memorial Sloan Kettering
2004	Immune Compromised Host Society - Grenada, Spain Keystone Symposia on Bioterrorism and Emerging Infectious Diseases, Keystone, CO.

Mathematical Biosciences Inst. 'Disease Models of Host-Pathogen Interactions' Columbus OH
Public Health Research Institute, Newark, NJ
ASM Meeting Symposium: 'Immune Mechanisms in Polymicrobial Infections', New Orleans
Keynote Speaker, Candida Meeting, Austin. TX
11th International Congress of Infectious Diseases, Cancun, Mexico
Mycology Unit, Pasteur Institute
Coexistence and Collisions at the Host/Microbe Interface, Burroughs Wellcome Fund, Miami, Fl.
American Phytopathological Society Mycology Committee, Anaheim, CA
New York University – Department of Microbiology
FASEB Summer Research Conference on Polysaccharides, Tucson, AZ
University of Iowa – Division of Infectious Diseases
University of Gainesville, FL -- Department of Oral Biology
Wyeth Vaccine Division, Pearl River, NY
University of Colorado Health Science Center – Dept of Microbiology
Biodefense Regional Center of Excellence meeting in Bethesda, MD
Environmental Protection Agency workshop on Virulence Factor-Activity Relationships
American Society of Tropical Medicine and Hygiene
5th Louis Pasteur Conference on Infectious Diseases, Pasteur Institute

2005 Plenary Session, Mycology Division of IUMS, San Francisco
La Jolla Institute of Allergy and Immunology
Scripps Institute
Keynote Speaker – 6th International Conference on Cryptococcus and Cryptococcosis
Focus on Fungal Infections 15, Miami, FL
ASM Biodefense Workshop
ASM Meeting Symposium, Atlanta, GA
IUMS Meeting, San Francisco
CDC Distinguished Lecturer
Koch Centennial Postulates Workshop, Berlin
Keynote Speaker, University of Michigan Public Health Retreat
New York Hospital in Queens
Maimonides Hospital
NIH, Biodefense Clinical Research Branch
FDA, Immunology Section
JASON General Meeting, San Diego
Monoclonal Antibody Meeting, Rome, Italy
Eastern Pennsylvania Branch of the American Society for Microbiology
Thaler Lecture, Aeras Global TB Vaccine Foundation
Koch's postulate - Centennial Workshop
University of Kansas, Department of Microbiology
New York Academy of Sciences
NIAID scientists from the Division of AIDS (DAIDS)

2006 Biodefense clinical research workshop (poxvirus meeting) Bethesda, MD
ASM 2006 Biodefense meeting. Panel Discussion
Grand Rounds, University of Virginia
Department of Microbiology, Drexel University
ASM 2006 Candida Meeting

	International Conference on Emerging Infectious Disease, Atlanta
	International Society for Human and Animal Mycoses, Paris
	Maxwell L. Littman Award Lecture – New York Society for Medical Mycology
	ASM General Meeting in Orlando, FL
	B cell workshop Trudeau Institute
	New York Medical College
	Maxwell L. Littman Award Lecture – New York Society for Medical Mycology
2007	University of Texas Southwestern Medical School
	University of Connecticut
	Keynote speaker, XIII Fungal Genetics Conference
	Berkeley U
	University of California San Francisco
	University of Illinois – Urbana Champaign
	ASM General Meeting Toronto Canada
	Princeton U - Program on Science and Global Security's Carnegie Biodefense Seminar
	Keynote Speaker Second FEBS Advanced Lecture Course Human Pathogens
	U. Louisville Distinguished Speaker Lecture
	Harold C. Neu Conference (Chicago)
	University of Wisconsin – Graduate Student Invited Speaker
	University of Alabama
	Keynote Speaker Merck Retreat
	APUA Congress - Boston
2008	IDSA Kass Lecture
	U Mass Worcester
	ISDA/ICAAC
	Schimelbureau Amsterdam
	Gordon Conference
	EPA conference on emerging threats
	Brooklyn College Dept Biology Keynote Retreat Speaker
	St. Louis University
	VA ASM Branch Lectureship speaker
	NIAID Biodefense Network Meeting
	University of Minnesota
2009	Aztra Zeneca, MA, Waltham
	University of Buffalo
	Rio Grande ASM Branch Keynote speaker
	UAB Program in Immunology
	Puerto Rico ASM Branch Keynote Speaker
	Critical Path for ID Therapeutics Targeting Host NIAID/DMID/OBRA Workshop
	Forum on Microbial Threats (IOM)
	Rinat-Pfizer, SF
	IOM Committee on Science, Technology and Law
	Semmering Vaccine Symposium, Vienna
	University of Wurzburg symposium on Living with Pathogens
	University of Pittsburg
	Merck
	Medical Mycology Society of New York
	Novartis

Tufts University
Wadsworth Center
Intermountain ASM Branch Keynote Speaker
Southeastern ASM Branch Keynote Speaker
Florida ASM Branch Keynote Speaker
Hawaii Branch ASM Keynote Speaker
Farness Lecture, Tucson, AZ
Duke University, Dept of Genetics

2010 Keynote Speaker, First International Conference on Model Hosts, Crete Greece
Keynote Speaker European Fungal Genetics Conference, Amsterdam, Netherlands
Distinguished Faculty Seminar in Infectious Diseases, Medical College of Wisconsin
Association of Medical School Microbiology and Immunology Chairs
Forum on Microbial Threats (IOM)
Vienna Biocenter, Vienna, Austria.
Columbia University Dept of Microbiology and Immunology
Mount Sinai Dept of Infectious Diseases
8th World Congress on Trauma, Shock, Inflammation and Sepsis, Munich, Germany
ASM General Meeting, San Diego
ICCAC, Boston
IDSA, Vancouver
Ann Arbor, MI
University of Rio de Janeiro
IOM Forum on Fungal diseases
2010 Nelson Lecture, Bozeman, Montana
2010 Theobald Smith Lecture at Albany
2010 Arthur White Lecture, U Indiana

2011 Scripps Institute, La Jolla
Stanford University
Naval Research Laboratory, Washington DC
GRC Immunology of Fungal Infections (Galveston)
Mark Wilson Conference, San Juan
Keystone Symposia on Lung Immunity
University of Pennsylvania, Philadelphia
Keynote Speaker, Annual Pew Scholars Meeting, Cozumel
Keynote Speaker, GRC on Chemical and Bioterrorism Threats
Department of Microbiology and Immunology, Loyola University
Inter Urban Clinical Club
National Biodefense RCE Meeting, Denver
Cryptococcus and cryptococcosis meeting
Weinstein Lecture, Tufts
Keynote Speaker, Brazilian Microbiology Society
Keynote Speaker, Australian Microbiology Society
Bacterial Toxins Meeting, Oslo Norway
Brown University
Massachusetts General Hospital
Merck Vaccine Symposium (Toronto)
ICAAC Boston
Brown University
University of North Carolina

National Plant Diagnostic Network
Harvard University

2012 Bard College
Keystone meeting on Fungal pathogenesis and drug discovery, Santa Fe
University of Calgary
University of Tennesse
University of Puerto Rico
Pasteur Institute
2012 Pugwash Conference
Symposium on fungal pathogenesis, Oviedo, Spain
ICAAC Lecture 2012
Translational Sciecne 2012 Meeting, Washington DC
University of Arkansas
International Conference of Emerging Infectious Diseases (Emerging Fungal Diseases) Atlanta
Keynote speaker, 8th National Symposium on Recent Advances in Carborhydrate Sci. Banff, Alberta
Vanderbilt University
Duke Mycology Symposium
NYAS Symposium 'Discovering antibacterial and anticancer therapeutics in unexpected places'
Keynote speaker – Tularemia meeting, Breckenridge CO
Keynote Speaker – U Cleveland Immunology retreat
Health Research Alliance, Washington DC
Jenner Lecture, St. Georges Hospital, London

2013 Human Fungal Pathogens 2013 Nice, France
NIH Immunology Program, Bethesda MD
GRC Fungal Infections – Galveston, TX
Ohio State University, Columbus, OH
ASM Biodefense and Emerging Infectious Meeting, Washington, DC
Virginia Commonwealth University, Richmond, VA
Columbia University (Responsible conduct of research course)
Texas A&M, College Station, TX
University of Texas at San Antonio
University of Texas at Austin
University of Jena
American Society for Microbiology General Meeting, Denver, CO
BWF Meeting in Calgary, Canada
Swiss Society for Microbiology, Interlaken
Capetown, South Africa
Human Fungal Pathogens Course, Nice, France
Keynote Speaker, Donaghue Foundation
Rheumatology Division, Beth Israel Medican Center
Snowmass Microbial Pathogenesis Meeting
Kynnoun Lecture, NIAID

2014 Association of American Law Schools (AALS) Annual Meeting, New York
Bridging Lecture, International Union of Microbiological Societies 2014 meeting, Montreal, Canada

Departmet of Microbiology and Immunology, UC Davis
2014 Keystone Symposium on Prophylactic and Therapeutic Antibodies
Keynote Speaker, Israeli Society of Microbiology 2014 meeting
Keynote Speaker 17th Upstate NY Immunology Conference
Keynote Speaker International Life Sciences Institute Annual meeting, Bermuda
Keynote Speaker, The 2nd Annual Infection, Inflammation, and Immunity Summer Symposium, U Utah
Benard Fields Memorial Lecture, The Scripps, La Jolla
2014 American Association of Immunology Minority Affairs Guest Lecturer
Student Invited Speaker, Graduate Biosciences Society at the University of Virginia, Charlottesville
Invited speaker, GRC Cellular and Molucular Fungal Biology
Group on Research Advancement and Development (GRAND), AAMColleges
San Antonio Vaccine Development Center Conference titled "Infections, Immunity and Vaccines
Keynote Speaker Department of Microbiology and Molecular Genetics Retreat, UTHSCenter, Houston
Keynote Speaker Upstate NY Immunology Conference, Lake George
Keynote Speaker ASM Eastern NY Branch, Albany, NY
Symposium on Microbes in Health and Disease at Weill Medical College
Keynote Speaker XII International Meeting on Paracoccidioidomycosis, Brasilia, Brasil.

2015 14th Annual St. Jude/PIDS Pediatric Infectious Diseases Research Conf., Memphis, TN
Invited Speaker, Icahn School of Medicine at Mount Sinai, New York, NY
Invited Speaker, Albert Einstein, New York, NY
Invited Speaker, Princeton University, Princeton, NY
Invited Speaker, Baylor College, Houston, TX
Invited Speaker and Organizer, Model Host Conference, Crete, Greece
Invited Speaker, Universidad de la RepAblica, Montevideo, Uruguay
Invited Speaker, North Dakota State University, Fargo, ND
Invited Workshop Speaker, National Diversity Equity Workshop, Arlington, VA
Invited Speaker, Merck, East Brunswick, NJ
Invited Speaker, University of Kentucky, Lexington, KY
Invited Speaker, University of Maryland, Baltimore, MD
Invited Speaker, Nationwide Children's Hospital, Columbus, Ohio
Invited Speaker, ASM Maryland Branch, Hunt Valley, MD
McCollum Colloquim, Dartmouth, Hanover, NH
Columbia University ethics course, New York, NY
NIH Director's Wednesday Afternoon Lecture Series, NIH, Bethesda, MD
Invited Speaker, East Tennessee University, Johnson City, TN
Keynote Speaker, New York Hospital Queens, New York, NY
Douglas McGregor Keynote Address, Cornell University, Ithaca, NY
McGinnis Memorial Lecture, Duke University, Durham, NC
Annual Microbial Sciences Symposium, Harvard University, Cambridge, MA
Keynote Speaker, University of California Irvine, Lake Arrowhead, CA
3rd Conference on Model Hosts, Crete, Greece

2016 Plenary Speaker, ASM Biodefense Conference, Arlington VA
Microbiology 2016, Liverpool, UK
Medoff Lecture, Washington University, St. Louis
Department of Biomedical Sciences, East Tenesse University, TN

Naff Lecture, Case Western Reserve
McGhee Lecture, University of Arkansas
National Library of Medicine
Keynote Speaker, Canadian Society of Microbiology, Toronto
Microbe 2016, American Society of Microbiology, Boston, NY
Karling Lecture, The Mycological Society of Americas, Berkeley, CA.
Emerging Infectious Disease Workshop, Madrid, Spain
15th CRG-Centre for Genomic Regulation Symposium, Barcelona, Spain
Keynote Speaker, MSGERC Meeting, Asilomar, CA
Society for Glycobiology, New Orleans
Retreat Keynote Speaker, Department of Microbiology, U Maryland
Student Invited Speaker, McMaster University, Ontario, Portland
Reed College, Portland, Oregon
Merck Sharp and Dohme
Keynote Speaker (student invited), McMaster University, Ontario, Canada
Reed College, Portland, Oregon
Merck Sharp and Dohme
Boston University, Boston, MA
Plenty Speaker, 2016 Society for Glycobiology, New Orleans, LA
University of Pittsburgh, Pittsburgh, PA

2017

Westmere Lecture, Birmingham UK
Harry Smith Lecture, Birmingham UK
Boston University, Boston, MA
Queens College, New York, NY
University of Wisconsin-Madison, Madison, WI
University of Kansas, Manhattan, KS
Plenary Speaker, 2017 International Mtg of Microbiological Society of Korea, Seoul
5th International Symposium of the Collaborative Research Centre, Tubingen, Germany
GAP Summit 2017, Georgetown University, Washington, DC
Food & Drug Administration, Silver Spring, MD
Keynote Speaker, 2017-2018 Icahn SOM at Mount Sinai Annual Retreat, Ellenville, NY
Mahmoud Ghannoum 20th Anniversay Symposium, University Hospitals Cleveland Medical Ctr, Ohio
Middle Tennessee State University, Murfreesboro, TN
National Research Council of the Swiss Nation, Berne, Switzerland
Columbia Law School, New York, New York

2018

SPRIG Speaker, National Institutes of Health, Bethesda, MD
Columbia Law School, New York, New York
Plenary Speaker, 14th European Conference on Fungal Genetics, Haifa, Israel
Speaker, Biosecurity Luncheon, The National Academies of Science, Engineering and Medicine, Washington, DC
Speaker, Israel Society for Medical Mycology, Tel Aviv, Israel
Speaker, United States Uniformed Health Services, Bethesda, MD
Speaker, University of Connecticut, Storrs, CT
Speaker, Signals of Trust Science Communicaiton, Cold Spring Harbor, Lloyd Harbor, NY
Speaker, University of Nebraska Medical Center, Omaha, NE
Speaker, Broad Institute, Cambridge, MA
Keynote Speaker, Kelsey Lecture, The University of Texas MD Anderson Cancer Center, Houston, Texas

Keynote Speaker, Van Andel Institute, Grand Rapids, MI
Speaker, Gordon Research Conference Extracellular Vesicles, Newry, ME
Speaker, Duke University MGM annual retreat, Durham, NC
Speaker,8th BMMC Conference, Dublin, Ireland
Speaker Fungal CIFAR Workshop, Toronto, Canada
Speaker, Center for Valley Fever Symposium, Sacramento, California
Speaker, Tulane University School of Medicine, New Orleans, LA
Speaker, University of Pittsburgh, Pittsburgh, PA
Speaker, Columbia Law, New York, NY
Speaker, Albert Einstein College of Medicine, New York, NY

2019 Speaker, University of Alabama, Birmingham, Alabama
Speaker, University of Maryland Baltimore, Baltimore, Maryland
Speaker, Johns Hopkins School of Medicine, Baltimore, Maryland
Speaker, Columbia Law, New York, NY
Speaker, University of Arizona, Tucson, Arizona
Speaker, Baruch College CUNY, New York, NY
Speaker, APSA, Chicago, Il
Speaker, World Vaccine Congress, Washington, DC
Speaker, University of Buffalo, Buffalo, New York
Speaker, UT Southwestern Medical Center, Dallas, TX
Speaker, Merck Research Laboratories, Boston, MA
Speaker, Rocky Mountain Laboratories, Hamilton, MT
Speaker, Melanin Workshop, Silver Spring, MD
Speaker, Cancer Biology Training Consortium, Baltimore, MD
Keynote Speaker, Queen's University of Belfast, Belfast
Speaker, Cornell University, New York, New York
Speaker, NASA Glenn Research Center, Cleveland, Ohio
Speaker, National Academies of Sciences, Engineering and Medicine, Washington, DC
Speaker, Rockefeller University, New York, New York

Appendix B

APPENDIX B

Exh. No.	Description
AMG1001	U.S. Patent No. 9,732,149 to Bell et al.
AMG1002	Declaration of Joseph P. Balthasar, Ph.D.
AMG1003	Curriculum Vitae of Joseph P. Balthasar, Ph.D.
AMG1004	Hillmen, P., et al., "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria," N. Engl. J. Med. 350:552-559 (2004) ("Hillmen '04")
AMG1005	Bell, L. and Rother, R., "Method of Treating Hemolytic Disease," U.S. Patent Application Publication No. 2005/0191298 A1 (filed February 3,2005; published September 1, 2005)
AMG1006	Bowdish, K., et al., "Rationally Designed Antibodies," U.S. Patent Application Publication No. 2003/0232972 A1 (filed December 2, 2002; published December 18, 2003)
AMG1007	Evans, M., et al., "C5-Specific Antibodies for The Treatment of Inflammatory Diseases," U.S. Patent No. 6,355,245 B1 (filed June 7, 1995; issued March 12, 2002)
AMG1008	Mueller, J., et al., "Porcine Cell Interaction Proteins," International Patent Application Publication No. WO 97/11971 A1 (filed September 27, 1996; published April 3, 1997)
AMG1012	Hillmen, P., et al., "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria," N. Engl. J. Med. 355:1233-1243 (2006)
AMG1014	File History for U.S. Patent No. 9,725,504 B2
AMG1015	File History for U.S. Patent No. 9,732,149 B2
AMG1016	File History for U.S. Patent No. 9,718,880 B2
AMG1018	Harlow and Lane, Chapter 2: Antibody Molecules, in Antibodies, A Laboratory Manual (1988)
AMG1019	Brekke, O. and Sandlie, I., "Therapeutic antibodies for human diseases at the dawn of the twenty-first century," Nature Reviews Drug Discovery 2: 52-62 (2003)
AMG1020	Pierangeli, S., et al., "Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia," Arthritis & Rheumatism 52: 2120-2124 (2005)
AMG1021	Kaplan, M., "Eculizumab (Alexion)," Curr. Opin. Investig. Drugs 3:1017-1023 (2002)

Samsung Bioepis Exhibit No. 1002
Page 11642

Exh. No.	Description
AMG1023	Thomas, T., et al., "Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv.," Molecular Immunology, 33: 1389- 1401 (1996)
AMG1028	Wang, Y., "Nebulization of Monoclonal Antibodies for Treating Pulmonary Diseases," U.S. Patent Application Publication No. 2005/0271660 A1 (filed May 11, 2005; published December 8, 2005)
AMG1029	Wang, W., et al., "Antibody Structure, Instability, and Formulation," Journal of Pharmaceutical Sciences 96: 1-26 (2007)
AMG1031	Mueller, P., et al., "Humanized Porcine VCAM-Specific Monoclonal Antibodies With Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding To Porcine Endothelial Cells," Molecular Immunology 34: 441 -452 (1997)
AMG1032	Rother, R., et al., "Antibodies and Fusion Proteins That Include Engineered Constant Regions," International Patent Application Publication No. WO 2005/007809 A2 (filed May 28 2004; published January 27, 2005)
AMG1033	Rother, R., et al., "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," Nature Biotechnology 25: 1256-1264 (2007)
AMG1034	Tacken, P., et al., "Effective induction of naive and recall T-cell responses by targeting antigen to human dendritic cells via a humanized anti–DC-SIGN antibody," Blood 106: 1278-1285 (2005)
AMG1039	Matis, L. and Rollins, S., "Complement-specific antibodies: Designing novel anti-inflammatories," Nature Medicine 1: 839-842 (1995)
AMG1042	Hillmen, P., et al., "Eculizumab, a C5 complement blocking antibody, is the first therapy to reduce transfusion requirements in patients with paroxysmal nocturnal haemoglobinuria (PNH)," British Journal of Haematology - Supplement 121:87, Abstract 257 (2003)
AMG1047	Hill, A., et al., "Sustained response and long-term safety of eculizumab in paroxysmal nocturnal Hemoglobinuria," Blood 106: 2559-2565 (2005) ("Hill '05")
ALXN2005	Original SOLIRIS® Label (2005-2007)
ALXN2006	Dmytrijuk et al., FDA Report: Eculizumab (SOLIRIS®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, THE ONCOLOGIST, 13:993-1000 (2008)
ALXN2007	Janeway and Travers, Immunobiology: The Immune System in Health and Disease (Garland Science, 6th ed. (2005))

Exh. No.	Description
ALXN2008	McCloskey et al., Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)
ALXN2009	Torres et al., The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917–27 (2007)
ALXN2010	Janda et al., Ig Constant Region Effects on Variable Region Structure and Function, FRONT.MICROBIOL., 7(22): 1-10 (2016)
ALXN2011	Pritsch et al., Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)
ALXN2012	Pritsch et al., Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)
ALXN2013	McLean et al., Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379–86 (2002)
ALXN2014	Greenspan et al., Complementarity, Specificity and the Nature of Epitopes and Paratopes in Multivalent Interactions, IMMUNOL. TODAY, 16(5): 226-30 (1995)
ALXN2015	Radbruch, et al., Drastic Change in Idiotypic but Not Antigen-Binding Specificity of an Antibody by a Single Amino-Acid Substitution, NATURE, 315(6): 506-508 (1985)
ALXN2017	Hawkins et al., The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J.MOL. BIO., 234: 958-964 (1993)
ALXN2019	Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)
ALXN2020	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p (last visited May 15, 2019)

Exh. No.	Description
ALXN2021	BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France (last visited May 15, 2019)
ALXN2023	Curriculum Vitae of Arturo Casadevall
ALXN2028	Hill, et al., Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria, THE HEMATOLOGY JOURNAL, 31-33, 2007
ALXN2029	Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, U.S. Dept. of Health and Human Services, Food and Drug Admin., 1997
ALXN2030	3/16/2007 FDA Approves Alexion's Soliris™ for all Patients with PNH
ALXN2031	Janeway, et al.,Immunobiology, The Immune System in Health and Disease, Appendix I: Immunologists' Toolbox, 6th ed. 2005
ALXN2032	Deposition Transcript of Joseph P. Balthasar, Ph.D., Amgen, Inc. v. Alexion Pharmaceuticals, Inc., IPR No. 2019-00740 (Oct. 23, 2019)
ALXN2033	Kim, et al., Antibody Engineering for the Development of therapeutic Antibodies, MOLECULES AND CELLS, Vol. 20, No. 1, pp. 17-29, 2005
ALXN2034	Hwang, et al., Immunogenicity of engineered antibodies, SCIENCE DIRECT, 17 Jan. 2005
ALXN2035	Shepherd, et al., Monoclonal Antibodies, Oxford University Press, pp. 58-5 (Appendix) 2000
ALXN2036	Lo, Benny K., Antibody Engineering Methods and Protocols, METHODS IN MOLECULAR BIOLOGY, Vol. 248 2004
ALXN2037	Welt, et al., Phase I Study of Anticolon Cancer Humanized Antibody A33, CLINICAL CANCER RESEARCH, 2003
ALXN2038	Haller, et al., Safety Issues Specific to Clinical Development of Protein Therapeutics, NATURE PUBLISHING GROUP, 2008
ALXN2039	Torres, et al, Exchanging Murine and Human Immunoglobulin Constant Chains Affects the Kinetics and Thermodynamics of Antigen Binding and Chimeric Antibody Autoreactivity, PLOS ONE, 2007
ALXN2040	Torres, et al., Variable-Region-Identical Antibodies Differing in Isotype Demonstrate Differences in Fine Specificity and Idiotype, JOURNAL OF IMMUNOLOGY, 2005

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ALXN2042	Mathieu, Barbara G., Clinical Testing of Biologically Derived Therapeutics, Biologics Development: A Regulatory Overview, 3d ed., 2004
ALXN2043	Andersen, et al,, Production technologies for monoclonal antibodies and their fragments, SCIENCE DIRECT, 2004
ALXN2044	Chadd, et al., Therapeutic antibody expression technology, 2001
ALXN2045	2007 USP Dictionary of USAN and International Drug Names
ALXN2046	Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances, 1997
ALXN2047	McClean, et al., A point mutation in the CH3 domain of huan IgG3 inhibits antibody secretion without affecting antigen specificity, MOLECULAR IMMUNOLOGY, 2005
ALXN2049	HemOnc Today, Eculizumab's triumph over PNH, https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh (Aug. 25, 2008)
ALXN2050	Fatimah Al-Ani et al., "Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selction and special considerations, Ther. Clin. Risk Manag.; 12: 1161–1170 (2016)
ALXN2051	Foote, Jefferson and Winter, Greg, "Antibody Framework Residues Affecting the Coformation of the Hypervariable Loops," J. Mol. Biol., 224:487-449 (1992)
ALXN2052	Xiang, Jim et al., Framework Residues 71 and 93 of the Chimeric B72.3 Antibody are Major Determinants of the Conformation of Heavy-chain Hypervariable Loops," J. Mol. Biol. 253:385-390 (1995)
ALXN2053	June 2019 Soliris Label
ALXN2054	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris(TM) (eculizumab)," (Sept. 20, 2006)
ALXN2055	Alexion Press Release, "Alexion Submits Market Authorization Application for Soliris(TM) (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency," (Sept. 26, 2006)
ALXN2075	GenScript, "Final Report – Antibody Full Length Sequencing of Hybridoma 5G1.1 T175," Order Number: U856UEK140-1 (Nov. 15, 2019)
ALXN2086	Stebbings, R., *et al.*,"After TGN1412: Recent developments in cytokine release assays," J. of Immunotoxicology, 10(1):75-82 (2013)
ALXN2088	Amgen Biosimilar Pipeline Approved Products (2019)

Exh. No.	Description
ALXN2089	Generium Pharmaceutical, "Elizaria" Product (2019)
ALXN2090	Samsung Bioepis - Biosimilar candidates and Novel biologic (2019)
ALXN2091	Harlow and Lane, Chapter 15: Antibody Molecules, in Antibodies, A Laboratory Manual, 622-25 (1988)

APPENDIX B

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00740
Patent: 9,718,880

DECLARATION OF BERNHARDT L. TROUT, Ph.D.

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TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND AND QUALIFICATIONS 3

III. SUMMARY OF OPINIONS 6

IV. LEGAL PRINCIPLES PROVIDED BY COUNSEL 7

V. PERSON OF ORDINARY SKILL IN THE ART AS OF MARCH 15, 2007 9

VI. STATE OF THE ART REGARDING FORMULATION OF THERAPEUTIC ANTIBODIES AS OF MARCH 15, 2007 11

A. Monoclonal Antibodies for Human Therapeutic Use 11

B. Challenges to Formulation of Therapeutic Monoclonal Antibody Products as of March 15, 2007 14

VII. THE '880 PATENT 23

VIII. BELL (AMG1005) AND WANG (AMG1028) DID NOT MOTIVATE A POSA TO MAKE THE CLAIMED COMPOSITIONS OF THE '880 PATENT, OR GIVE A POSA A REASONABLE EXPECTATION OF SUCCESS IN DOING SO 27

A. A POSA Prior to March 15, 2007 Would Not Have Been Motivated to Make, or Reasonably Expected Success in Making, a Pharmaceutical Composition of an Unstudied Antibody Comprising SEQ ID NOs: 2 and 4 32

B. Bell (AMG1005) and Wang (AMG1028) Would Not Have Motivated a POSA Prior to March 15, 2007 to Make the Pharmaceutical Compositions of '880 Patent Claims 1 and 3, or Given a POSA a Reasonable Expectation of Success in Doing So 39

Samsung Bioepis Exhibit No. 1002
Page 11650

I, Bernhardt L. Trout, Ph.D., hereby declare and say as follows:

I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I understand that the Patent Trial and Appeal Board has granted Amgen Inc.'s ("Amgen") petition to institute this *Inter Partes* Review ("IPR") regarding claims 1-3 of U.S. Patent No. 9,718,880 ("the challenged claims of the '880 patent"). (AMG1001.) I understand from counsel that the '880 patent is owned by Alexion Pharmaceuticals Inc. ("Alexion").

3. This Declaration sets forth my opinions with respect to the challenged claims of the '880 patents, including the documents I considered, and my response to certain opinions set forth in the Declaration of Dr. Joseph P. Balthasar, Ph.D. (AMG1002) as they relate to issues of pharmaceutical formulation and pharmaceutical compositions of monoclonal antibodies.

4. I have been asked whether, from the perspective of a person of ordinary skill in the art ("POSA") prior to March 15, 2007, the pharmaceutical compositions recited in claims 1 and 3 of the '880 patent would have been obvious in view of Hillmen (2004) (AMG1004), Bell (AMG1005), and Wang (AMG1028) as asserted in Amgen's Ground 3.

5. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical compositions recited in claims 1 and 3 of the '880 patent would have been obvious in view of Hill (2005) (AMG1047), Bell, and Wang as asserted in Amgen's Ground 4.

6. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical compositions recited in claims 1, 2, and 3 of the '880 patent would have been obvious over Bell, Wang, Bowdish (AMG1006), and Evans (AMG1007) as asserted in Amgen's Ground 5.

7. Finally, I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical compositions recited in claims 1, 2, and 3 of the '880 patent would have been obvious over Bell, Wang, Evans, and Mueller (AMG1008) as asserted in Amgen's Ground 6.

8. Below is a complete Table of the Grounds upon which I will opine in this declaration.

Ground	Claims	Basis	Asserted References
3	1, 3	35 U.S.C. § 103(a)	Hillmen (2004), Bell, and Wang
4	1, 3	35 U.S.C. § 103(a)	Hill (2005), Bell, and Wang
5	1-3	35 U.S.C. § 103(a)	Bell, Bowdish, Evans, and Wang
6	1-3	35 U.S.C. § 103(a)	Bell, Evans, Mueller, and Wang

9. I am being compensated at my usual rate for consultation on patent matters of $ 900/hr, plus any additional reasonable expenses. My compensation is in no way dependent on the outcome of this proceeding.

II. BACKGROUND AND QUALIFICATIONS

10. I am currently a Professor of Chemical Engineering at the Massachusetts Institute of Technology (MIT). I am also Director of the Society, Engineering and Ethics (SEE) Program at MIT.

11. I received my B.S. and M.S. degrees from MIT (1990) and my Ph.D. from the University of California at Berkeley (1996), all in chemical engineering. I performed post-doctoral research at the Max-Planck Institute for Solid-State Physics in Stuttgart. In 1998, I became an Assistant Professor of Chemical Engineering at MIT. I was promoted to Associate Professor of Chemical Engineering in 2003, and I was promoted to Full Professor of Chemical Engineering at MIT in 2008. Since 2014, I have held the Raymond F. Baddour, ScD, (1949) Chair as Professor of Chemical Engineering.

12. I am a member of various scientific societies including the American Institute of Chemical Engineers, the American Association of Pharmaceutical Scientists, and the American Chemical Society.

13. I have been a reviewer for several journals including mAbs, Proceedings of the National Academy of Sciences, The Journal of Physical

Chemistry, Chemical Physics Letters, Pharmaceutical Research, Journal of the American Chemical Society, Biochemistry, Journal of Pharmaceutical Sciences, Biophysical Journal, The Journal of Organic Chemistry, Analytical Biochemistry, Research Letters in Physical Chemistry, Nature Materials, Molecular Pharmaceutics, Chemical Physics Letters, and Angewandte Chemie.

14. I have given more than 150 invited talks on pharmaceuticals including difficulties associated with antibody formulation and stability, including at the FDA, the American Association of Pharmaceutical Sciences, the Industrial Society of Pharmaceutical Engineering, the American Chemical Society, PEP Talk, and many companies.

15. I have published more than 200 papers in refereed journals and have 18 patents pending or issued.

16. I have over 20 years' experience working with protein formulation and have focused my research on monoclonal antibody formulation since 2004.

17. My current research group at MIT consists of approximately 5 Masters or Ph.D. students, Post-Doctoral Associates, and technical research staff, most of whom focus on antibody formulation research. My research consists of a wide range of areas in pharmaceutical and biopharmaceutical (protein and antibody) development and manufacturing, including formulation and stabilization. Target formulations and manufacturing approaches include both liquid and

lyophilized final dosage forms. My research investigates the underlying science of pharmaceutical and biopharmaceutical development and manufacturing and aims to develop new technologies in those areas.

18. My work includes developing approaches to antibody stabilization, developing tools to mitigate antibody aggregation, evaluating monoclonal antibody aggregation, and developing stable antibody formulations. Since starting as a professor at MIT in 1998, I have worked on about 50 or more biologic therapeutics, most of them monoclonal antibodies. The vast majority of this work has been sponsored by industry and includes characterization, formulation, and design of antibodies. My laboratory has elucidated mechanisms of degradation, including aggregation, oxidation, deamidation, and hydrolysis. Current research includes developing approaches for the rational formulation of monoclonal antibodies and determining key molecular descriptors responsible for various degradation routes in addition to enhanced viscosity.

19. Since 2010, I have been the lead instructor (with a colleague from the FDA and a colleague from industry) of an MIT professional short course entitled, "Formulation and Stabilization of Biotherapeutics." This course is offered annually and mainly consists of professionals in the area of formulation who want to enhance their knowledge in the subject.

Samsung Bioepis Exhibit No. 1002
Page 11655

20. I also consult and have given invited talks and plenary lectures on topics including stabilizing proteins and antibodies for industry, including for Amgen and Biogen-Idec. I have also lectured at the Biomanufacturing Summit, Cambridge, MA., and have been a consultant for the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Overall, my consulting consists of a range of endeavors from technical problem solving to strategy. Much of this consulting is related to formulation of biopharmaceuticals, including mAbs to be commercialized. At least one monoclonal antibody that I have consulted on is now a commercial product, and several others are being commercialized.

21. A full description of my background, awards, and qualifications can be found in my curriculum vitae attached as an appendix to this declaration. My curriculum vitae is attached hereto as Appendix A (ALXN2025).

III. SUMMARY OF OPINIONS

22. In forming my opinions contained in this Declaration, I have relied on my education, background and experience in antibody formulation. I have also reviewed the '880 patent, the Balthasar Declaration (AMG1002), the transcript for the October 23, 2019 Deposition of Dr. Joseph Balthasar (ALXN2032); the Institution Decision (Paper No. 15), and the publications, patents, patent applications and other documents cited in this Declaration.

23. In connection with the opinions and conclusions contained within this Declaration, I have reviewed and considered the documents listed in Appendix B attached to this Declaration, as well as any other documents cited throughout this Declaration.

24. I understand that the documents Bell (AMG1005) and Wang (AMG1028) are cited in Amgen's asserted Grounds 3-6 for *inter partes* review of the '880 patent. Based on my experience and expertise, and the documents and information I have reviewed and considered, I disagree with Dr. Balthasar's positions that Bell (AMG1005) and Wang (AMG1028) disclosed the pharmaceutical compositions recited in claims 1-3 of the '880 patent. I further disagree with Dr. Balthasar's opinions that a person of ordinary skill in the art ("POSA") would have been motivated to make and use the pharmaceutical compositions claimed in the '880 patent, or that a POSA would have had a reasonable expectation of success in doing so.

IV. LEGAL PRINCIPLES PROVIDED BY COUNSEL

25. I am not an attorney. However, I have been advised of the following legal principles, and they have helped to form my conclusions in this report. I understand that Petitioner has asserted that the challenged claims of the '880 patent are unpatentable under 35 U.S.C. § 103 as obvious in view of the various prior art combinations I listed in paragraphs 4-7, above.

26. I understand that it is Amgen's burden to show that the challenged claims are obvious, and that to do this Amgen must show, without the benefit of hindsight, that the claimed invention as a whole would have been obvious to a POSA prior to the date of invention or "priority date."

27. I understand the Board will consider the following factors when assessing whether Amgen has met its burden to show obviousness: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness. I have been informed by counsel that objective evidence of non-obviousness can include: that the invention satisfied a long-felt but unmet need that existed at the time of the invention; commercial success of products embodying the claimed invention; teaching away from the invention in the prior art; copying of the invention; and industry praise.

28. I understand that, when considering obviousness, I must not use hindsight knowledge of the invention claimed in the '880 patent. I understand that I must consider only documents or information that would have been available before the priority date. I further understand that I must consider the full scope and content of the prior art that would have been available to a POSA as of March 15, 2007, and that I may not use hindsight to select references from the prior art to be considered in the obviousness analysis. I understand that I must consider the prior

art as a POSA would have viewed it as of March 15, 2007, without the benefit of knowing how the invention was successfully achieved.

29. I understand that Amgen must show that, without the benefit of hindsight, a POSA would have been motivated to combine a particular set of prior art references, and that in doing so a POSA would have had a reasonable expectation of success in achieving the claimed invention.

V. PERSON OF ORDINARY SKILL IN THE ART AS OF MARCH 15, 2007

30. I understand from counsel that, for purposes of this proceeding, the '880 patent is to be read from the perspective of a person of ordinary skill in the art ("POSA") at the time of invention. I further understand that a POSA is a hypothetical person who is presumed to know the relevant art at the time of the invention.

31. I understand that the Board has accepted a definition of POSA as a person with an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry. (Paper No. 15 at 21.) I agree with this definition, and I provide my opinions from the perspective of a POSA of March 15, 2007, with a focus on issues pertaining to antibody formulation.

32. I also understand that Dr. Balthasar proposed that "a POSA may have worked as part of a multidisciplinary team and drawn upon not only her or her own skills, but also taken advantage of certain specialized skills of others on the team," including "a clinician and a formulation chemist." (AMG1002 ¶ 21.) I agree that a POSA with respect to the '880 patent could have – and in the context of drug development, would have – consulted with others having specialized skill and experience concerning the formulation of pharmaceutical compositions of monoclonal antibodies, as well as others having specialized skill and experience in clinical therapy.

33. I understand from counsel that, for purposes of this proceeding, the '880 patent and other pertinent information is to be considered from the perspective of a POSA **prior to March 15, 2007**, which counsel informs me is the earliest filing date for the '880 patent.

VI. STATE OF THE ART REGARDING FORMULATION OF THERAPEUTIC ANTIBODIES AS OF MARCH 15, 2007

A. Monoclonal Antibodies for Human Therapeutic Use

34. As of March 15, 2007, a POSA would have known that antibodies[1] are large, roughly Y-shaped protein molecules. Figure 1 below, adapted from Dr. Balthasar's declaration, is a simplified two-dimensional illustration of the general structure of an antibody. (AMG1002 ¶ 26.) As seen in the figure, antibody structure can be divided into two regions: the "variable" region at the top of the Y-shaped structure, and the "constant" regions that start below the variable regions through the stem of the Y structure. The variable regions at the top of the "Y"

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[1] Unless otherwise noted, I use the term "antibodies" to refer to intact, full-length antibody structures. A POSA would have also known of various antibody-related molecules that are structurally different from full-length, intact antibodies. These would have included "Fab" fragments, each consisting of one antigen-binding "arm" of an IgG antibody – *i.e.*, the variable and constant regions from a light chain, and the variable and first part of the constant region from a heavy chain – and "single-chain variable fragments," or "scFv," each consisting of the variable region of a heavy chain linked by a synthetic peptide to the variable region of a light chain. (AMG1029 at 8; *see also* AMG1030 at 699-700.)

were understood to include the sites that bind to certain target compounds, known as "antigens," and were also referred to as the "antigen binding region."

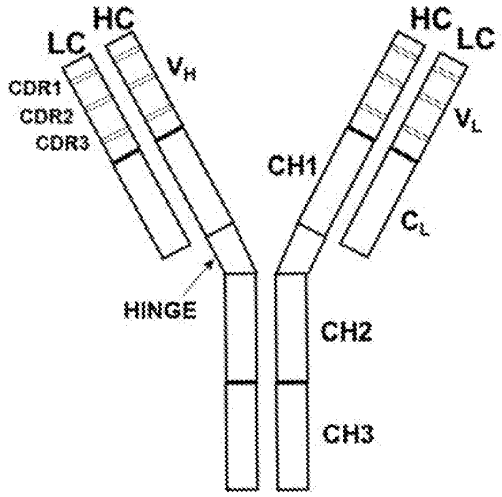


Figure 1: General structure of an IgG-class antibody

35. Following the creation of "monoclonal" antibody technology that (if successfully carried out) could potentially result in the development of highly selective antibodies directed only against a specific target antigen, monoclonal antibodies became an area of interest of pharmaceutical development. (AMG1030 at 686-87.) As Dr. Balthasar notes, and I do not dispute, there were at least 23 monoclonal antibody products (including partial antibody structures ("Fab") and conjugates) approved for commercial marketing in the United States as of March 15, 2007. (AMG1002 ¶¶ 28, 98 fn 7, Appendix I; AMG1029 at 2-4 (Table 1).)

36. The majority of commercial monoclonal antibody products were full-length antibodies of the IgG class. (AMG1029 at 2-4 (Table 1).) Of "humanized"

antibodies – *i.e.*, antibodies made from the combination of human variable and constant regions with mouse CDRs – the IgG1 subclass was most common, followed by IgG4. (*Id.*; AMG1030 at 688.) All of the approved antibodies used naturally-occurring isotypes – there were no approved antibodies with a non-naturally occurring, engineered (*e.g.*, "hybrid") constant region isotype. (*Id.*)

37. These 23 commercial monoclonal antibody products were developed for a variety of therapeutic and diagnostic applications in humans, including treatment of cancer (*e.g.*, Avastin (bevacizumab)) and chronic inflammatory conditions (*e.g.*, Humira (adalimumab)). (AMG1029 at 2-4 (Table 1).) A POSA as of March 15, 2007 would have known that, to be marketed commercially in the United States, the makers of these 23 products had to demonstrate to the U.S. Food and Drug Administration ("FDA") that these products were safe and effective for their indicated use. (ALXN2032 at 46:20-48:2; ALXN2079 at 19.)

38. A POSA would have further known that, to obtain the FDA's authorization to even study these monoclonal antibody products in human clinical trials prior to their approval for commercial marketing, the FDA would have required the submission of extensive information characterizing the product to be administered to humans – including information regarding the monoclonal antibody in the form of the pharmaceutical composition to be used in clinical trials. (ALXN2029 at 12-13, 23, 31-33; ALXN2079 at 19.) As a POSA understood, the

purpose of this FDA review was to ensure that human subjects would not be put at undue risk when receiving the antibody product in experimental clinical trials. (*See* ALXN2032. at 46:20-48:2.)

B. Challenges to Formulation of Therapeutic Monoclonal Antibody Products as of March 15, 2007

39. A POSA would have understood that, for a monoclonal antibody to be made available for therapeutic use in humans, a "formulation" or "pharmaceutical composition" would need to be developed, which would include the monoclonal antibody itself as the active ingredient, as well as additional, "inactive" ingredients. (AMG1029 at 14; AMG1030 at 701; ALXN2080 at 163-64, 175-76, 178.) But, as of March 15, 2007, developing suitable pharmaceutical compositions of new, previously-unformulated monoclonal antibodies was not a straightforward task. In particular, a POSA would have understood that a suitable formulation for one antibody might not be suitable for another antibody – even if the two were closely related in sequence and structure. In fact, a POSA would understand that the approach to formulating a given antibody was to develop a formulation from scratch, not plug the antibody into formulations that were developed for other antibodies. (*See, e.g.*, AMG1029 at 5 ("[T]he behavior of antibodies [in pharmaceutical compositions] seems to vary, even though they have similar structures."); AMG1030 at 690 ("Each antibody seems to have a unique personality related to its requirements for stability. . . . [T]he interfacial surface of

each antibody drug is unique and thus requires specific formulation components to provide maximal stability and retention of activity.").)

40. In my 20-plus years of experience working in conjunction with pharmaceutical companies on the development of pharmaceutical formulations, I have personally seen on many occasions that an antibody that appeared to be promising from studies in the "discovery" phase of development could not move forward into clinical development because it was not capable of being made into a suitable pharmaceutical composition.

41. As discussed below, there were a variety of issues that a POSA would have needed to address in formulating a monoclonal antibody, with numerous options for addressing them. For example, a POSA would have needed to consider the intrinsic stability of the monoclonal antibody, and the effects of a formulation on its rates of chemical and physical degradation. (AMG1029 at 15-17; AMG1030 at 689-90; ALXN2080 at 163-64, 175-76, 178.) Formulation development – including the concentration of an antibody formulation – could be influenced by the desired route of administration (*e.g.*, intravenous or subcutaneous) and type of formulation (liquid vs. lyophilized), and, vice versa, the desired route of administration and chosen formulation type could be influenced by the outcome of studies during formulation development. (ALXN2079 at 2, 4 (Table 2), 10-12; *see also* ALXN2080 at 178; AMG1029 at 14-15; AMG1030 at 694-95.) As of March

15, 2007, monoclonal antibody formulation development was not a linear process, but instead involved significant empirical testing, and rounds of decisions made based on the results of formulation development studies.

42. Overall, a POSA as of March 15, 2007 would have understood that a primary goal of developing an antibody formulation was to achieve sufficient **stability** so that the product could be **stored and transported**, and thereafter, **safely and effectively** administered to human patients. As one major 2007 review cited by Dr. Balthasar explained, "The **major purpose** of formulating antibodies as therapeutic agents [was] to **control the rate of antibody degradation** to provide an acceptable shelf life for worldwide shipping and storage."[2] (AMG1029 at 14 (emphases added); *see also* ALXN2079 at 19 ("[T]he formulation should maintain the safety and efficacy profile of the protein drug during all the handling and uses specified on the label."); ALXN2080 at 178 ("In the development of a protein formulation, the most challenging task is the stabilization of a protein to achieve an acceptable shelf life.").)

43. In general, a POSA understood "stability" in the context of monoclonal antibody pharmaceutical compositions to refer to a variety of types of physical or chemical degradation, resulting in unwanted "degradants" or

[2] Unless otherwise noted, all emphases are added.

"degradation products." (*See* AMG1029 at 8-14; AMG1030 at 690-94; ALXN2080 at 137-45; *see also* ALXN2082 at 300-01.)

44. A POSA developing an antibody for therapeutic use would have been particularly concerned about the effects on patients resulting from administering an insufficiently stable formulation containing such degradation products. For example, a POSA understood that the degradation products may have reduced therapeutic activity relative to the therapeutic antibody itself. (AMG1029 at 14; AMG1030 at 690; ALXN2079 at 9; ALXN2080 at 137; *see also* ALXN2082 at 300-01.) A POSA would have also understood that administering an insufficiently stable formulation could result in safety risks, such as increased immunogenicity – which could lead to "neutralization" of the therapeutic antibody by the patient's immune system, as well as immune reactions against a patient's own endogenous proteins. (ALXN2083 at E503; ALXN2082 at 300-01; AMG1029 at 14; *see also* ALXN2081 at 897, 901; ALXN2080 at 137; ALXN2079 at 9.)

45. As of March 15, 2007, a POSA would have understood that multiple pathways could contribute to antibody physical and chemical degradation. For example, types of physical instability included denaturation (misfolding of the protein) and partial denaturation, which could be caused by temperature change, shear-stress, certain processing steps, or time; and aggregation, which can be impacted by antibody concentration, temperature, storage, shaking, viscosity, ionic

strength, pH, and lyophilization process parameters, amongst other factors. (AMG1029 at 8-9; AMG1030 at 689-90, 692-95; *see also* ALXN2080 at 137-40; ALXN2079 at 13 (Table 6).)

46. A POSA would have also been aware of various potential pathways for chemical instability of antibody formulations, including, for example, cross-linking (potentially resulting in chemical aggregation); deamidation, isomerization, and oxidation (resulting in changes to certain amino acids of the primary amino acid sequence); formation of acidic or basic species; C-terminal clipping (removal of certain lysine amino acids); fragmentation; and sugar adduct formation. (AMG1029 at 11-14; AMG1030 at 690-92; *see also* ALXN2080 at 140-145; ALXN2079 at 13 (Table 6).) Chemical instability was known to be influenced by factors such as storage, temperature, pH, and (for oxidation) light exposure. (AMG1029 at 11-14.) It was understood that, generally speaking, both physical and chemical instability tended to increase with increased temperature and storage time. (*See* AMG1029 at 8-14; ALXN2079 at 15-16.)

47. Aggregation in particular was a prevalent stability issue for antibody formulations. It was one of the more commonly experienced physical instability issues and could potentially limit the concentration of an antibody formulation. (AMG1029 at 8, 14-15; *see also* AMG1030 at 692-93; ALXN2080 at 137-140.) Antibody aggregates were generally known to have reduced activity and greater

potential to cause immune reactions due to the aggregates' altered conformation and interaction with epitopes. (AMG1029 at 9; ALXN2080 at 137; ALXN2079 at 9; *see also* ALXN2082 at E503; ALXN2081 at 901 (describing aggregation as a concern for immunogenicity of even fully human proteins).) Due to aggregates' potential to impact safety and efficacy, even low levels could be unacceptable for a pharmaceutical composition to be administered to human patients. (ALXN2079 at 9 ("[E]ven at levels of a few percent or less of the total protein population, non-native aggregates can cause adverse reactions in patients such as immune responses and even anaphylactic shock."); ALXN2080 at 137.)

48. A POSA would also have understood that development of liquid formulations was especially challenging. This was because liquid formulations were known to have more stability issues than lyophilized formulations, including concentration-dependent aggregation, physical instability due to shaking/shear-stress, and increased potential for chemical instability due to storage in water-based formulations, which could facilitate the chemical reactions known to cause antibody degradation. (AMG1029 at 14-17; AMG1030 at 694; ALXN2080 at 150, 152; ALXN2079 at 10.) Although liquid formulations were generally preferred because they were easier to administer and less expensive to manufacture, as of 2007 many commercial antibody products could not be stabilized as a liquid formulation. (AMG1029 at 2-4 (Table 1), 14; *see also* AMG1030 at 694;

ALXN2079 at 10-11 ("Because lyophilized products have less stability-related issues and have a much greater potential tolerance for room-temperature storage, many biopharmaceutical industries consider the lyophilized formulation as a default option.").) Lyophilized formulations were often used where stability issues prevented development of a liquid formulation. (ALXN2079 at 10.)

49. Although generally considered more stable than liquid formulations, a POSA would still have understood that lyophilized formulations were associated with their own set of potential instabilities and development challenges. (*See* ALXN2080 at 175 ("[F]reeze-dried solid protein formulation is generally more stable [than liquid formulation], although lyophilization often causes significant protein instability.").) For example, a POSA would have understood that design of a lyophilized formulation would require selection of an acceptable bulking agent and stabilizers to form a solid "cake," and that lyophilization came with a risk of aggregation and other degradation processes during lyophilization, reconstitution and storage. Such risk could be exacerbated depending on the moisture content. (AMG1029 at 18-20; AMG1030 at 694-95.)

50. A POSA would have been aware of antibody stability issues related to the concentration of antibody formulations. Sufficiently high antibody concentration was understood to be desirable for formulations to be administered by subcutaneous injection, to achieve low enough injection volume required for

patient administration. (AMG1029 at 14; AMG1030 at 688, 692.) However, in liquid formulations higher antibody concentration was generally thought to increase the risk of antibody aggregation by increasing the frequency of protein-protein interactions. (AMG1029 at 14; AMG1030 at 692; ALXN2080 at 152.)

51. Accordingly, a POSA as of March 15, 2007 would have understood that antibody formulation development would encompass significant empirical work to develop a formulation with sufficient stability for therapeutic use, and still might not succeed. (ALXN2029 at 23; ALXN2084 at 2; AMG1029 at 21; ALXN2080 at 175; ALXN2079 at 2, 4-5, 10.) A POSA would have generally understood that stability testing was to reflect the various "external conditions which can affect the [antibody] product's potency, purity and quality." (ALXN2084 at 2.) Stability testing typically would include, among other things, studies of the integrity of the antibody and its degradation under various conditions over time, to account for stability in storage and shipment. (ALXN2085 at 2; *see also* ALXN2079 at 5-7, 15-16.)

52. Typically, testing would be done early in the development process to assess an antibody's susceptibility for various forms of degradation, identify likely formulation challenges, and develop relevant analytical methods for assessing stability. (ALXN2079 at 5.) These tests would include accelerated stability studies, in which an antibody's stability was assessed under stress conditions to try

to predict instability that could develop over its shelf-life. (ALXN2079 at 5; ALXN2080 at 177; ALXN2084 at 7; ALXN2085 at 17; ALXN2029 at 23; *see also* AMG1029 at 17-18, 20.) Stress conditions could include exposing an antibody formulation to high temperature, mechanical stress such as agitation (shaking / stirring), light, multiple freeze/thaw cycles, oxidation, or exposure to denaturants. (ALXN2079 at 5-6; ALXN2080 at 177.)

53. A POSA would have known to examine various product characteristics to assess stability. These included biologic activity, rate of antibody degradation and identity of degradants, formation of aggregates / precipitation (antibody coming out of solution – typically due to formation of aggregates), solution color, pH, viscosity, and sterility. (ALXN2080 at 177; ALXN2079 at 7; *see also* ALXN2084 at 5-6; ALXN2029 at 23.) Analytical methods used to assess these characteristics could have included various forms of chromatography (*e.g.*, HPLC), electrophoresis (*e.g.*, SDS-PAGE), spectroscopy, thermal analysis, and light scattering / turbidity. (ALXN2079 at 7.) It was understood that a variety of analytical methods were necessary to accurately assess antibody stability, due to the complex nature and multiple pathways for antibody degradation. (ALXN2079 at 6; ALXN2080 at 178 ("[N]o single technique can satisfactorily provide sufficient information about a protein. Thus, a combination of analytical methods needs to be used to characterize a protein and to monitor protein instability.").)

54. As development progressed, additional studies would need to be performed to further progress development of candidate formulations, and to assess the impact of transportation and handling and process scale-up on antibody stability. (ALXN2079 at 13-16.) Further, a POSA would have understood that real-time storage studies, lasting months to years, would need to be performed to assess the actual stability of an antibody over the course of its shelf-life, as accelerated studies were known to be not entirely predictive. (ALXN2079 at 16; ALXN2080 at 178; ALXN2084 at 2; ALXN2085 at 4, 10; ALXN2029 at 23.)

VII. THE '880 PATENT

55. In forming my opinions in this case, I have reviewed and considered the '880 patent, including its specification and claims. I understand from counsel that the '880 patent was not available to a POSA prior to March 15, 2007, and that analysis of whether the claims of the '880 patent would have been obvious to a POSA prior to March 15, 2007 must be done from the perspective of a POSA without hindsight knowledge of the '880 patent or its claims.

56. Claim 1-3 of the '880 patent read as follows:

> **1.** A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution, wherein the antibody comprises

a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

2. A pharmaceutical composition comprising an anti-C5 antibody, wherein the anti-C5 antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

3. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition is a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution.

57. The specification of the '880 patent includes a description of a randomized, multi-center, double-blind, placebo controlled clinical trial ("TRIUMPH") assessing the efficacy of eculizumab to treat paroxysmal nocturnal hemoglobinuria ("PNH"). (AMG1001 at 19:41-28:31.) Eculizumab, or placebo, was administered by intravenous infusion, at 600 mg every 7 days for 4 doses, followed by 900 mg (or placebo) by IV infusion 7 days later, followed by a maintenance dose of 900 mg (or placebo) by IV infusion every 14 days, for a total of 26 weeks of treatment. (AMG1001 at 20:36-48.) The results of the study showed that eculizumab was a "safe and effective therapy for patients with the rare disorder PNH." (AMG1001 at 28:14-17.) Patients in the study experienced an

improvement in PNH symptoms, including reduced intravascular hemolysis, stabilized hemoglobin levels, reduced fatigue, and a reduction in the need for blood transfusions such that most patients became transfusion independent, and an improved quality of life. (AMG1001 at 28:18-31.)

58. The '880 patent identifies "eculizumab" as an antibody comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. (AMG1001 at 30:14-30, 30:38-47.)

59. The '880 patent describes the invention as including "a method of treating a patient suffering from [PNH] by administering a pharmaceutical composition comprising an antibody that binds C5," and, more specifically, eculizumab. (AMG1001 at 3:13-19.) The '880 patent further states that the antibody can be administered in a "300 mg single-use dosage form, comprising 30 ml of a 10 mg/ml sterile, preservative free solution." (AMG1001 at 4:15-18, 4:22-24.)

60. I understand that there is a dispute between Amgen and Alexion as to, among other things, (1) whether an antibody comprising the heavy and light chain sequences SEQ ID NO: 2 and 4 was disclosed by, or obvious in view of, the prior art available prior to March 15, 2007, and (2) whether, prior to March 15, 2007, a POSA would have known that "eculizumab" was an antibody comprising the heavy and light chain sequences SEQ ID NO: 2 and 4. For purposes of this

proceeding, I am not offering an opinion on what was known prior to March 15, 2007 regarding the claimed amino acid sequence, except to say that in my review of Bell (AMG1005) and Wang (AMG1028), I did not see **any** disclosure of the specific amino acid sequence recited in claims 1-3 of the '880 patent, or **any** disclosure that "eculizumab" had the specific amino acid sequence recited in claims 1-3 of the '880 patent.

61. I further understand that there is a dispute between Amgen and Alexion as to whether it was known prior to March 15, 2007 that "eculizumab" had a hybrid IgG2/IgG4 constant region structure. I understand that it is known **today** that, eculizumab, as used the commercial product SOLIRIS®, contains a non-naturally occurring, engineered heavy chain constant region including a specific combination of sequences from human "IgG2" and human "IgG4" constant regions. I further understand it is known **today** that the heavy chain consisting of SEQ ID NO: 2 in claims 1-3 of the '880 patent reflects the sequence of the non-naturally occurring heavy chain constant region in SOLIRIS® (eculizumab). For purposes of this proceeding, I am not offering an opinion on what was known prior to March 15, 2007 regarding the identity of the constant region or isotype of "eculizumab." It is my opinion, however, that prior to March 15, 2007, there were no FDA-approved or commercially marketed products in the United States containing any non-naturally occurring, engineered "hybrid" isotypes, let alone the

specific hybrid isotype of SOLIRIS® reflected in SEQ ID NO: 2 of the '880 patent. (*See* AMG1029 at 2-4 (Table 1).)

VIII. BELL (AMG1005) AND WANG (AMG1028) DID NOT MOTIVATE A POSA TO MAKE THE CLAIMED COMPOSITIONS OF THE '880 PATENT, OR GIVE A POSA A REASONABLE EXPECTATION OF SUCCESS IN DOING SO

62. In my opinion, nothing in the Bell (AMG1005) and Wang (AMG1028) documents, alone or in any combination, would have motivated a POSA as of March 15, 2007 to make the pharmaceutical compositions recited in claims 1-3 of the '880 patent, or would have given a POSA a reasonable expectation of success in doing so.

63. I have reviewed and considered Dr. Balthasar's arguments regarding the teachings of Bell (AMG1005) and Wang (AMG1028) as they relate to the claims of the '880 patent, and I disagree. In my opinion, Dr. Balthasar uses his hindsight knowledge of the claimed inventions of the '880 patent to make assumptions about Bell and Wang that are not supported by the text available to a POSA prior to March 15, 2007, and misconstrues how a POSA without hindsight would have understood the teachings of those documents.

64. While both Bell (AMG1005) and Wang (AMG1028) refer to the antibody "eculizumab," I have seen nothing in either document that discloses the complete amino acid sequence for "eculizumab," or in any way associates "eculizumab" with an antibody comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4, the sequence that is recited in the claims of the '880 patent. I also did not see anything in my review of Bell or Wang that identified "eculizumab" as having a hybrid IgG2/IgG4 isotype. I understand Dr. Balthasar agrees with me that Bell and Wang (AMG1028) did not disclose the specific amino acid sequence of the '880 patent claims. (*See, e.g.*, AMG1002 ¶ 127 (Bell and Wang did not teach "the claimed anti-C5 antibody sequence"); AMG1002 ¶¶ 140, 155, 159 (Bell and Wang did not teach an antibody that "comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4"); ALXN2032 at 146:15-25, 256:15-257:20.)

65. Despite his admissions regarding the limits of Bell and Wang, Dr. Balthasar contends a POSA would have connected the "eculizumab" antibody of Bell and Wang with the '880 patent's specific claimed amino acid sequence, based on information he combines from other documents outside of Bell and Wang. (*See, e.g.*, AMG1002 ¶ 140 ("Bowdish and Evans together"); AMG1002 ¶¶ 155, 159 (citing "Evans and Mueller"). I understand that Alexion disagrees that Dr. Balthasar's cited combinations of documents disclosed the claimed amino acid

sequence of the '880 patent, or that a POSA as of March 15, 2007 would have known the "eculizumab" antibody of the Bell (AMG1005) or Wang (AMG1028) to have the claimed amino acid sequence of the '880 patent.

66. Regardless of whether Alexion or Amgen is correct on what a POSA as of March 15, 2007 knew, if anything, about the specific amino acid sequence of the "eculizumab" antibody referenced in Bell (AMG1005) and Wang (AMG1028), it is my opinion that a POSA would **not** have been motivated by Bell and Wang to make the claimed pharmaceutical compositions of the '880 patent, and would not have reasonably expected success in doing so. Specifically:

- **If Bell's and Wang's "eculizumab" was *not* known to be an antibody with the claimed sequence of the '880 patent:** A POSA as of March 15, 2007 would not have been motivated by Bell and Wang to make the claimed pharmaceutical compositions of the '880 patent, and would not have reasonably expected to succeed in doing so, because, among other things, a POSA would have had no evidence that an antibody with the sequence claimed in the '880 patent had **ever** been successfully formulated for therapeutic use. In view of the challenges regarding therapeutic antibody formulation (*see* Section VI.B above), a POSA would not have reasonably assumed that any particular new, previously-unformulated antibody could be made into a pharmaceutical composition suitable for human therapeutic use, let alone the specific compositions recited in claims 1 and 3 of the '880 patent. And even if, hypothetically, a POSA had understood generally that eculizumab had a hybrid IgG2/IgG4 isotype, but did not know that "eculizumab" corresponded to the specific claimed amino acid sequence, a POSA would not have been motivated by Bell and Wang to create the claimed compositions with a reasonable expectation of success. In particular, there were no commercial antibodies with a non-natural IgG2/IgG4 isotype available as of March 15, 2007, and Bell and Wang do not provide specific guidance

Samsung Bioepis Exhibit No. 1002
Page 11680

as to a suitable formulation for an antibody with an IgG2/IgG4 isotype. Even if there were, knowledge of a suitable formulation for a given antibody with an IgG2/IgG4 isotype would not motivate a POSA to formulate another antibody with an IgG2/IgG4 isotype, nor would it give the POSA a reasonable expectation of success.

- **Even under Amgen's theory that Bell's and Wang's "eculizumab" was known to be an antibody with the claimed sequence of the '880 patent:** It is my opinion that, in this scenario, a POSA as of March 15, 2007 would have not been motivated by Bell and Wang to make the specific claimed pharmaceutical compositions of at least claims 1 and 3 of the '880 patent (*i.e.*, "a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution"), and would not have reasonably expected success in doing so. Nothing in Bell (AMG1005) provided a POSA with any specific guidance towards the pharmaceutical compositions of claims 1 and 3. And Wang (AMG1028) – which described various antibodies for inhalation administration with nebulizers – neither disclosed the specific pharmaceutical compositions of claims 1 and 3, nor would it have motivated a POSA to make those compositions, or provided a POSA with a reasonable expectation of success in doing so. Further, as stated above, Bell and Wang would not

have provided a POSA with motivation to create a formulation for an antibody with a non-natural, IgG2/IgG4 isotype, because there were no commercial antibodies at the time with this isotype, and Bell and Wang did not provide any guidance as to a suitable formulation for an antibody with an IgG2/IgG4 isotype. Even if they did, knowledge of a suitable formulation for a given antibody with an IgG2/IgG4 isotype would not motivate a POSA to formulate another antibody with an IgG2/IgG4 isotype, nor would it give the POSA a reasonable expectation of success.

A. A POSA Prior to March 15, 2007 Would Not Have Been Motivated to Make, or Reasonably Expected Success in Making, a Pharmaceutical Composition of an Unstudied Antibody Comprising SEQ ID NOs: 2 and 4

67. If it were the case that a POSA as of March 15, 2007 did not know that the "eculizumab" antibody described in Bell (AMG1005) and Wang (AMG1028) was the claimed antibody comprising SEQ ID NOs: 2 and 4 recited in the '880 patent, then in my opinion, a POSA would not have been motivated to make, and would not have reasonably expected to succeed in making, the pharmaceutical compositions recited in claims 1-3 of the '880 patent. In this scenario, neither Bell nor Wang would have taught a POSA that **any** pharmaceutical composition of an antibody comprising SEQ ID NOs: 2 and 4 had ever been created or even attempted. With no evidence that an antibody comprising SEQ ID NOs: 2 and 4 even **could** be formulated into a pharmaceutical

composition suitable for therapeutic use, and understanding the complexity of antibody formulation development as of March 15, 2007, a POSA would not have been motivated to make such a composition, or reasonably expected success in doing so.

68. With respect to motivation, Dr. Balthasar argues that a POSA would have combined the clinical trial reports, Hillmen (2004) and Hill (2005), with Bell and Wang because these references, according to Dr. Balthasar, all relate to "methods of treatment that 'employ . . . eculizumab as the antibody therapeutic." (AMG1002 ¶¶ 95, 110.) Dr. Balthasar also argues that a POSA would have combined the references in Grounds 5 and 6 based on a POSA's desire to create eculizumab compositions "to treat PNH patients." (*Id.* at ¶¶ 124, 156.) Further, Dr. Balthasar argues Wang taught that, at concentrations of 1 to 30 mg/mL, eculizumab could be formulated so that it would be "sufficiently stable to be used as a therapeutic." (*Id.* at ¶ 105; *see also id.* at ¶ 118 ("Wang disclosed that eculizumab could be stably formulated at a concentration between 1 and 30 mg/mL"), ¶ 138 (same).) While I agree with Dr. Balthasar that developing a formulation that would be sufficiently stable for therapeutic use was an important aspect of antibody formulation development, I disagree that the disclosures of Bell and Wang would have motivated a POSA to prepare a stable formulation of an antibody with the amino acid sequence claimed in the '880 patent – which is not

disclosed in Bell or Wang and which, under this first scenario, I assume would not have been understood by a POSA to correspond to "eculizumab." Moreover, I disagree with Dr. Balthasar that Bell and Wang, read alone or in combination, would have taught a POSA that "eculizumab" would be stable when formulated as in the claimed compositions.

69. As discussed above in Section VI.B, the pharmaceutical formulation development of a new, previously-unformulated monoclonal antibody required many experiments the results of which were unpredictable as of March 15, 2007. A POSA as of March 15, 2007 knew that, even for closely-related antibody sequences, the formulation that is suitable for one antibody could not be assumed to be suitable for another.[3] (*See* Section VI.B; AMG1029 at 5; AMG1030 at 690.) For that reason, a POSA having no information about whether an antibody comprising SEQ ID NOs: 2 and 4 had ever been attempted to be formulated into a

[3] For this reason, even assuming hypothetically that a POSA would have known that an antibody comprising SEQ ID NOs: 2 and 4 was related in sequence to the "eculizumab" antibody described in Bell (AMG1005) and Wang (AMG1028), a POSA would not have reasonably expected any formulation used for Bell and Wang's "eculizumab" to also work for antibody comprising SEQ ID NOs: 2 and 4.

pharmaceutical composition, or whether that antibody had ever been administered to humans to test its clinical effects, would not have reasonably expected that the antibody was even capable of being used in a suitable pharmaceutical formulation. Without significant empirical testing, a POSA would not have known whether an antibody comprising SEQ ID NOs: 2 and 4 could be formulated into a sufficiently stable product using known antibody formulation approaches, including those in Wang (AMG1029) and Daugherty (AMG1030), as of March 15, 2007. (*See* ALXN2029 at 23; ALXN2084 at 2; AMG1029 at 21; ALXN2080 at 175; ALXN2079 at 2, 4-5, 10.)

70. If, as Dr. Balthasar argues, a POSA had known that an antibody comprising SEQ ID NOs: 2 and 4 had a hybrid IgG2/IgG4 constant region (*e.g.*, AMG1002 ¶ 47), that further supports my opinion that a POSA would not have been motivated to make, and would not have reasonably expected to succeed in making, any pharmaceutical compositions of that antibody suitable for therapeutic use. As of March 15, 2007, there were no commercially marketed antibodies demonstrating that an antibody with a hybrid IgG2/IgG4 constant region was capable of pharmaceutical formulation.[4] (AMG1029 at 2-4 (Table 1); ALXN2032

[4] And hypothetically, even if a different IgG2/IgG4 isotype antibody had been previously formulated, it was still the case that a POSA could not assume from the

at 251:3-7.) Furthermore, nothing in Bell (AMG1005) or Wang (AMG1028) stated that an antibody with a hybrid IgG2/IgG4 constant region was capable of pharmaceutical formulation or had been used in any human clinical studies.[5]

71. A POSA would have been particularly concerned about whether a new, previously-unformulated and untested antibody comprising SEQ ID NOs: 2 and 4 could be formulated as a single-use dosage form in **solution**, as claims 1 and 3 of the '880 patent require. A POSA as of March 15, 2007 would have known

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formulation of one antibody construct to a particular concentration in liquid that a different antibody could be formulated to a given concentration, if at all, because even slightly different antibodies could have markedly different formulation properties. (*See* Section VI.B above.)

[5] Dr. Balthasar also asserts that Evans (AMG1007) "provided information regarding how to prepare pharmaceutical compositions comprising eculizumab." (AMG1002 ¶¶ 80, 91 (citing AMG1007, 18:30-43.) I have reviewed Evans (AMG1007), as well as Dr. Balthasar's deposition testimony regarding Evans, and it is my understanding that Evans does not disclose "eculizumab," an antibody with SEQ ID NOs: 2 and 4, or any other full-length humanized antibodies, and thus does not provide any information on pharmaceutical compositions of such antibodies. (ALXN2032 at 163:5-15, 163:25-164:19, 169:13-18, 199:15-17.)

that, even "[a]mong all the **commercial antibody products**," only "**about half** are stable enough to be formulated in a liquid form" (which a solution is). (AMG1029 at 14.) For a previously-unformulated and unstudied antibody, a POSA would have had an even lower expectation of success in making a solution formulation than what was known for the products that had already been commercially marketed.

72. I note that Dr. Balthasar is mistaken when he says that "each of the . . . monoclonal antibodies approved by the FDA were formulated in . . . solution." (AMG1002 ¶ 133 (citing AMG1056-1076).) Dr. Balthasar's "Appendix I" is misleading on this point as well – because while all the products he lists were injectables, many of them were formulated as single-unit dosage forms of **lyophilized powders** – a **solid** form, not a solution.[6] (AMG1029 at 2-4 (Table 1);

[6] While lyophilized (solid) formulations are eventually reconstituted into a solution just prior to administration by injection, a POSA as of March 15, 2007 would have understood that does not make the **pharmaceutical composition** itself (*i.e.*, the product of manufacture) a "solution." (*See* AMG1029 at 2-4 (Table 1) (containing entries for formulations described as "solution[s]" and, separately, entries for formulations with a specific concentration "on reconstitution"), 14; AMG1030 at 694; ALXN2079 at 10-11.) As a POSA would have known, there

AMG1059 at 1; AMG1061 at 1; AMG1066 at 1; AMG1067 at 1; 1070 at 1; 1071 at 1; AMG1074 at 1.) For example, while the product Remicade® (infliximab) was administered by intravenous infusion, its pharmaceutical composition was "a sterile, white, **lyophilized powder**." (AMG1067 at 1.) As discussed above, lyophilization was a formulation approach that generally leads to a more stable formulation than a solution formulation. (*See* Section VI.B above.)

73. Accordingly, if a POSA as of March 15, 2007 had no information regarding the pharmaceutical formulation or clinical use of an antibody comprising SEQ ID NOs: 2 and 4, it is my opinion that a POSA would not have been motivated to make the pharmaceutical compositions recited in claims 1-3 of the '880 patent, and would not have reasonably expected to succeed in doing so.

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were potential advantages to making a liquid (solution) composition for injection versus a lyophilized composition – but obtaining the benefit of these potential advantages was dependent on the unpredictable question of whether a suitable solution formulation was even possible. (AMG1029 at 14; AMG1030 at 694; ALXN2079 at 10-11.)

B. Bell (AMG1005) and Wang (AMG1028) Would Not Have Motivated a POSA Prior to March 15, 2007 to Make the Pharmaceutical Compositions of '880 Patent Claims 1 and 3, or Given a POSA a Reasonable Expectation of Success in Doing So

74. Assuming, hypothetically, that a POSA prior to March 15, 2007 would have identified the "eculizumab" antibody of Bell (AMG1005) and Wang (AMG1028) as an antibody comprising SEQ ID NOs: 2 and 4 of the '880 patent,[7] it is my opinion that a POSA prior to that date would not have been motivated by Bell and Wang to make a "sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml [anti-C5] antibody solution" of the antibody comprising SEQ ID NOs: 2 and 4, as recited in claims 1 and 3 of the '880 patent, and that a POSA prior to that date would not have reasonably expected to succeed in doing so. Nothing in Bell or Wang, alone or in any combination, disclosed a pharmaceutical composition of "eculizumab" featuring a 300 mg single-use dosage form a 10 mg/ml solution of "eculizumab," or would have motivated or given a

[7] As noted throughout my Declaration, I have not seen any evidence in my review of Bell (AMG1005) or Wang (AMG1028) that a POSA prior to March 15, 2007 would have known the specific, complete amino acid sequence of the "eculizumab" antibody they disclose, or that a POSA would have connected an antibody comprising SEQ ID NOs: 2 and 4 to the "eculizumab" antibody of Bell and Wang.

POSA a reasonable expectation of success in making such a pharmaceutical composition of "eculizumab."

75. First, nothing in Bell (AMG1005), Wang (AMG1028) or Dr. Balthasar's other cited documents would have motivated a POSA prior to March 15, 2007 to specifically make a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single-use dosage form. Neither Bell nor Wang disclosed such a pharmaceutical composition, or would have given a POSA any confidence that a 10 mg/ml concentration of "eculizumab" in solution would have been suitable for a pharmaceutical composition as claimed in the '880 patent.

76. Bell (AMG1005) discloses nothing about a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" (or any other concentration of "eculizumab") in a single use dosage form. Bell described, among other things, the results of an 11-patient, 12 week clinical trial (and 52-week and 2-year extensions of that clinical trial), where "eculizumab" was administered to PNH patients by "intravenous infusion," in 600 mg weekly doses for four weeks, followed by 900 mg for all successive doses, and was shown to alleviate their symptoms. (AMG1005 ¶¶ [0081]-[0096].) A POSA reading Bell would have understood that "eculizumab" could in fact be formulated as some kind of pharmaceutical composition suitable for therapeutic use (including for use in treating patients with PNH). But a POSA would **not** have known from Bell any of

the details regarding that pharmaceutical composition, including, for example, whether the composition was in solution or was a solid, lyophilized composition; and if the composition was in solution, what was the specific **concentration** of "eculizumab" in that solution.

77. Dr. Balthasar's suggestion that Bell provided information for "formulating eculizumab" or "prepar[ing] pharmaceutical compositions comprising eculizumab" is thus misleading. (*E.g.*, AMG1002 ¶¶ 80, 91 (citing AMG1005 ¶ [0062]); AMG1002 ¶ 130 (citing AMG1005 ¶¶ [0060], [0062]).) A POSA prior to March 15, 2007 would have seen that paragraphs [0060] and [0062] of Bell were very general statements discussing, for example, all conceivable routes of administration (whether feasible or not), and reference to a general reference book for the concept of "[f]ormulations suitable for injection." Nothing in Bell suggested specifically making a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single use dosage form, or would have given a POSA a reasonable expectation that such a composition would have been suitable as a pharmaceutical formulation, for the treatment of patients with PNH or otherwise.

78. Further, even if Bell were combined with the information in Wang (AMG1028), a POSA prior to March 15, 2007 would not have envisioned or been motivated to make a pharmaceutical composition containing a 10 mg/ml solution

of "eculizumab" in a single use dosage form, and would not have reasonably expected success in making or using such a composition.

79. First, I disagree with Dr. Balthasar's premise that a POSA prior to March 15, 2007 would have had any motivation to combine Bell (AMG1005) with Wang (AMG1028). (AMG1002 ¶ 149.) While Bell described clinical studies showing that "eculizumab" safely and effectively treated **PNH** when administered by **intravenous infusion** (AMG1005 ¶ [0082]),[8] Wang (AMG1028) had an entirely different focus – "treating **pulmonary diseases**" (*i.e.*, respiratory diseases such as asthma) by "**nebulization**" (dispersing into small particles for inhalation) of various different monoclonal antibodies (AMG1028 at, e.g., ¶¶ [0004]-[0009], [0058]-[0066]; ALXN2032 at 256:24-258:9.) A POSA would have had no reason to disregard the clinically proven intravenous route for "eculizumab" in treating PNH – a systemic blood condition – and instead use Wang's "nebulization" technology intended to deliver drugs locally to the respiratory tract. (*See* AMG1004 at 553-54; AMG1012 at 1234-35; AMG1047 at 2559-60; ALXN2032 at 258:10-16.)

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[8] I understand that the other reported clinical trials of "eculizumab" in treating PNH prior to March 15, 2007 likewise administered the drug by intravenous infusion. (AMG1004 at 554; AMG1012 at 1235; AMG1047 at 2560.)

80. As Dr. Balthasar concedes, nothing in Wang (AMG1028) disclosed a 10 mg/ml composition of "eculizumab" for intravenous infusion. (ALXN2032 at 260:5-13.) And even if a POSA were to have combined Bell with Wang, it is my opinion that nothing in that combination disclosed a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single use dosage form.

81. While I agree with Dr. Balthasar that ensuring adequate stability is an important part of formulation development, contrary to Dr. Balthasar's assertions, nothing in Wang "disclose[d] that eculizumab is stable when formulated at a range of concentrations between 1 mg/ml and 30 mg/ml." (*E.g.*, AMG1002 ¶ 17.) First, the range of "1 to 30 mg/ml" that Dr. Balthasar cites from paragraph [0170] and Figure 10 of Wang (AMG1028) is **not a range for eculizumab**, but refers to a broad range that can include different possible antibodies, including at least the anti-mouse C5 antibody "BB5.1." (*See* AMG1028 ¶ [0170], Figure 10; *see also id.* at ¶ [0067] (describing "an antibody of the present application" as including antibodies specific to various targets, full-length antibodies and fragments, amongst others).) Neither paragraph [0170] nor Figure 10 use the term "eculizumab"; instead, paragraph [0170] refers to "examples for nebulization of **an antibody**," and Figure 10 provides two "Example" formulations with no specific

antibody identified.[9] (*Id.* at ¶ [0170], Figure 10.) While Wang (AMG1028) contains some examples of a **30 mg/ml solution** of "eculizumab" (which, as explained below, was **not** shown to be stable), there is simply nothing in Wang disclosing a 10 mg/ml solution composition of "eculizumab," for nebulization or any other use.

82. Nor does anything in Wang (AMG1028) state that "eculizumab could be stably formulated at a concentration between 1 and 30 mg/ml," as Dr. Balthasar further asserts. (*E.g.*, AMG1002 ¶ 105 (citing AMG1028 at Fig. 10 and ¶¶ [0170]-[0172]).) Rather, all that Wang showed with respect to "eculizumab" was that a 30 mg/ml solution of "eculizumab" could be "effectively and efficiently nebulized" by a nebulizer. (AMG1028 at Fig. 10 and ¶¶ [0170]-[0172].) Nothing in Wang provided any of the standard data that a POSA as March 15, 2007 would have expected to see in establishing the stability of an antibody formulation, including, for example, data **over time** and under various **storage conditions** to establish that the composition is sufficiently stable to be stored for a reasonable time prior to

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[9] In Formulation 1 in Figure 10, only a generic "mAb" is listed with no names or indication of any specific mAb, and certainly not "eculizumab"; and in Formulation 2, there is no monoclonal antibody listed, not even a generic one. (AMG1028, Fig. 10.)

human administration. (ALXN2085 at 2; ALXN2084 at 2, 5-6; ALXN2029 at 23; ALXN2080 at 177-78; ALXN2079 at 6-7, 15-16.)

83. For example, paragraph [0170] and Figure 10 of Wang, which Dr. Balthasar cites for the range of "1-30 mg/ml," does not state anything about the stability of eculizumab formulations within that range. Paragraph [0170] merely says that "[e]xamples of formulations suitable for nebulization of an antibody are shown in FIG. 10." Furthermore, paragraph [0170] mentions "BB5.1," but not "eculizumab." (AMG1028 ¶ [0170]; *see also* AMG1028 ¶ [0025] ("FIG. 10 shows exemplary formulations suitable for nebulization of an antibody.") Figure 10 of Wang, in turn, lists a "Formulation 1," with 1-30 mg/ml of an unspecified antibody, and a "Formulation 2," with 40-200 mg/ml of an unspecified antibody. (AMG1028, Fig. 10.) Nothing in these statements would have indicated to a POSA that **eculizumab** "could be stably formulated at a concentration between 1 and 30 mg/ml," let alone in a 10 mg/ml solution specifically.

84. The **only** statement in Wang (AMG1028) actually mentioning "stability" states: "The antibody may be stable in a formulation at a concentration ranging from 1 mg/ml to 200 mg/ml." (AMG1028 ¶ [0067].) First, in the context of this statement, a POSA would have understood that "[t]he antibody" refers to a wide variety of possible antibodies, fragments and other compounds "specific to C5" (including even different antibodies for different epitopes). (AMG1028 ¶ [0067].) Second, in light of the use of the term "may," a POSA would not have viewed this isolated statement as teaching that every possible anti-C5 antibody and fragment within its scope would necessarily be stable at all concentrations within the broad recited range. Accordingly, a POSA would have understood that this statement was, at best, hypothetical, with no specific consideration of "eculizumab" or any other antibody, and that it did not reflect the results of any actual stability testing performed on any specific antibody at any specific concentration – including a 10 mg/ml solution of "eculizumab." With no understanding that Wang provided any specific guidance for a stable "eculizumab" formulation, a POSA would not have looked to Wang to make such a composition, as Dr. Balthasar contends.

85. Figures 11-15 referenced in paragraphs [0170]-[0172] of Wang (AMG1028) also provide no evidence that, as Dr. Balthasar contends, "eculizumab could be stably formulated" in a 10 mg/ml solution composition. (AMG1002 ¶ 105.) Figure 11, described further in Wang paragraph [0170], is a test of a **different** antibody ("BB5.1") in a mouse respiratory model.[10] (AMG1028 at Fig. 11, ¶ [0170].) Figure 12, using 30 mg/ml eculizumab in "Formulation 1," likewise did not test for stability pertinent to developing a single-use dosage form of a solution for intravenous infusion (*e.g.*, degradation over time and under potential storage conditions). Instead Figures 12 and 13 rather looked at whether the composition could be "effectively and efficiently delivered through a nebulizer" – using *in vitro* tests designed to measure the size of particles being delivered by the nebulizer and the efficiency of nebulizer delivery. (AMG1028 at Fig. 12-13, ¶¶ [0171]-[0172]; ALXN2032 at 259:6-9.) Figures 12 and 13, referenced in paragraphs [00171-0172], only disclose data related directly to the testing of the nebulization process, do not include any stability information, and neither in Figure 13 nor in the description of it in [0172] and [0028] is the specific tested concentration of "eculizumab" disclosed.

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[10] I note that Wang (AMG1028) does not disclose the administration of any "eculizumab" composition even to animals, let alone to humans.

86. I also disagree with Dr. Balthasar that Figures 14 and 15 of Wang (AMG1028) "indicate[] that eculizumab is sufficiently stable to be used as a therapeutic when formulated at a concentration of 1 to 30 mg/ml." (AMG1002 ¶ 105.) Figures 14 and 15 of Wang only studied one type of stress very specific to formulations for use in nebulization: "the integrity of the nebulized antibody through various sizes of the spray mouth piece." (AMG1028 ¶ [0173].) Further, there is nothing in Wang indicating exactly what concentration of eculizumab was used in the experiments reported in Figs. 14 and 15, just identifying it as "[e]culizumab in a suitable formulation." (AMG1028 ¶ [0173].) Figures 14 and 15 do not report the stability of their undefined "suitable formulation" over time, or under any stresses or conditions that a POSA would have understood to be pertinent to assessing the stability of a single use dosage form containing a monoclonal antibody solution.

87. Without suitable information disclosed in Wang (AMG1028) or elsewhere regarding the stability of a single use dosage form containing 10 mg/ml eculizumab formulated in solution, a POSA would not have reasonably expected success with the pharmaceutical compositions recited in claims 1 and 3 of the '880 patents. As discussed above in Section VI.B, an insufficiently stable antibody formulation could lack efficacy and result in serious safety issues. A POSA prior to March 15, 2007 would not have had a reasonable expectation of success in

making the claimed pharmaceutical compositions of claims 1 and 3 the '880 patent without evidence that a 10 mg/ml eculizumab solution composition was suitably stable –particularly with respect to Claim 1 requiring "[a] pharmaceutical composition for use in treating a patient afflicted with [PNH]." (*See* Section VI.B above.)

88. A POSA prior to March 15, 2007 also could not have reasonably predicted from any of the commercialized products as of that date that a single-use dosage form containing a 10 mg/ml solution of "eculizumab" could be used in a suitable pharmaceutical composition. (*See* AMG1029 at 5 (antibody formulation development not straightforward due to antibodies' variable behavior, despite similar structures); AMG1030 at 690 (each antibody presents unique requirements for stability).) Dr. Balthasar is mistaken that 5 out of 23 commercially marketed antibodies as of March 15, 2007 were 10 mg/ml antibody solutions (AMG1002 ¶ 106), because one of the five products that he identifies was not even a solution composition (Remicade®). (AMG1002 ¶ 106, Appendix I; AMG1029 at 2-4 (Table 1); AMG1067 at 1.) And even counting Remicade®, only **one** of the 23 commercialized antibodies as of March 15, 2007 was a **full-length humanized**

antibody formulated as a 10 mg/ml solution (Campath®)[11] – and that product had an IgG1 isotype, not the "hybrid" isotype that Dr. Balthasar attributes to "eculizumab." (AMG1002 ¶ 106, Appendix I; AMG1029 at 2-4 (Table 1); AMG1058 at 13; AMG1063 at 4; AMG1067 at 1; AMG1069 at 1; AMG1073 at 1.) Further, a POSA would have seen that many commercialized full-length humanized antibodies appeared unsuitable for solution compositions, and instead were produced as solid, lyophilized compositions. (AMG1029 at 2-4 (Table 1), 14; AMG1056 at 1; AMG1071 at 1; AMG1074 at 1; AMG1061 at 1.) Having said all of that, even if were the case that 10 mg/ml were a common concentration for antibody formulations, that would have given a POSA no indication of whether or not a particular antibody (*e.g.,* eculizumab) could be formulated at 10 mg/ml without applying hindsight reasoning. (*See* VI.B above.)

89. I also disagree with Dr. Balthasar that it would have been obvious in view of Bell (AMG1005) to formulate "eculizumab" as a 300 mg single-use dosage form. (*E.g.*, AMG1002 ¶ 99.) Dr. Balthasar asserts, with no support, that a POSA would have necessarily been motivated to make a 300 mg single-use dosage form to achieve the 600 and 900 mg doses described in Bell, rather than make 600

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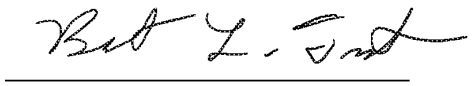
[11] The other products were a mouse Fab (Verluma®), mouse/human chimeric antibodies (Rituxan®, Remicade®), and a humanized IgG1 fragment (Lucentis®).

mg and 900 mg single use dosage forms, asserting that it would have been "the simplest, most efficient, and most convenient way." (AMG1002 ¶ 102.) I disagree. For example, it would be beneficial for ease and accuracy of administration for providers to use a single unit for each administration, rather than to use two or three. It is quite common for pharmaceutical products, including monoclonal antibody products, to be available in different dosage amounts, for the convenience of patients and health care providers. Dr. Balthasar's own references provide information on multiple antibody products that are available in difference doses. For example, bevacizumab was supplied in both 100 mg and 400 mg doses (AMG 1056 at 2, 25); tositumomab was supplied in both 35 mg and 225 mg doses, and a given carton contains two 225 mg vials and one 35 mg vial (AMG 1057 at 2, 3); and rituximab was supplied in both 100 mg and 500 mg doses (AMG 1069 at 1, 2).

Samsung Bioepis Exhibit No. 1002
Page 11701

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that I made these statements with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: November 22, 2019



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Appendix A

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Director: Michele Parrinello

Teaching:

10.01 Ethics for Engineers, 10.02 Foundations of Principled Entrepreneurship for Engineers , 10.213: Undergraduate Thermodynamics, 10.40: Graduate Thermodynamics, 10.65: Chemical Reactor Engineering, 10.541: Kinetics of Biological and Chemical Systems, 10.37: Chemical Kinetics and Reactor Design, 10.27: Process Engineering Laboratory, 10.675: Molecular Computational Methods in Chemical Engineering, 10.491: Chemical Engineering Design Module, 10A16: Freshman Advising Seminar, 10.04J Philosophical History of Energy,

Samsung Bioepis Exhibit No. 1002
Page 11704

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Massachusetts Institute of Technology
M.S. in Chemical Engineering Practice, 1990

Massachusetts Institute of Technology
B.S. in Chemical Engineering, 1990

Awards and Honors:

The Medicine Maker "Power List", 2019
ISCMP Co-Chair, 2018
The Medicine Maker "Power List", 2017
ISCMP Co-Chair, 2016
The Medicine Maker "Power List", 2016
AIChE Division 15 (FPBE) Plenary Speaking Award, 2015
Armenian Academy of Engineering, Foreign Member, elected 2015
The Medicine Maker "Power List", 2015
AIChE Excellence in Process Development Research Award, 2014
ISCMP Co-Chair, 2014
ISCMP Downstream Pharmaceutical Panel Chair, 2014
CCR Research Collaboration Award, 2014
Manufacturing Technology Runner-up for the Wall Street Journal Technology Innovation Award, 2012
Impact Award from the Computational Molecular Science and Engineering Forum of the AIChE (CoMSEF), 2011
ACS Plenary Lecture, 2011
AIChE Area 1A Program Chair, 2006
National Academy of Engineering participant in "Frontiers in Engineering," 2001
Henry L. and Grace Doherty Professorship, 2001 – 2003
Ford Motor Company Young Investigator Award, 2001
NSF CAREER Award, 2000 – 2004
Joseph R. Mares Junior Faculty Chair, 1998 – 2001
Max-Planck Institute Fellowship, 1996 – 1997
NSF Graduate Fellowship, 1991 – 1994

Committees/Memberships:

Samsung Bioepis Exhibit No. 1002
Page 11705

MIT Advisory Board for Social and Ethical Responsibilities of Computing (SERC), 2019-2020
MIT Schwarzman College of Computing Committee on Social Implications, 2019
MIT Task Force on Open Access, 2017 – 2019
Task Force on Open Access, Contracts subteam, 2017-2019
United States Pharmacopeia Expert Panel: Quality Standards for Pharmaceutical Continuous Manufacturing, 2016 – present
Molecular Systems Design & Engineering (MSDE), Royal Society of Chemistry Journal, Editorial Board Member, 2016 – present
FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, Consultant, 2015 – 2018
MIT Chemical Engineering Department Head Search Advisory Committee, 2015
FDA Coordination Group at MIT, 2014 – 2016
MIT Committee on Intellectual Property, 2011 – 2016
MIT Committee on the Undergraduate Program, 2006 – present
MIT Faculty Search Committee, 2006 – present
MIT Practice School Steering Committee, 2004 – 2015
ISPE Subcommittee on Pharmaceutical Manufacturing, 2010 – 2011
ISPE Subcommittee on Continuous Production, 2008
MIT Graduate Committee, 2006 – 2009
DuPont-MIT Advisory Committee, 2005 – 2007
Hottel Lecture Committee, 2004 – 2007
SMA Annual Report Committee, 2003 – 2012
Department Computer Committee, 2002 – 2007

Conferences Organization:

Co-Chair, International Symposium on Continuous Manufacturing, October 2018
Co-Chair, International Symposium on Continuous Manufacturing, September 2016
Chair, MIT Mastery of Nature Conference, May 2016
Organizing Committee, AIChE/FDA P2DM Workshop on Continuous Manufacturing, March 2016
Co-Chair, International Symposium on Continuous Manufacturing, May 2014

Scientific Publications:

203. Jensen, K., Xiang, A., Fitch, H., Alden, E., Myerson, A.S., and Trout, B.L., "Water-soluble Placebo Polymer Thin Films for Continuous Manufacturing of Tablets," *J. Appl. Polym. Sci., submitted.*

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Samsung Bioepis Exhibit No. 1002
Page 11706

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Samsung Bioepis Exhibit No. 1002
Page 11707

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13. "Plasticity Induced Bonding," U.S. Patent No.: 10,213,**960**, Date of Patent: Feb. 26, 2019, PCT/US2015/031666, International Filing Date: May 20, 2015.

12. "Methods and Systems for Manufacturing a Tablet." U.S. Patent No.: 10,053,798, Date of Patent: Aug. 21, 2018, Filed: Apr. 30, 2015.

11. "Layer Processing for Pharmaceuticals." U.S. Patent No.: 9,205,089, Date of Patent: Dec. 8, 2015, Filed Apr. 27, 2012.

10. "Compositions, Methods, and Systems Relating to Controlled Crystallization and/or Nucleation of Molecular Species." U.S. Patent No.: 9,138,659, Date of Patent: Sept. 22, 2015, Filed: Aug. 23, 2011.

9. "Immunoglobulins with Reduced Aggregation.", U.S. Patent No.: 9,676,841, Date of Patent: Jun. 13, 2017, PCT/US2009/047948, International Filing Date: June 19, 2009.

Samsung Bioepis Exhibit No. 1002
Page 11726

8. "Immunoglobulins with Reduced Aggregation.", U.S. Patent No.: 8,747,848, Date of Patent: Jun. 10, 2014, PCT/US2009/047948, International Filing Date: June 19, 2009.

7. "HER2 and VEGF-A-binding Proteins with Enhanced Stability." U.S. Patent No.: 9,777,067, Date of Patent: Oct. 3, 2017, PCT/US2013/062108, International Filing Date: Sept. 27, 2013

6. "Methods to Identify Amino Acid Residues Involved in Macromolecular Binding and Uses Therefor." U.S Patent No.: 10,431,325, Date of Patent: Oct. 1, 2019, PCT/US2013/053499, International Filing Date: Aug. 2, 2013.

5. "Methods and Systems Relating to the Selection of Substrates Comprising Crystalline Templates for the Controlled Crystallization of Molecular Species," U.S. Patent No.: 9,822,467, Date of Patent: Nov. 21, 2017, Filing Date: Nov. 15, 2012.

4. "Dendrimer-Based Excipients for the Attenuation of Protein Aggregation," U.S. Patent No.: 9,410,142, Date of Patent: Aug. 9, 2016, PCT/US2011/060400, International Filing Date: Nov. 11, 2011.

3. "Methods for Identification of Sites for IgG Conjugation.", U.S. Patent No. 9,629,925, Date of Patent: Apr. 25, 2017, PCT/US2010/037517, International Filing Date: June 4, 2010.

2. "Methods for Identification of Sites for IgG Conjugation.", U.S. Patent No. 8,834,885, Date of Patent: Sept. 16, 2014, PCT/US2010/037517, International Filing Date: June 4, 2010.

1. "Methods to Identify Macromolecule Binding and Aggregation Prone Regions in Proteins and Uses Therefor,", U.S. Patent No.: 9,922,164, Date of Patent: Mar. 20, 2018, PCT/US2009/047954, International Filing Date: June 19, 2009.

Invited Talks and Plenary Lectures:

160. November 20, 2019, "Machine Learning for Developability and Formulation Design," CDD for Biologics, Boston, MA.

159. October 30, 2019, "Ethical Issues in AI and Implications for the Law," Artificial Intelligence Driving Life Sciences, Cambridge, MA.

158. October 23, 2019, "Continuous Lyophilization of Unit Doses," Lyophilization USA, Boston, MA.

Samsung Bioepis Exhibit No. 1002
Page 11727

157. September 26, 2019, "Continuous Manufacturing: State of the Art, Challenges, and Future Prospect," IMA conference "Can't Stop the Future: Spotlight on Continuous Manufacturing," Bologna, Italy.

156. June 11, 2019, "Formulation Starts in Discovery," Gordon Research Conference on Preclinical Form and Formulation, Waterville Valley, NH.

155. May 14, 2019, "Developability and Machine Learning for Formulation Design," Biovia Community Day, Dusseldorf, Germany (via webcast).

154. February 27, 2019, "Living a Life of Leisure While Teaching Science in a Classical Secondary School Education," Great Heats Academies, Sandra Day O'Connor College of Law, Phoenix, Arizona.

153. December 1, 2018, "Truths About Quantum Mechanics," St. John's College, Santa Fe, NM.

152. November 7, 2018, "Product and Process Development Start in Discovery," Takeda Pharmaceutical Company, Cambridge, MA.

151. October 25, 2018, "Product and Process Development Start in Discovery," Biovia Community Day, Boston, MA.

150. September 10, 2018, "Developability for Biologics and Approaches to Formulation Design," BioMan Process Intensification Conference, Cambridge, MA.

149. August 3, 2018, "Biomolecular Computational Methods for Protein Engineering Against Aggregation and Other Molecular Liabilities," Acceleron Pharma, Cambridge, MA.

148. May 30, 2018, "Continuous Lyophilization of Pharmaceutical Products in Unit Doses," Hudson Valley LyoMac Webinair.

147. December 7, 2017, "Enabling Developability via Molecular Modeling," CDD for Biologics, Boston, MA.

146. December 1, 2017, "The Significance of Quantum Mechanics," St. John's College, Annapolis, MD.

145. October 17, 2017, "Biomolecular Computational Methods for Protein Engineering Against Aggregation and Other Molecular Liabilities", Biovia Community Day, Cambridge, MA.

144. September 21, 2017, "Developability for Biologics and Approaches to Formulation Design," Biologics, Modeling, and Informatics (BMI) Discussion Group, Cambridge, MA.

Samsung Bioepis Exhibit No. 1002
Page 11728

143. July 19, 2017, "Biopharmaceuticals and Continuous Manufacturing," Senate Competitive Caucus, U.S. Senate, Washington D.C.

142. May 10, 2017, "New Continuous Crystallization Technologies for Small Molecule Pharmaceutical Manufacturing," Vertex Pharmaceuticals, Boston, MA.

141. April 13, 2017, "Ethics and Engineering: How to Think About the Ethics of AI," MIT Course 6 Super UROP, Cambridge, MA.

140. February 10, 2017, "New Technologies for Holistic Pharmaceutical Creation," United States Pharmacopeia, Rockville, MD.

139. February 1, 2017, "New Technologies for Holistic Pharmaceutical Creation: Focus on 3D Printing," Takeda, Zurich, Switzerland.

138. January 31, 2017, "Developability and Manufacturability in Pharmaceutical Creation," Roche, Basel, Switzerland.

137. January 31, 2017, "Developability and Manufacturability in Pharmaceutical Creation," Lonza, Basel, Switzerland.

136. December 15, 2016, "Enabling Developability Via Molecular Modeling," IBC Antibody Engineering & Therapeutics, San Diego, CA.

135. October 26, 2016, "Integrating Discovery, Development and Manufacturing in Pharmaceutical Creation," University of Pennsylvania Department of Chemical and Biomolecular Engineering, Philadelphia, PA.

134. May 13, 2016, "Quantum Mechanics and Political Philosophy," MIT Conference on Mastery of Nature, Cambridge, MA.

133. March 17, 2016, "Ethics in Engineering," MIT Course 6 Super-UROP, Cambridge, MA.

132. October 5, 2015, "New Technologies for Enabling Continuous Manufacturing," PQRI Meeting, Bethesda, MD (plenary lecture)

131. September 16, 2015, "Rational Approaches for the Developability of Biotherapeutics" Boston University Department of Physical Chemistry, Boston, MA

130. September 7, 2015, "MIT's Success at Teaching and Research," National Polytechnic University, Yerevan, Armenia

129. June 4, 2015 "Continuous Processing in (Bio)Pharmaceutical Manufacturing," Ipsen Corporation, Paris, FR

Samsung Bioepis Exhibit No. 1002
Page 11729

128. May 15, 2015 "Advanced Formulation, Stabilization, and Manufacturing of Therapeutic Antibodies" MassBiologics, Boston, MA

127. April 29, 2015 "Continuous Pharmaceutical Manufacture and Advances in Biopharmaceuticals Formulation" The Pall Corporation Technology Symposium, Cambridge, MA. (Keynote Address)

126. April 14, 2015 "Rational Approaches for the Development of Biotherapeutics,"4th International Symposium on Higher Order Structure of Protein Therapeutics, Boston, MA

125. March 27, 2015 "Molecular and Macroscopic Engineering of Small Molecular Crystallization," Department of Mechanical and Chemical Engineering, ETH, Zurich, Switzerland

124. March 24, 2015 "Holistic Pharmaceutical Process Development," Department of Mechanical and Chemical Engineering, ETH, Zurich, Switzerland

123. Sept. 16, 2014 "Enabling Technologies for the Continuous Manufacturing of APIs: Continuous Crystallization" at FDA/PQRI Conference, Silver Spring, MD

122. June 10, 2014 "How 'Continuous' Manufacturing will Transform Biotherapeutic Manufacturing" The Annual Bio Manufacturing & Process Innovation Leaders Summit USA 2014 (MANU-BIO), Boston, MA (Keynote Address)

121. June 6, 2014 "Strategic Approaches for Understanding and Hindering Aggregation" IBC's Protein Aggregation, Stability & Solubility Conference, San Francisco, CA (Keynote Address)

120. March 26, 2014 "Rational Approaches to Developability and Manufacturability" Accelyrs, Cambridge, MA

119. March 21, 2014 "Rational Approaches to Developability and Manufacturability" Bayer, Wuppertal, Germany

118. January 21, 2014 "Rational Approaches for Biologics and Small Molecule Pharmaceutical Development and Manufacturing" Columbia University, New York, NY

117. January 8, 2014 "Rational Approaches to Developability and Manufacturability" Pfizer, Cambridge, MA

116. December 16, 2013 "Rational Approaches to Developability and Manufacturability"BMS, Devens, MA

115. November 7, 2013, "Recent Updates at the Novartis-MIT Center for Continuous Manufacturing", FDA, Silver Spring, MD

Samsung Bioepis Exhibit No. 1002
Page 11730

114. November 5, 2013 "Transforming Manufacturing to "Continuous": Flexible API and Final Dosage Form" ISPE Meeting, Washington, DC

113. October 21, 2013 "Transforming Small Molecule Pharmaceutical Manufacturing to Continuous and the Potential for Continuous Biologics Manufacturing," Integrated Continuous Biomanufacturing, an ECI Conference, Barcelona, Spain (Keynote Address)

112. September 11, 2013 "Rational Approaches to Developability and Manufacturability," Biogen Idec, Cambridge, MA

111. September 10, 2013 "Rational Approaches to Developability and Manufacturability," Pfizer, Andover, MA

110. July 10, 2013 "What Molecular Modeling in Pharmaceutical Development Can Do for You," BMS Symposium on Modeling, New Brunswick, NJ (Keynote Address)

109. June 27, 2013 "Capitalizing on Continuous Manufacturing," 8th Global Pharma Manufacturing Summit, Boston, MA (Plenary Lecture)

108. June 12, 2013, "Transforming Small Molecule Pharmaceutical Manufacturing to Continuous and the Potential for Continuous Biologics Manufacturing," Biomanufacturing Leaders Summit, Boston, MA (Keynote Address)

107. April 24, 2013 "From Molecular Computations to Continuous Manufacturing and Their Role in Shaping a Sustainable Future," 9th European Congress of Chemical Engineering, The Hague, Netherlands (Plenary Lecture)

106. April 19, 2013 "Transforming Pharmaceutical Manufacturing Continuous: The Ultra Lean Way of Manufacturing," Pharmintech, Bologna, Italy (Keynote Address)

105. March 26, 2013, "Rational Approaches to Developability for Stabilization Against Aggregation and Other Routes," 6th Annual Proteins Conference, London, UK.

104. November 15, 2012, "Rational Approaches to Developability, Formulation, and Design of Biobetters," MIT Center for Biomedical Innovation: Biomanufacturing Summit, Cambridge, MA

103. November 14, 2012, "Advanced manufacturing for pharmaceuticals and the Novartis-MIT center for continuous manufacturing," MIT ILP R&D Conference, Cambridge, MA

102. August 21, 2012, "Technical Update for the FDA on the Downstream Continuous Manufacturing Toolbox," FDA, Cambridge, MA

101. May 5, 2012, "Rational Approaches to the Stabilization of Biologics: Incorporating Developability and Manufacturability," Ispen, Milford, MA.

Samsung Bioepis Exhibit No. 1002
Page 11731

100. November 18, 2011, "Protein Aggregation Modeling and Novel Excipients for Downstream Processing: Incorporating Rational Approaches to Developability and Manufacturability for Biotherapeutics," BioMan, Cambridge, MA.

99. November 9, 2011, "Predication of Aggregation Prone Regions in Proteins: Incorporating Rational Approaches to Developability and Manufacturability for Biotherapeutics," CASSS Symposium on Immunogenicity, Gaithersburg, MD

98. October 20, 2011, "Heterogeneous Crystallization of API's on Excipients for "Continuous" Process and Product Design," Peck Symposium at Purdue University, West Lafayette, IN

97. October 19, 2011, "Transforming Pharmaceutical Development and Manufacturing with Molecular Computations ," AIChE Annual Symposium, CoMSEF Award, Minneapolis, MN

96. September 15, 2011, "Transforming Pharmaceutical Manufacturing, Continuous: The Ultra Lean Way of Manufacturing," President Obama's Advanced Manufacturing Partnership, Cambridge, MA

95. August 4, 2011 "Rational Approaches to Stabilization: Incorporating Developability in Discovery through Development Phases," GSK, King of Prussia, PA

94. July 28, 2011 "Rational Approaches to Stabilization: Incorporating Developability in Discovery through Development Phases," Pfizer Research, Cambridge, MA

93. July 21, 2011, "Molecular Modeling Approaches for Predicting The Stability of Biotherapeutics, Antibodies in Particular," Colorado Protein Stability Conference , Breckenridge, CO

92. May 19, 2011, "Computational Approaches for Identifying Degradation "Hotspots": Spatial Aggregation Propensity and Implementation in Pipeline Pilot,"Accelrys North America-UGM Conference, Newark, NJ

91. March 29, 2011, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization," ACS, Anaheim, CA (Plenary Lecture)

90. March 15, 2011, "Transforming Pharmaceutical Manufacturing Continuous: The Ultra Lean Way of Manufacturing," ISPE-NJ

89. November, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," AAPS Annual Meeting, New Orleans, LA

Samsung Bioepis Exhibit No. 1002
Page 11732

88. October, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," PEGS Biotechnology conference, Hannover, Germany

87. September, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Ipsen Corporation, Milford, MA

86. September, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," IBC Protein Formulation Conference, Providence, RI

85. August, 2010, "Molecular Modeling for the Rational Control of Polymorphism and Morphology," Sepracor Corporation, Marlborough, MA

84. July, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," MedImmune Corporation, Gaithersburg, MD

83. July, 2010, "Continuous Manufacturing: The Ultimate in Quality by Design," Sepracor Corporation, Marlborough, MA

82. May, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Accelrys Annual International Conference, Boston, MA

81. April, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," ISPE Biotech Meeting, Cambridge, MA

80. April, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Merck, West Point, PA

79. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Genzyme, MA

78. March, 2010, "Molecular Modeling for the Rational Control of Polymorphism and Morphology," Gilead Corporation, Foster City, CA

77. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Genentech, South San Francisco, CA

Samsung Bioepis Exhibit No. 1002
Page 11733

76. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Amgen, Thousand Oaks, CA

75. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Biogen-Idec, Cambridge, MA

74. December, 2009, "Continuous Manufacturing of Small Molecule Pharmaceuticals," Leaders for Global Manufacturing, MIT, Cambridge, MA

73. November, 2009, "Order parameter methods for reactions in complex systems," Princeton Center for Theoretical Sciences, Department of Physics, Princeton, NJ

72. October, 2009, "Rational approaches to protein and antibody stabilization," Schering-Plough, Elizabeth, NJ

71. September, 2009, "Rational approaches to protein and antibody stabilization," Merck & Co., West Point, PA.

70. September, 2009, "Modeling of crystallization processes," Merck Research Laboratories, Rahway, NJ.

69. September, 2009, "Rational approaches to pharmaceutical manufacturing," Merck Research Laboratories, Rahway, NJ.

68. July, 2009, "Continuous manufacturing: the ultra lean way of manufacturing," Biochemical Engineering XVI, Burlington, VT.

67. June, 2009, "Rational approaches to protein and antibody stabilization," Bristol-Meyers Squibb, New Brunswick, NJ.

66. April, 2009, "Reactivity in complex systems," University of Washington.

65. March, 2009, "Reactivity in complex systems," North Carolina Theory Seminar.

64. February, 2009, "Reactivity in complex systems," UCLA.

63. September, 2008, "Continuous manufacturing of pharmaceuticals: the ultra lean way of manufacturing," Global Pharmaceutical Manufacturing Summit, Chicago.

62. June, 2008, "Rational design of solvent formulations via molecular computations," American Association of Pharmaceutical Science National Biotechnology Conference, Toronto, Canada.

Samsung Bioepis Exhibit No. 1002
Page 11734

61. March, 2008, "Frontiers in chemical reactivity and pharmaceutical manufacturing," Department of Chemical Engineering, University of Puerto-Rico.

60. March, 2008, "Frontiers in chemical reactivity and pharmaceutical manufacturing," Department of Chemical and Biomolecular Engineering, University of Illinois, Urbana-Champaign.

59. Oct., 2007, "Formulation approaches for the future," IBC Life Sciences on Formulation Strategies for Protein Therapeutics, Hynes Convention Center, Boston, Keynote Address.

58. July, 2007, "Understanding reaction processes in complex media such as liquids," Gordon Conference on the Chemistry of Liquids, Holderness School, New Hampshire

57. June, 2007, "Molecular Design of New Excipients for Large Molecule Stabilization," AAP National Biotechnology Conference, San Diego, CA.

56. March, 2007, "Finding reactions coordinates for complex processes via likelihood maximization," ACS Spring Meeting, Chicago, IL.

55. November, 2006, "Understanding complex reaction processes," Department of Chemical Engineering, University of Buffalo, Buffalo, New York.

54. July, 2006, "Molecular simulations of ice and gas hydrate nucleation," Physics and Chemistry of Ice Conference, Bremerhaven, Germany, Keynote Address.

53. June, 2006, "Reaction coordinates from likelihood maximization," U.S.-Poland Workshop on Nanoscience and Nanostructured Materials, Poznan, Poland.

52. June, 2006, "Understanding complex reaction processes with applications to pharmaceuticals and heterogeneous catalysis," Department of Chemistry, University of Western Ontario, London, Ontario, Canada.

51. February, 2006, "Statistical physics applied to the development of biopharmaceuticals," Department of Physics, University of Rome "La Sapienza," Rome, Italy.

50. February, 2006, "Statistical physics applied to the development of biopharmaceuticals," SISSA, International School for Advanced Studies, Trieste, Italy.

49. September, 2005, "Molecular engineering of chemical systems," Department of Chemical Engineering, Drexel University, Philadelphia, Pennsylvania.

48. September, 2005, "Molecular engineering of chemical systems," Department of Chemical Engineering, Texas A&M, College Station, Texas.

47. September, 2005, "Reactivity in complex systems," Meeting in honor of Michele Parrinello's 60th Birthday, Agno, Switzerland.

Samsung Bioepis Exhibit No. 1002
Page 11735

46. July, 2005, "Molecular computational engineering: mechanism of methionine oxidation and rational design of additives for hindering aggregation," Protein Stability Conference, Breckenridge, Colorado.

45. May, 2005, "Transition Path Sampling Calculations in Complex Systems or How Can We Find the Reaction Coordinate?" 2005 International Conference on Scientific Computation and Differential Equations (SciCADE), Nagoya, Japan.

44. March, 2005, "Molecular computations for predictions of clathrate-hydrate nucleation and phase-behavior of multi-component hydrates," Hydrate Symposium at the American Chemical Society Spring Meeting, San Diego, California.

43. March, 2005, "Water structuring in phase transitions and in chemical reactions at sulfur sites in proteins," Water: Structure, Dynamics and Reactions Across the Phase Diagram at the American Chemical Society Spring Meeting, San Diego, California.

42. July, 2004, "A unified approach for the nucleation of ice and ice-like systems in homogeneous and inhomogeneous environments," Telluride Workshop on Studies of ice, icy particles, ice surfaces, and ice-adsorbate interactions: a molecular view," Telluride, Colorado.

41. April, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Tufts University, Medford, Massachusetts.

40. April 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemistry, Boston University, Boston, Massachusetts.

39. March, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Cornell University, Ithaca, New York.

38. March, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Department of Chemical Engineering, University of Rochester, Rochester, New York.

37. February, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Tsinghua University, Beijing, China.

36. February, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Department of Chemistry, Fudan University, Shanghai, China.

35. February, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Center for Atomic-Scale Materials Physics (CAMP) and Department of Physics, Technical University of Copenhagen, Copenhagen, Denmark.

34. November, 2003, "Ordering of water in phase transitions and biological systems," Department of Chemistry, Washington University, St. Louis, MO.

Samsung Bioepis Exhibit No. 1002
Page 11736

33. November, 2003, "Ordering of water in phase transitions and biological systems," Department of Physics, University of Missouri, Columbus, MO.

32. October, 2003, "Nucleation and growth of clathrate-hydrates and ice and a new theoretical framework to address those," Dartmouth University, Thayer School of Engineering, Dartmouth, NH.

31. September, 2003, "Finding reaction pathways for industrial chemical problems," Statistical Mechanics of Rare Events, Paris, France.

30. September, 2003, "Analyses of reactions in acid zeolites and of proteins via nudged elastic band calculations and Car-Parrinello simulations," CECAM Workshop on Reactivity, Lyon, France.

29. May, 2003, "Reactivity of acidic zeolites via quantum chemical and Car-Parrinello molecular dynamical methods," Advances in the Understanding and Application of Catalysis, Moscow, Russia, *Plenary Lecture.*

28. April, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, Princeton University, Princeton, NJ.

27. April, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, University of Pittsburgh, Pittsburgh, PA.

26. March, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, University of Texas, Austin, TX.

25. March, 2003, "Reactivity of acidic zeolites via quantum chemical and Car-Parrinello molecular dynamical methods," invited talk in "Mechanistic Surface Chemistry," Spring Meeting of the American Chemical Society, New Orleans, LA.

24. March, 2003, "Effects of solvation on biological processes," invited talk in "Symposium in Honor of Professor Clayton J. Radke, recipient of the American Chemical Society Award in Colloid Chemistry," Spring Meeting of the American Chemical Society, New Orleans, LA.

23. March, 2003, February, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, Stanford University, Palo Alto, CA.

22. February, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, Tsinghua Univeristy, Beijing, China.

21. February, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, North Carolina State University, Raleigh, NC.

Samsung Bioepis Exhibit No. 1002
Page 11737

20. November, 2002, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, University of California, Berkeley, CA.

19. November, 2002, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, California Institute of Technology, Pasadena, CA.

18. July, 2002, "Nucleation of and transport in clathrate-hydrates and ice," Physics and Chemistry of Ice Conference, New Foundland, Canada.

17. June 2002, "Quantum mechanical calculations applied to engineering problems," Steacie Institute of Molecular Sciences, National Research Council, Ottawa, Ontario, Canada.

16. April, 2002, "Molecular simulations for the stabilization of therapeutic proteins and the quantification of nucleation of clathrate-hydrates," Rensselaer Polytechnic Institute, Troy, NY.

15. April, 2002, "Quantification of reactive sites in zeolitic and transition metal catalysts via first-principles," ACS Meeting, Orlando, Fl.

14. February, 2002, "The identification and study of sites of varying activity in zeolites and transition metal catalysts," First-Principles Catalysis, Vienna, Austria.

13. February, 2002, "Order-disorder transitions on the surface of ice and in bulk ice and clathrate-hydrates," Swiss Center for Computational Sciences, Manno, Switzerland.

12. February, 2002, "Molecular simulations for the stabilization of therapeutic proteins and the quantification of nucleation of clathrate-hydrates," Colorado School of Mines, Golden, CO.

11. August, 2001, "Car-Parrinello simulations of the disordering of ice and dissociation of HCl, relevant to stratospheric chemistry," ACS Meeting, Chicago, IL.

10. July, 2001, "Insight into the stabilization of therapeutic proteins via molecular simulations," National University of Singapore, Singapore.

8. June, 2001, "Insight into the stabilization of therapeutic proteins via molecular simulations," Hong Kong University of Science and Technology, Hong Kong.

8. April, 2001, "Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics," University of Connecticut, Storrs, CT.

6. February, 2001, "Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics," Georgia Institute of Technology, Atlanta, GA.

6. January, 2001, "Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics," National University of Singapore, Singapore.

Samsung Bioepis Exhibit No. 1002
Page 11738

5. November 1999, "Sustainable development," TBII Leonardo Lecture, MIT.

4. June, 1999, "Application of molecular modeling to automotive catalysis," Workshop held at Ford Motor Company, Dearborn.

3. March, 1999, "Defect structure and its relation to methanol activation", ACS Annual Conference, Annaheim, CA.

2. April, 1998, "Quantum mechanical methods in catalysis: a primer", New England Catalysis Society, Worchester, MA.

1. September, 1996, "Dynamic Monte Carlo study of reaction and diffusion sites in ZSM-5 Zeolites", Technical University of Athens, Athens, Greece.

Professional Affiliations:

AIChE, ACS, ASEE, AAPS

Languages:

French, German, Ancient Greek

Samsung Bioepis Exhibit No. 1002
Page 11739

Appendix B

APPENDIX B

Exh. No.	Description
AMG1001	U.S. Patent 9,718,880 to Bell et al.
AMG1002	Declaration of Joseph P. Balthasar, Ph.D.
AMG1003	Curriculum Vitae of Joseph P. Balthasar, Ph.D.
AMG1004	Hillmen, P., et al., "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria," N. Engl. J. Med. 350:552-559 (2004) ("Hillmen '04")
AMG1005	Bell, L. and Rother, R., "Method of Treating Hemolytic Disease," U.S. Patent Application Publication No. 2005/0191298 A1 (filed February 3,2005; published September 1, 2005)
AMG1006	Bowdish, K., et al., "Rationally Designed Antibodies," U.S. Patent Application Publication No. 2003/0232972 A1 (filed December 2, 2002; published December 18, 2003)
AMG1007	Evans, M., et al., "C5-Specific Antibodies for The Treatment of Inflammatory Diseases," U.S. Patent No. 6,355,245 B1 (filed June 7, 1995; issued March 12, 2002)
AMG1012	Hillmen, P., et al., "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria," N. Engl. J. Med. 355:1233-1243 (2006)
AMG1014	File History for U.S. Patent No. 9,725,504 B2
AMG1016	File History for U.S. Patent No. 9,718,880 B2
AMG1028	Wang, Y., "Nebulization of Monoclonal Antibodies for Treating Pulmonary Diseases," U.S. Patent Application Publication No. 2005/0271660 A1 (filed May 11, 2005; published December 8, 2005)
AMG1029	Wang, W., et al., "Antibody Structure, Instability, and Formulation," Journal of Pharmaceutical Sciences 96: 1-26 (2007)
AMG1030	Daugherty, A. and Mrsny, R., "Formulation and delivery issues for monoclonal antibody therapeutics," Advanced Drug Delivery Reviews 58: 686-706 (2006)
AMG1031	Mueller, P., et al., "Humanized Porcine VCAM-Specific Monoclonal Antibodies With Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding To Porcine Endothelial Cells," Molecular Immunology 34: 441 -452 (1997)

Samsung Bioepis Exhibit No. 1002
Page 11741

Exh. No.	Description
AMG1047	Hill, A., et al., "Sustained response and long-term safety of eculizumab in paroxysmal nocturnal Hemoglobinuria," Blood 106: 2559-2565 (2005) ("Hill '05")
AMG1056	Genentech, Inc., Avastin 2004 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf
AMG1058	Millennium, Campath 2001 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm
AMG1059	Immunomedics, Inc., CEA-Scan 1999 Package Insert, available at https://pharmacyce.unm.edu/nuclear_program/neolibrary/libraryfiles/package_inserts/CEA-scan.pdf
AMG1061	Genentech, Inc., Herceptin 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/trasgen092598lb.pdf
AMG1063	Genentech, Inc., Lucentis 2006 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/125156lbl.pdf
AMG1066	Genentech, Inc., Raptiva 2009 Package Insert, available at https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM143346.pdf
AMG1067	Centocor, Inc., Remicade 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/inflcen082498lb.pdf
AMG1069	Genentech, Inc., Rituxan 1997 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-lab.pdf
AMG1070	Novartis Pharm. Corp., Simulect 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/basnov051298lb.pdf
AMG1071	MedImmune, Inc., Synagis 1999 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/palimed102302LB.pdf
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Samsung Bioepis Exhibit No. 1002
Page 11742

Exh. No.	Description
AMG1074	Genentech, Inc., Xolair 2007 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf
ALXN2005	SOLIRIS® Label (2007)
ALXN2025	*Curriculum Vitae* of Bernhardt L. Trout, Ph.D.
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Samsung Bioepis Exhibit No. 1002
Page 11743

APPENDIX C

Therapeutics and Clinical Risk Management

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REVIEW

Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations

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Abstract: Paroxysmal nocturnal hemoglobinuria (PNH) is a nonmalignant clonal disorder resulting from somatic mutation in the *PIG-A* gene leading to a deficiency of the membrane-anchoring molecule glycosylphosphatidylinositol. The lack of expression of two glycosylphosphatidylinositol-anchored proteins involved in the regulation of the complement system renders PNH erythrocytes susceptible to complement-mediated lysis. Clinical manifestations include thromboembolic disease, chronic kidney injury, pulmonary hypertension, smooth muscle dysfunction, and chronic hemolysis. Until recently, treatment was mainly supportive with most patients suffering from significant morbidity and shortened survival compared to age-matched controls. The development of eculizumab, a humanized monoclonal antibody directed against the terminal complement protein C5, has resulted in dramatic improvements of survival and reduction in complications. In this paper, we review some special considerations pertaining to the use of eculizumab for PNH.

Keywords: somatic mutation, GPI, survival, hemolysis, MDS, anemia

Overview of paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic anemia resulting from a somatic mutation in the *PIG-A* gene in the hematopoietic stem cells.[1] This mutation leads to a deficiency of glycosylphosphatidylinositol (GPI) membrane-anchoring proteins on the surface of PNH cells. Two of these anchoring proteins, CD55 and CD59, are complement inhibitors, and the deficiency of such proteins will render PNH erythrocytes susceptible to complement-mediated lysis.[2] Recently, new evidence on PNH pathogenesis supports the notion that the expansion of the PNH clone results from escape from T-cell-mediated autoimmune damage to hematopoietic stem cells, with the GPI molecule as a target. This might further consolidate the observed association between PNH and aplastic anemia (AA).[3] PNH is a very rare disease with a prevalence of ~16 per million people,[4] and it can present at any age but mainly occurs in young adults, with the usual age at diagnosis being early 30s.[4–6]

Despite being rare, PNH is "the most vicious acquired thrombophilic state known", yet the mechanism of this virulent thrombotic behavior is still elusive.[3,7] Thromboembolic (TE) events occur in ~50% of PNH patients, and it is the main cause of death in approximately one-third of patients with PNH.[8] The intravascular hemolysis in PNH is a critical factor in triggering thrombosis. The release of hemoglobin (Hb) into the blood stream results in massive nitric oxide scavenging leading to vasospasm and to increase in platelets' reactivity and aggregation.[9,10] Therefore, the process of nitric

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Samsung Bioepis Exhibit No. 1002
Page 11745

oxide depletion by the free Hb will not only predispose patients to developing thromboembolism but also lead to vascular constriction (manifested as pulmonary hypertension, renal dysfunction, and erectile dysfunction) and smooth muscle dystonia of the gastrointestinal tract (manifested as abdominal pain, dysphagia, and esophageal spasm).[2,9,11] Additionally, renal dysfunction is also caused by chronic hemolysis-induced hemosiderin deposition in the proximal renal tubules, in addition to alterations in renal blood flow caused by nitric oxide depletion.[9,10]

Until a decade ago, the treatment options for PNH were mainly supportive including blood transfusion, erythropoiesis-stimulating agents, corticosteroids, anabolic steroids, iron therapy, thrombosis prophylaxis, and sometimes thrombolytic therapy or allogenic bone marrow transplantation.[2,3] Eculizumab was first introduced in 2004 in a preliminary pilot study of eleven participants.[12] It was found to dramatically reduce intravascular hemolysis and blood transfusion requirements. Despite the open-label design, the potential risk of bias was minimal as all the reported outcomes were objectively measurable. However, other issues including the small sample size, short-term follow-up, and the potential risk of selection bias (only transfusion-dependent patients were included) should be considered when interpreting the results of this study. Subsequently, two Phase III trials – the TRIUMPH and SHEPHERD studies – proved that eculizumab therapy for PNH is effective, safe, and well tolerated in a standardized setting with predefined outcome criteria.[11,13] A total of 87 and 97 patients were enrolled in these studies, respectively, overcoming the small sample size issue of the pilot study. However, issues such as selection of only transfusion-dependent patients and failure to report on TE rates as most patients were receiving concomitant anticoagulants remained. Eculizumab was finally approved for the treatment of patients with PNH in 2007 by the US Food and Drug Administration and by the European Medicines Agency.[2,8]

In this review, we focus on the up-to-date established positive impacts of eculizumab on PNH and its potential adverse events, highlighting certain issues that need to be addressed with eculizumab use.

Eculizumab

Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5, which blocks the formation of the membrane attack complex (C5–9), thus protecting PNH red blood cells from complement-mediated intravascular hemolysis.[3,14] Its effectiveness has been evidenced by reduction or elimination of the need for blood transfusion, decrease in the incidence of thrombosis, improvement in anemia and quality of life (QoL), and prolongation of overall survival (OS).[1,8,11] Furthermore, due to its use, stem cell transplantation is only considered for cases of severe marrow failure.[3,15]

Pharmacodynamics and pharmacokinetics

An inhibition of C5 sufficient to prevent hemolysis occurs at eculizumab plasma concentrations in excess of 35 g/mL.[2] At therapeutic doses, maximum plasma concentrations of eculizumab are achieved within 1 hour of infusion.[2] Eculizumab reduces hemolysis in ~1 week, and its half-life elimination is ~11 days (range: 8–15 days). The clearance for a typical PNH patient weighing 70 kg is ~22 mL/h, and the volume of distribution is ~7.7 L.[16]

Dose and schedule

For PNH, eculizumab is administered as a weekly dose of 600 mg by intravenous infusion for 35 minutes from week 1 to week 4, followed by infusion of 900 mg at week 5, and then 900 mg every 14 days for an indefinite period.[1,2]

Eculizumab and PNH – clinical efficacy

The effect of eculizumab on PNH patients has dramatically changed the clinicians' management and patients' perspective toward this disease.

Reducing blood transfusion requirement and stabilizing Hb level

Symptoms of PNH are often disproportionate to the degree of anemia.[11] However, achieving sustained stability of Hb and transfusion independence were the main outcomes measured with eculizumab therapy in PNH studies.[11–13] Those two outcomes were chosen because both are measurable, and can be easily compared with pre- or no-eculizumab treatment end points to assess its response. Studies assessing the transfusion requirement and transfusion independence rates with eculizumab are illustrated in Table 1.

In the TRIUMPH study, 43 patients on eculizumab were compared with 44 patients on placebo in a double-blind randomized controlled trial, with the outcomes being the stabilization of Hb and transfusion independence.[11] Hb stabilization occurred in 49% in the eculizumab group compared to 0% in the placebo group ($P<0.001$). Furthermore, there was a significant reduction in the median number of units transfused in eculizumab group as compared to the placebo group. Similar findings were also reported in the SHEPHERD study.[13]

Kelly et al evaluated 79 consecutive PNH patients over 8 years, and compared them with 30 matched historical

Samsung Bioepis Exhibit No. 1002
Page 11746

Table 1 Studies assessing hematological response and transfusion requirement in PNH patients treated with eculizumab

Study	Total N	Hb stabilization	Median number of PRBC units transfused (eculizumab vs placebo)	*P*-value	Overall transfusion reduction	% of transfusion independence	Transfusion reduction in dependent group
TRIUMPH[11]	87	49% ($P<0.001$)	0 vs 10	<0.001	73%	51% (at 6 months)	Yes
SHEPHERD[13]	96	–	0 vs 8	<0.001	52%	51% (at 12 months)	–
Kelly et al[8]	79	–	5 vs 19 (mean number)	<0.001	–	66% (at 6 months)	Yes ($P<0.03$)
Hillmen et al[17]	195	–	–	–	54.7%	82% (at the last 6 months of study)	Yes ($P<0.001$)
AEGIS[18]	29	31% Hb increase ($P<0.001$)	0.7 vs 4.9	0.0016	–	96% (at 18–24 months)	–

Abbreviations: PNH, paroxysmal nocturnal hemoglobinuria; Hb, hemoglobin; PRBC, packed red blood cell.

controls from the pre-eculizumab era.[8] The 12-month mean transfusion requirement was significantly reduced in patients receiving eculizumab compared to controls. Although this study was non-randomized, the inclusion of consecutive patients might reduce the risk of bias.

Long-term safety and efficacy data of eculizumab have been reported in two studies: the study by Hillmen et al and AEGIS study.[17,18] The first study included a total of 195 patients from three Phase III trials with a maximum duration of 66 months, and reported a total transfusion independence in 82% of patients.[17] The AEGIS trial was an open-label, noncomparative, multicenter Phase II study of 29 Japanese PNH patients, followed by a further 2-year extension study.[18] Only 27 patients were included in the extension study with a total transfusion independence of 96%.[17,18] The importance of the AEGIS extension study lies in the fact that it is the first study reporting long-term data of eculizumab in a trial setting among Asian PNH patients, a population in which PNH seems to be more frequent than in the Western population.[19]

In patients in whom transfusion independence was not reached, the TRIUMPH trial[11] and the studies by Kelly et al[8] and Hillmen et al[17] reported similar findings of reduction in the number of red cell units transfused after starting eculizumab as compared to before eculizumab treatment.

Finally, a recent retrospective study included 123 PNH patients treated with eculizumab and 191 historical controls from the French registry. Although the transfusion requirements were not reported in the study, the authors did suggest that anemia could persist in some patients.[1]

Improving QoL

QoL is affected in the majority of patients with PNH with 96% complaining of fatigue and >40% having symptoms of smooth muscle spasm often of sufficient severity to require narcotic analgesics.[20] Fatigue is multifactorial and is not simply the result of anemia, as 60% of these patients are transfusion independent.[20] The fluctuation in Hb and the inconvenience of the frequent blood transfusions may also contribute to the impaired QoL. Nevertheless, eculizumab has impacted favorably on the QoL in both transfusion-dependent and transfusion-independent patients.[3,9,11,21,22]

In the TRIUMPH study, QoL assessments were performed with the use of two instruments: the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Patients in the eculizumab group had a mean increase (improvement) in scores on the FACIT-F of 6.4±1.2 points from baseline to week 26, compared to the placebo group in which the mean score decreased by 4.0±1.7 points during this period ($P<0.001$).[11] Importantly, only transfusion-dependent patients were included, and QoL was assessed prior to transfusion and after eculizumab, without posttransfusion assessments. Therefore, it is not possible to fully determine whether differences are a result of eculizumab or the anemia correction.[2] However, improvement in the FACIT-F score was also noted independent of improvement in Hb level in patients receiving eculizumab as compared to placebo, supporting the positive impact of eculizumab on QoL regardless of Hb level.

With respect to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, the eculizumab group had overall significant improvements in scores of functional status, fatigue, pain, dyspnea, loss of appetite, and insomnia, compared to placebo.[11] Similarly, improvements were demonstrated in several QoL parameters including physical, emotional, and cognitive functioning, global health, fatigue, dyspnea, and insomnia.[12] Similarly, the AEGIS study also showed a consistent improvement in QoL in the majority of patients with sustained reductions in fatigue and dyspnea.[18]

Of note, ~25% of PNH patients treated with eculizumab still need recurrent blood transfusions; however, even these patients report improved QoL.[3] Improvements in symptoms including abdominal pain, dysphagia, and erectile

Samsung Bioepis Exhibit No. 1002
Page 11747

dysfunction have been reported during eculizumab therapy despite the observation that total Hb levels were unchanged or not completely corrected.[11,12,21] This supports the notion that intravascular hemolysis plays an important role in diminishing QoL in PNH patients.[11]

Reducing intravascular hemolysis

As previously mentioned, intravascular hemolysis results in symptoms of smooth muscle dystonia, including abdominal pain, dysphagia, and erectile dysfunction.[3,11] Eculizumab therapy results in a reduction of hemolysis and a new steady-state Hb level, due to balance of the underlying bone marrow dysfunction, the increased half-life of PNH erythrocytes, and the new level of transfusions (if any) required.[11] High percentages of PNH-type red blood cells have been observed after eculizumab treatment, indicating that these cells have not undergone hemolytic destruction.[10,18]

Lactate dehydrogenase (LDH), a biochemical marker of hemolysis, is used frequently to assess intravascular hemolytic activity. In the pre-eculizumab era, PNH patients with hemolysis (LDH $\geq$1.5× upper limit of normal) had a 4.8-fold increase in mortality compared to the general population.[23] The TRIUMPH study showed a rapid, significant, and sustained reduction in the LDH to normal or near-normal levels in patients on eculizumab.[11] Other studies have reported similar findings that last beyond 8 years of eculizumab therapy, reflecting inhibition of chronic hemolysis.[8,17,18]

Preventing thrombosis

Thromboembolism occurs in 50% of patients, and represents the major cause of death in PNH.[6,24,25] Once an initial thrombosis occurs, the risk of further thrombotic events increases, with a five- to ten-fold increase in mortality.[8] Interestingly, TE events in PNH are not restricted to the venous system.[4,6,22] Eculizumab was able to show a substantial impact in lowering the risk of thrombosis in PNH as summarized in Table 2.

It has been shown that patients on eculizumab have a significant and sustained decrease in activation of both the plasmatic hemostatic system and the endothelium.[26] Compared to pretreatment values, patients on eculizumab were found to have lower levels of coagulation factors such as von Willebrand factor, of by-products of coagulation such as D-dimer, and also of endothelial cell molecules such as vascular cell adhesion molecule 1.[26] These changes might be due to the blocking effect of eculizumab on C5, thus reducing platelet and endothelial activation, intravascular hemolysis, and release of thromboplastin-like substances.[7,27]

Table 2 Studies assessing thromboembolism rates with eculizumab

Study	TE event rate/100 PYs with eculizumab vs without eculizumab	*P*-value	Notes
Hillmen et al[22]	0.72 vs 11.54	<0.001	
Kelly et al[8]	0.8 vs 6.5	<0.001	
AEGIS[18]	Zero TE events		
Hillmen et al[17]	3.6% vs 32.6%[a] 2.3 vs 7.3[b]		96.4% of total patients free of thromboembolism
Loschi et al[1]	4% vs 29%[a]		

Notes: [a]Percentage, not rate. [b]Incidence rate calculated from information available in the study.
Abbreviations: TE, thromboembolic; PYs, person-years.

Initial studies were not designed to establish the effect of eculizumab on thrombosis as most trial patients were receiving concomitant anticoagulants.[2,12,13] However, in later studies, eculizumab has consistently shown a protective effect against thrombosis.[8,17,22,26] In a prespecified analysis, data from three combined studies[11–13] showed that TE rate in patients receiving exclusively anticoagulants was reduced from 11.54 events per 100 patient-years before eculizumab treatment to 0.72 events per 100 patient-years during eculizumab treatment ($P<0.001$), with a relative risk reduction of 94%.[22] Despite heterogeneity in the individual pre-study TE event rates, eculizumab treatment consistently resulted in a marked reduction in thromboembolism (Table 2). Other studies have also reported dramatic reductions in thrombosis after initiating eculizumab therapy (0.8 vs 5.6 events per 100 patient-years; $P<0.001$) even after accounting for the shorter duration of follow-up since starting eculizumab.[8] Of note, in the latter study, 50% of the pre-eculizumab thrombosis events occurred on anticoagulants, which supports the notion that in PNH patients with a previous history of thrombosis, anticoagulation alone may not be sufficient in preventing thromboses. On the other hand, after eculizumab treatment, primary prophylaxis with warfarin was stopped, whereas anticoagulation for secondary prophylaxis was not routinely stopped. Thus, cessation of anticoagulation in patients on eculizumab with no prior history of thrombosis is the current recommended practice in some centers.[8] Similar TE reductions have been reported in other studies.[17,18] TE events decreased by 81.8%, with 96.4% of patients remaining free of TE events.[17] In the AEGIS study, no TE events were reported during the 2-year extension period.[18]

A recent study from the French registry also provided evidence for significantly lower TE rates in patients on eculizumab compared to historical controls (4% vs 29%).

Samsung Bioepis Exhibit No. 1002
Page 11748

However, the study showed that thromboembolism remains a major issue in PNH, even in the eculizumab era, as highlighted by the negative impact of a previous thromboembolism on OS in adjusted analysis (hazard ratio [HR] 4.48, 95% confidence interval [CI] 2.46–8.16; $P<0.001$).[1]

Improving renal function

Renal dysfunction has been well reported in PNH,[11,18] and patients with PNH have a sixfold greater risk of chronic kidney disease (CKD) compared to the general population.[9,11,18] More importantly, CKD is associated with an elevated risk of premature mortality contributing to 8%–18% of PNH-related deaths.[6,17] Renal impairment in PNH is multifactorial and involves a direct effect of nitric oxide depletion, induced by cell-free Hb, on the glomerular filtration rate and on renal plasma flow, and the repetitive exposure to cell-free Hb leading to chronic hemosiderin deposition in the proximal renal tubules.[9,10] Supportive care measures do not prevent the occurrence or the progression of CKD. However, by inhibiting terminal complement activation and intravascular hemolysis, treatment with eculizumab significantly improves renal function. Several studies have shown consistently that eculizumab has a protective role leading to improvement in, or less progression of, renal disease.[9,10,17]

Hillmen et al provided evidence that sustained long-term therapy with eculizumab can reverse early-stage renal damage sustained prior to treatment initiation, particularly when administered early and prior to advanced renal impairment.[17] In this study, CKD stages[28] were assessed following each 6-month eculizumab treatment period. Continued time-dependent improvement in CKD was observed with sustained eculizumab treatment, with 24.4% of patients showing improvement in CKD after only 6 months of treatment and 45% of patients showing improvement after 36 months. Overall, patients were significantly more likely to experience an improvement than a worsening in renal function ($P=0.015$).[17]

Similar findings have been reported in the AEGIS study. Sustained administration of eculizumab in patients with CKD at baseline was associated with improved renal function in 71%, whereas 29% had their renal function stabilized. Eculizumab also improved renal function, particularly if administered early in the course of disease and before the kidney is more severely impaired. Improvements in renal function were observed in 88% of patients with stage 1 CKD, 67% of patients with stage 2 CKD, and 33% of patients with stages 3–4 CKD.[18]

A large cohort of 195 PNH patients from parent eculizumab clinical trials was also assessed for their kidney function by Hillmen et al.[9] In this study, improvement in renal function was more commonly seen in patients with baseline CKD stages 1–2 (67.1% improvement), although improvement was also observed in patients with CKD stages 3–4. Overall, 40 (21%) of 195 patients who demonstrated renal dysfunction or damage at baseline were no longer classified as such after 18 months of treatment.[9]

Improving OS

Historical studies have shown the median survival in PNH patients to be between 10 and 15 years from the time of diagnosis.[4] More recently, data from a French series of patients in the pre-eculizumab era showed an improvement in median survival to 22 years, which is probably the result of improvements in supportive care and in the management of disease complications.[25] With the use of eculizumab, the OS of PNH patients has consistently shown a remarkable improvement, approaching that of the general population.[1,8,17] The survival rate of PNH patients in eculizumab studies was 97.6% at 3 years,[17] 95.5% at 5 years ($P<0.03$ as compared to eculizumab-untreated patients),[8] and 92% at 6 years ($P=0.037$ as compared with controls).[1,8,17] Furthermore, Kelly et al reported no significant difference in OS between the PNH patients treated with eculizumab compared with sex- and age-matched controls from the UK population.[8] Another study suggested that the two factors statistically associated with a worse OS were the absence of treatment with eculizumab (HR 6.26, 95% CI 2.72–14.43; $P<0.001$) and a previous history of TE events (HR 4.48, 95% CI 2.46–8.16; $P<0.001$).[1]

Absent or inadequate response to eculizumab in PNH

It has been reported that, with eculizumab, up to two-thirds of PNH patients who are transfusion dependent become transfusion independent.[3] However, ~25% of them still need recurrent albeit less frequent blood transfusion.[3] The authors suggested that these heterogeneous hematological responses may be related to factors including underlying AA,[1–3] C3-mediated extravascular hemolysis,[3,15,29] breakthrough hemolysis,[30] or the presence of a specific mutation in the C5 gene which prevents eculizumab from binding to C5 protein.[6]

The association of PNH with AA

In some patients, a poor or suboptimal response to eculizumab may indicate that the extent to which bone marrow

Samsung Bioepis Exhibit No. 1002
Page 11749

failure was contributing to anemia had been underestimated.[3] There is a close relationship between AA and PNH, and a history of severe AA is present in at least one-half of all newly diagnosed PNH cases,[31] whereas PNH clones are found in up to 70% of patients with AA.[2,31] Recently, new evidence on PNH pathogenesis supports the notion that expansion of the PNH clone results from escape from T-cell-mediated autoimmune damage to normal hematopoietic stem cells, with the GPI molecule as target, consolidating further the observed association between PNH and AA. Indeed, GPI-specific $CD8^+$ T cells – which have been identified in PNH patients – would spare selectively GPI-negative stem cells, thus enabling them to repopulate the marrow of a patient who would otherwise have AA.[3]

In the AEGIS trial, the effect of eculizumab was assessed in patients with PNH plus AA/myelodysplastic syndrome (MDS) and those with PNH alone, and no significant differences were found between the two groups in the end points assessed, namely hemolysis and blood transfusion. This finding suggests that patients with PNH and AA/MDS experience similar hemolysis-associated complications and can benefit from treatment with eculizumab.[18]

Another interesting observation has been reported by a case report of a PNH patient who was initially diagnosed with AA and treated subsequently with eculizumab.[32] Erythropoiesis improved, and the patient became transfusion independent shortly after initiation of iron chelation with deferasirox.[32] Similarly, the same finding has also been seen in MDS patients after starting deferasirox.[33,34] The significance of this management modality needs to be addressed in future studies.

It is too early to draw robust conclusions on the effect of eculizumab on patients with PNH plus AA, yet the evidence of the association between the two suggests that an inadequate marrow response to anemia may be a contributing factor to the observed persistent anemia in PNH patients receiving eculizumab. More importantly as many as 25% of patients with a previous diagnosis of AA treated with immunosuppression may progress on to develop hemolytic PNH requiring therapy.[35]

Extravascular hemolysis with eculizumab

Two studies have described the development of "iatrogenic" extravascular hemolysis with eculizumab.[15,29] Risitano et al have suggested that binding of C3 by PNH red blood cells may constitute an additional disease mechanism, strongly enhanced by eculizumab treatment and producing a variable degree of extravascular hemolysis.[15] Eculizumab affects only the distal complement pathway, thus neutralizing the deficiency of CD59 on PNH red blood cells by inhibition of C5 cleavage, but since these are also deficient in CD55, upstream complement activation may lead to C3 opsonization leading to a gradual accumulation of C3 fragments on their surface. These C3-opsonized red blood cells will be susceptible to phagocytosis by macrophages in the reticuloendothelial system, resulting in extravascular hemolysis.[3,7] This phenomenon may explain the residual low-level hemolysis occurring in some eculizumab-treated patients,[29] indicated by a positive Coombs test (classically negative in untreated PNH).[3,7,29]

More importantly, researchers have suggested that this process may play a role in limiting anemia improvement because it develops at the same time that intravascular hemolysis ceases.[3,7] However, fortunately in many cases, it seems to have little or no clinical relevance.[7] This conclusion has also been supported by studies in which a dramatic reduction in transfusion requirements was observed, indicating that the phenomenon of extravascular hemolysis is of limited clinical importance for most patients.[8,17] In the next decade, researchers may quest for a way to control extravascular hemolysis.[7] It has been recommended that selective splenic artery embolization can be used to treat severe extravascular hemolysis, as an alternative to splenectomy.[3] Of note, selective splenic artery embolization has also been used to reduce spleen size and alleviate cytopenias in splenomegaly with hypersplenism in PNH patients.[3]

Breakthrough hemolysis

According to Nakayama et al, eculizumab-dosing intervals >17 days may be associated with an increased risk of developing breakthrough hemolysis in patients with PNH (odds ratio 1.6, 95% CI 1.3–2.0; $P<0.01$).[30] The recommended schedule is thus to maintain eculizumab administration every 14 days, although this needs to be further confirmed.[1,2] Other factors may also account for breakthrough hemolysis such as pregnancy (detailed in the "Eculizumab in pregnancy" section).

C5 gene mutation

C5 gene mutation has been detected among Japanese patients with PNH, identified as having poor response to eculizumab.[6] A poor response was defined as markedly high levels of LDH during treatment, indicating that intravascular hemolysis remained unaffected, regardless of the persistence or improvement in other laboratory findings or clinical symptoms. This mutation prevents binding and blockade

Samsung Bioepis Exhibit No. 1002
Page 11750

by eculizumab while retaining the functional capacity of the mutant C5 to cause hemolysis. The prevalence of this mutation among the patients with PNH (3.2%) was similar to that among healthy Japanese persons (3.5%).

Special considerations

Meningococcal meningitis and other infections

Complement inhibition by eculizumab leads to impairment in neutrophil and monocyte function, consequently affecting their ability to clear infections by encapsulated organisms, such as *Neisseria meningitidis*.[2,8] Patients who are to be treated with eculizumab must be vaccinated against *N. meningitidis* at least 2 weeks prior to starting treatment.[2]

The tetravalent meningococcal vaccine is available against subgroups A, C, W, and Y but not for serogroup B, which is the most common serotype isolated in meningococcal sepsis in areas such as the UK.[8,9] This explains the reported rates of meningococcal infections in some studies despite all patients being vaccinated appropriately.[8,9] Hillmen et al and Kelly et al reported a rate of 1% and 2.5%, respectively, for meningococcal meningitis on eculizumab.[8,9] Therefore, in January 2010, the UK policy changed to include antibiotic prophylaxis for all patients (penicillin V 500 mg twice a day or erythromycin 500 mg twice a day for patients intolerant to penicillin), in addition to the tetravalent meningococcal vaccination.[8] In 2013, Bexsero® became the first broad-coverage vaccine to be licensed for active immunization against serotype B meningococcal disease.[36] Bexsero is now licensed in >35 countries worldwide for varying age groups, including the European Union, Australia, Brazil, Canada, Chile, Uruguay, and the USA, and it is usually combined with the tetravalent vaccine in PNH patients planned for eculizumab for full coverage of the five serotypes.[36] However, in daily practice, clinicians may still prefer to continue on penicillin or amoxicillin prophylaxis while awaiting the vaccines to kick in, and some would still choose to continue penicillin even after vaccinated because other subtypes may not be covered.

Other infections have also been reported in eculizumab studies. The AEGIS study reported a total of 159 treatment-emergent infections, of which the majority were mild in severity (87.4%). Only seven of the 159 infections (4%) were considered probably related to eculizumab, of which three (one case each of pneumonia, cellulitis, and sepsis) were severe. There were no meningococcal infections reported.[18] Hillmen et al also reported an overall infection rate of 12.8%.[9]

Overall, studies indicate that eculizumab is well tolerated over the long term, and its profile is consistently safe across studies. However, further precautions might be considered in immune-compromised categories such as elderly or neutropenic patients.

Eculizumab in pregnancy

The median age at diagnosis of PNH is 34 years, so affected females are often in the reproductive age group.[37] Although PNH is not known to adversely affect female fertility, several fetal–maternal complications have been reported in pregnant PNH patients related to exacerbated intravascular hemolysis, including spontaneous miscarriages (45%), premature births, increased blood transfusion requirements, thrombocytopenia, thromboembolism, and accelerated preeclampsia.[37–39] In PNH, maternal mortality has been reported to range between 8% and 21%, mostly occurring in the postpartum period, and thromboembolism being the primary cause. On the other hand, fetal mortality has been reported to range between 4% and 9%, mostly associated with premature births.[38,40,41] Close monitoring of all pregnant patients with PNH is thus recommended.

Pregnancy activates the complement cascade, with increased terminal complex formation in the third trimester.[14,42] Therefore, PNH has been considered a relative contraindication for pregnancy, and patients were usually discouraged from conceiving.[37,39] Because of the risk of life-threatening thrombotic complications, pregnant women with PNH in the pre-eculizumab era were to receive full anticoagulation during pregnancy and for at least 4–6 weeks postpartum.[38]

Several studies and case reports have described the use of eculizumab in pregnant PNH patients.[32,37,39,43–45] It has been noted that the dose of eculizumab required to block complement during the later stages of pregnancy is greater than that required in the nonpregnant state.[44] The increased activity of lysosomal enzyme, as well as the physiologic changes that occur during pregnancy, such as the physiologic expansion of intravascular volume, may account for the higher doses required.[32,39]

In pregnant patients, the eculizumab schedule has been modified by reducing the interval between eculizumab dose administration to ~7–12 days,[43–45] by administering higher doses of eculizumab (1,200 mg every 2 weeks during the third trimester),[37] or by using both modalities together,[32,39] according to physician discretion in order to control hemolysis as pregnancy progresses.[32,37,39,43–45]

The largest PNH study in pregnancy so far has been reported by Kelly et al in 2015.[39] Data were reported on 75 pregnancies in 61 women with PNH from the International PNH Interest Group and the International PNH Registry.[39] In 54% of

Samsung Bioepis Exhibit No. 1002
Page 11751

pregnancies that progressed past the first trimester, the dose or the frequency of use of eculizumab had to be increased. Requirements for transfusion of red blood cells increased during pregnancy, from a mean of 0.14 units per month in the 6 months before pregnancy to 0.92 units per month during pregnancy, and platelet transfusions were required in 21% of pregnancies, mostly administered at the time of delivery.[39] Furthermore, premature birth rate of 29% was reported. Two TE events were documented, and both occurred during the postpartum period, despite that thromboprophylaxis with low-molecular weight heparin was used in the majority of patients (88%). One of the thrombotic events occurred after a plasma infusion was administered to treat a postpartum hemorrhage. Plasma contains high levels of complement and can overcome the effects of eculizumab and thereby render the patient susceptible to complications of PNH. The use of plasma should probably be avoided if possible.

Initially, it was thought that eculizumab would cross the placenta and appear in breast milk.[2] However, subsequent studies reported that eculizumab does not appear to cross the placenta nor it is excreted in breast milk.[37,43–45] However, in a study on 21 cord-blood samples, eculizumab was detected in seven of the samples, whereas the drug was not detected in any of the ten breast milk samples tested.[39] Recently, two studies suggested that if eculizumab crosses the placenta, the level is not high enough to affect complement activation.[39,46]

Overall, studies highlighted the significance of regular and frequent monitoring of hemolytic parameters in PNH patients during pregnancy to detect early disease activity. In the end, there are no adequate and well-controlled studies of eculizumab in pregnant women, and a firm conclusion is difficult to be drawn. Nevertheless, all studies available suggested that eculizumab provided benefit for women with PNH during pregnancy, as evidenced by a high rate of fetal survival, a low rate of fetomaternal complications, and a reduced rate of blood transfusion, compared to pregnant PNH patients not treated with eculizumab.[37,39,43–45] It also appears that eculizumab can be safely used throughout pregnancy.

In summary, the recommended practice in pregnant women with PNH receiving eculizumab includes dose escalation and/or reduction in dose interval to control hemolysis, avoidance of the use of plasma if possible, and thromboprophylaxis with low-molecular weight heparin throughout the pregnancy up to 6 weeks following delivery, even with the use of eculizumab. However, whether combining thromboprophylaxis with eculizumab (specifically during the postpartum period) would be sufficient for preventing thromboembolism, or whether dose escalation is needed in high-risk patients, such as those having a prior history of thromboembolism or requiring C-section, still remain as questions.

Eculizumab in elderly

The median age at diagnosis of PNH is in the early 30s, and thus, patients aged >80 years were rarely enrolled, yet PNH can still present at any age.[5,6,37] In view of the known age-associated reduction in immune function and the effect of eculizumab on the suppression of the terminal complement pathway, one concern is that treatment with eculizumab may elevate the risk of infection in elderly patients.[10] In the TRIUMPH and SHEPHERD trials, there were no apparent age-related differences observed in patients aged 65 years or older treated with eculizumab. However, the number of those patients was only 15, and clearly, this number would not be sufficient to determine whether they respond differently than younger patients.[2]

A case report by Ooe and Nagai in Japan has described the use of eculizumab in an 86-year-old PNH patient.[10] Despite that poor prognosis was considered in this patient due to PNH-induced chronic renal failure and concomitant underlying myelodysplasia, eculizumab use was associated with rapid suppression of hemolysis, and significant improvement in both blood transfusion requirement and renal function from CKD stage 4 to stage 3 with no infections reported.

Although findings from available studies suggest that eculizumab can be used safely in elderly PNH patients with proved efficacy, the overall experience of eculizumab in geriatric population is still very limited, and decisions should be made on a case-by-case basis.

Risk of MDS/acute leukemia with eculizumab

An important concern with eculizumab is the possibility of clonal evolutions arising from a prolonged complement blockade. One study reported no significant difference regarding clonal evolution to MDS or acute myeloid leukemia in both eculizumab and control cohorts.[1] However, no conclusions can be drawn, since a longer follow-up will be necessary as the median time to clonal evolution is 10 years.[1] Furthermore, the rate of clonal myeloid evolution into MDS or acute leukemia was reported to be ~4% in PNH patients receiving eculizumab in another study,[8] which is a similar rate reported in PNH patients before eculizumab therapy.[6,25,26] Interestingly, in the study by Kelly et al, MDS and/or acute leukemia occurred within the GPI-negative clone of cells, indicating that the majority of hematopoiesis in these patients

Samsung Bioepis Exhibit No. 1002
Page 11752

was derived from PNH stem cells.[8] Long-term administration of eculizumab to Japanese patients with PNH showed that the burden of PNH disease and baseline characteristics were similar in patients with and without a history of bone marrow dysfunction such as AA or MDS.[18] No cases of clonal evolution were reported by Hillmen et al.[17]

In fact, the effect of eculizumab on the development of clonal diseases is still unclear, and long-term data are definitely required.

Paucity of long-term "real-world" data

In view of the rarity of PNH, and the relatively recent introduction and approval of eculizumab, long-term data are scarce. Perhaps, the best standardized long-term safety and efficacy data of eculizumab were presented by Hillmen et al.[17] They investigated 195 patients with PNH who had participated in one of three prospective parent trials: the Phase II pilot study and its extensions – TRIUMPH and SHEPHERD trials.[11–13] The median eculizumab treatment duration was 30.3 months, with a maximum duration of 66 months. Overall, long-term treatment with eculizumab resulted in sustained improvement in patient outcomes by rapidly reducing hemolysis and improving patient survival due to significant reduction in the frequency of severe and life-threatening morbidities, such as TE events and CKD with a favorable safety profile. However, "real-world" data with long-term follow-up are still lacking. The International PNH Registry (www.pnhregistry.com) is providing further opportunities to continue studying and understanding the long-term benefits of eculizumab in patients with PNH outside the clinical trial setting.[17]

Conclusion

The advent of eculizumab has resulted in a dramatic improvement of the natural history of PNH patients with improvement in virtually every aspect of these patients' lives. This is supported by the available data about which some limitations should be noted. First, the size of available studies is relatively small but dictated by the rarity of the disease. Second, most (if not all) research is funded by the pharmaceutical industry, which conveys an inherent risk of bias. Third, availability of randomized data is scarce, and many studies use historical controls, also risking the introduction of bias. Fourth, the treatment is very costly limiting access to it. In spite of these limitations, the data available so far are strong enough (and differences quite striking in some cases) to support the use of this therapy, although independent confirmatory data are sorely needed. Fifth, notwithstanding the available evidence, many questions remain unanswered, in particular regarding long-term safety (eg, infections, clonal evolution), optimal management of special populations (eg, pregnant, elderly), role of eculizumab in PNH/AA, and need/utility of clinical and laboratory monitoring, among others. Finally, since the main deterrent to a wide adoption of this therapy is mainly of an economic nature and many patients who might benefit from it are unable to access this treatment, patient support programs and access to public funding as well as novel and more accessible agents are highly desirable.

Disclosure

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Samsung Bioepis Exhibit No. 1002
Page 11753

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Samsung Bioepis Exhibit No. 1002
Page 11754

APPENDIX D

Priority Review

Prior to approval, each drug marketed in the United States must go through a detailed FDA review process. In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times – *Standard Review* and *Priority Review*. A Priority Review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).

A *Priority Review* designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

Significant improvement may be demonstrated by the following examples:

- evidence of increased effectiveness in treatment, prevention, or diagnosis of condition;
- elimination or substantial reduction of a treatment-limiting drug reaction;
- documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes; or
- evidence of safety and effectiveness in a new subpopulation.

FDA decides on the review designation for every application. However, an applicant may expressly request priority review as described in the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. It does not affect the length of the clinical trial period. FDA informs the applicant of a Priority Review designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement. Designation of a drug as "Priority" does not alter the scientific/medical standard for approval or the quality of evidence necessary.

Samsung Bioepis Exhibit No. 1002
Page 11756

APPENDIX E

COVER STORY

Eculizumab's triumph over PNH

The first-of-its-kind drug has provided patients with PNH their first viable treatment option.

HemOnc Today, August 25, 2008

The FDA approval of the orphan drug eculizumab in March 2007 marked a distinct change in how physicians were able to treat patients with paroxysmal nocturnal hemoglobinuria.

The results of several clinical trials have found that eculizumab (Soliris, Alexion) not only prevented the breakdown of red blood cells but also virtually eliminated many of the quality-of-life symptoms associated with PNH, **Wendell Rosse, MD**, told HemOnc Today.

"I have been with patients with PNH for more than 50 years now," Rosse said. "It has been fascinating to observe how by scientific method we have come to understand much of the disease and the causes of the disease. Now, we finally have a rational treatment based on that understanding."

HemOnc Today spoke with Rosse, professor emeritus at Duke University and Red Cells & Hemoglobinopathies Section Editor of the HemOnc Today Editorial Board, and several other experts in the field about how eculizumab has changed PNH and the questions that are still unanswered.

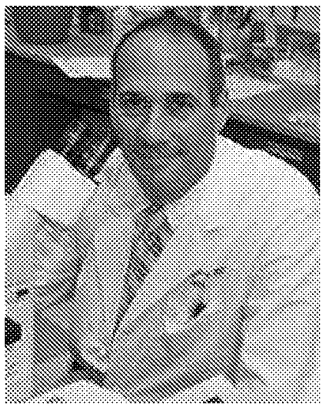
"Eculizumab has dramatically changed PNH," **Peter Hillmen, MD**, a consultant hematologist at the Leeds Teaching Hospitals NHS Trust in England, told HemOnc Today. "PNH is often diagnosed when people are in their 20s and 30s.

The symptoms of the disease — severe lethargy, abdominal pain, difficulty swallowing, hypertension and erectile problems for men — can persist for years.

"Until eculizumab arrived there was no specific treatment for PNH apart from transfusion and occasionally bone marrow transplant," he said.

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Bone marrow transplantation—which is the only thing that can cure the disease— has a 15% to 20% mortality rate, even with an identical donor, Rosse said. "It is not a very satisfactory alternative, although sometimes it is necessary," he said. "Beyond that, the only thing we had was symptomatic treatment. The hemolysis could be treated, but not very well, by high-dose prednisone, which could not be maintained on a daily dose." Iron replacement, transfusion, folic acid replacement and general medical care were all used to treat the symptoms of the disease, according to Rosse.



Robert A. Brodsky, MD, is Director, Division of Hematology, and Clara Lucas Lynn Chair in Medicine, The Johns Hopkins University. Photo by Frederick Dubs

DISCUSS IN OUR FORUM

How do you think eculizumab has changed PNH?

"We had very little to offer patients,"**Robert A. Brodsky, MD**, director of the division of hematology and Clara Lucas Lynn Chair in Medicine at The John Hopkins University, said in an interview. "I recently had a patient with PNH present in absolute crisis. Several years ago the only thing we would have had to offer him was narcotics and maybe fluids. Now that eculizumab is approved, all I have to do is call down to the pharmacy and tell them that we need to start the patient on this drug."

Prior to the drug's approval, patients with PNH had to cope with sometimes debilitating symptoms such as anemia, fatigue, thrombosis, hemoglobinuria, dyspnea, dysphagia, erectile dysfunction, hypertension and kidney problems for 10 to 15 years, with very few treatment options.

Patients with PNH whose symptoms are related to intravascular hemolysis will derive the most benefit from eculizumab, according to **Charles Parker, MD**, of the University of Utah School of Medicine, Salt Lake City. "This group of patients have a relatively large PNH clone and as a result of that have a great deal of intravascular hemolysis," he said. "Those patients, in addition to having anemia, will also have a variety of constitutional symptoms that greatly impact their quality of life."

By eliminating the intravascular hemolysis, eculizumab also ameliorates many of the symptoms of PNH.

Samsung Bioepis Exhibit No. 1002
Page 11759

"It relieves the symptoms of the disease in a way that many patients have not experienced since their diagnosis," Rosse said. "The esophageal spasm is gone, the abdominal pain is gone, the erectile dysfunction is gone, the hypertension is reduced and the kidney function is improved. … It makes a major difference in the way patients can live with the disease."

Testing an orphan drug



Charles Parker

The FDA approval of eculizumab was based on the results of clinical trials that examined the efficacy of eculizumab in treating transfusion dependence in patients with PNH.

"Although the leading cause of death in PNH is thrombosis, not everyone clots, so thrombosis could not be the primary endpoint of these trials," Brodsky said. "In addition, the median survival of the disease is long, 10 or 15 years, so survival could not be an endpoint. Therefore, the researchers examined hemolysis measured through transfusion avoidance as the primary endpoint."

An open-label pilot study was conducted from May to December 2002 in 11 transfusion-dependent patients with PNH. Patients received weekly IV infusions of 600 mg eculizumab for four weeks, followed by a 900-mg dose, and then 900 mg eculizumab every two weeks until week 12. The results of the study indicated a decrease in intravascular hemolysis, a decrease in transfusion requirements and an improved quality of life for patients receiving eculizumab.

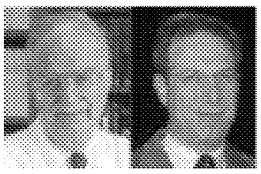
To test the drug under more rigorous standards, researchers from several institutions in the United States and Europe started the TRIUMPH trial. In this phase-3, double blind, randomized study, 87 patients were randomly assigned to either placebo or the pilot-study regimen of IV eculizumab for 24 weeks. Placebo was chosen instead of standard care because no method of treatment was considered an industry standard.

"The patients that went into TRIUMPH were a very restricted PNH group," Brodsky said. "They were patients who had to have a normal platelet count of over 100,000, and had to be fairly heavily red–cell-transfused dependent." Brodsky estimated that only about 10% to 20% of the patients with PNH that he sees would fit these eligibility criteria.

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Results of the TRIUMPH study were published in 2006 in The New England Journal of Medicine. Forty-nine percent of the patients in the eculizumab group achieved stabilization of hemoglobin levels in the absence of transfusion, compared with none in the placebo group (*P*<.001). Eculizumab reduced intravascular hemolysis compared with placebo and there were improvements in quality of life (*P*<.001) and fatigue scores (*P*<.001) in the eculizumab group compared with the placebo group.

"TRIUMPH showed a dramatic effect on reduction in intravascular hemolysis," Parker said. "It was the definitive study on the efficacy of eculizumab."



Wendell Rosse **Peter Hillmen**

Next, researchers began the SHEPHERD trial. This study was also phase-3 but was open label instead of randomized. It also relaxed its inclusion criteria to include patients with minimal transfusion requirements and lower platelet counts.

"The SHEPHERD study was a much larger, real-world population of PNH patients," Brodsky said. "This population probably captured more than 70% to 80% of patients with the disease. About 70% of patients on SHEPHERD would not have been eligible for TRIUMPH."

In this study, 97 patients were assigned to the pilot-study regimen of eculizumab for 52 weeks. Results showed an 87% reduction in hemolysis (*P*<.001). Treatment with eculizumab also resulted in an improvement in anemia and fatigue scores and a reduction in transfusion dependence.

"Both trials generated very compelling data for the use of the drug in patients with PNH whose clinical symptoms are related to intravascular hemolysis," Parker said.

Finally, all of the patients enrolled in these three studies were rolled over into an open-label extension study to examine the effect of eculizumab on thrombosis. "The major cause of morbidity and death in PNH is the tendency toward thrombosis," Rosse said. "This is because of abnormalities in the platelets. The activation of complement brings about the excessive thrombosis, particularly in the veins of the abdomen and liver."

Extension study

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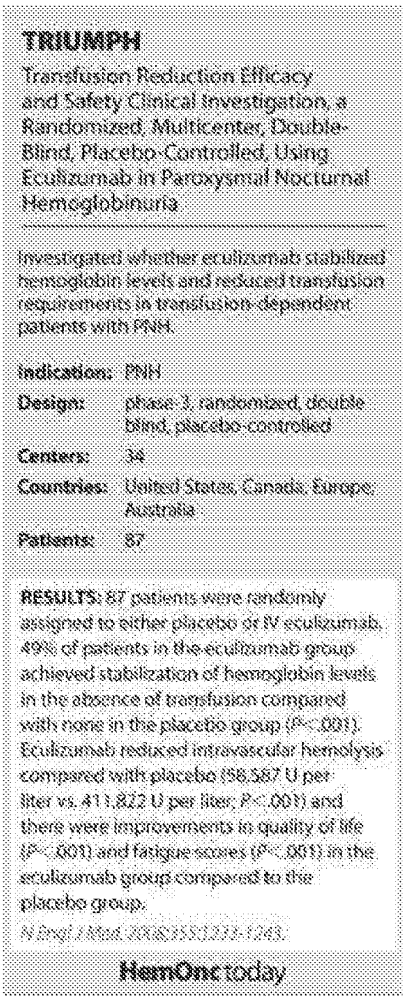
In the extension study, the researchers compared thromboembolism rate while on eculizumab with the pretreatment rate of thromboembolism in the same patients. At study end, the thromboembolism rate was 1.07 events per 100 patients years on eculizumab compared with 7.37 events per 100 patient years prior to treatment ($P<.001$). When the researchers compared an equal number of years before and during treatment, thromboembolism events were still reduced from 39 events prior to treatment to only three events on treatment ($P<.001$).

"It is very clear. There was a significant reduction in the number of thromboses in patients on eculizumab compared to patients not on the drug," Hillmen said.

However, the results of this trial still leave some room for questions, according to Brodsky. "Only about 40% to 50% of patients with PNH develop thrombosis, or it may take a patient four to five years from diagnosis before they have their first clot," he said. "In a perfect world you would want to do a randomized trial to examine thrombosis, but the disease is so rare that it would be too expensive and take too long to do a study like that." Despite that, Brodsky said that the drug greatly reduces, if not eliminates, the risk of thrombosis.

Despite the overwhelmingly positive results of the clinical trials leading to eculizumab's approval, treatment with the drug does have some drawbacks.

Samsung Bioepis Exhibit No. 1002
Page 11762



TRIUMPH

Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

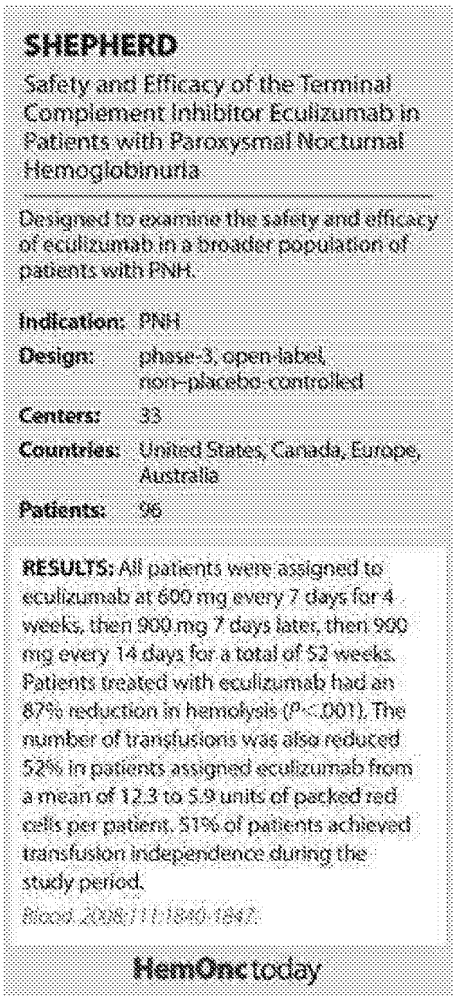
Investigated whether eculizumab stabilized hemoglobin levels and reduced transfusion requirements in transfusion-dependent patients with PNH.

Indication: PNH
Design: phase-3, randomized, double blind, placebo-controlled
Centers: 34
Countries: United States, Canada, Europe, Australia
Patients: 87

RESULTS: 87 patients were randomly assigned to either placebo or IV eculizumab. 49% of patients in the eculizumab group achieved stabilization of hemoglobin levels in the absence of transfusion compared with none in the placebo group ($P<.001$). Eculizumab reduced intravascular hemolysis compared with placebo (98,567 U per liter vs. 411,822 U per liter; $P<.001$) and there were improvements in quality of life ($P<.001$) and fatigue scores ($P<.001$) in the eculizumab group compared to the placebo group.

N Engl J Med. 2006;355:1233-1243.

HemOnc today



SHEPHERD

Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria

Designed to examine the safety and efficacy of eculizumab in a broader population of patients with PNH.

Indication: PNH
Design: phase-3, open-label, non-placebo-controlled
Centers: 33
Countries: United States, Canada, Europe, Australia
Patients: 96

RESULTS: All patients were assigned to eculizumab at 600 mg every 7 days for 4 weeks, then 900 mg 7 days later, then 900 mg every 14 days for a total of 52 weeks. Patients treated with eculizumab had an 87% reduction in hemolysis ($P<.001$). The number of transfusions was also reduced 52% in patients assigned eculizumab from a mean of 12.3 to 5.9 units of packed red cells per patient. 51% of patients achieved transfusion independence during the study period.

Blood. 2008;111:1840-1847.

HemOnc today

Pitfalls of PNH

"One of the major pitfalls of this drug is that it is intravenous," Brodsky said. Patients being treated with eculizumab have to get IV infusions of the drug every two weeks, potentially for the rest of their lives.

"If they stop, within a month they will have their disease back again," Brodsky said. "The IV infusion is given over 30 minutes and there is little in the way of side effects, but you still have to go to an infusion center and by the time you check in and get the IV started and the medicine comes up from the pharmacy you basically lose half a day every two weeks."

However, for patients with severe PNH, this inconvenience may be considered minor, according to Hillmen. "Prior to eculizumab, patients had to be transfused maybe once every week or two or once every few months," he said. "One of the

Samsung Bioepis Exhibit No. 1002
Page 11763

problems with PNH is that one day you can feel reasonably OK and the next day you cannot get out of bed. It's a very difficult disease to manage, so being treated by infusion every two weeks is trivial to those patients that are badly affected."

Another drawback to the treatment is that it is extremely expensive, Rosse said. "The estimated cost is about $380,000 per year per patient." Multiply that number over 20 or 30 years and it adds up.

"The disease is so rare that the insurers are not too bothered by it," Brodsky said. "But it is still a very expensive medication." The cost limits access to treatment in developing countries.

Finally, because eculizumab is an antibody against the C5 component of complement, patients with PNH treated with the drug are at an increased risk for *Neisseria* infections, particularly *Neisseria* meningitides, Rosse said.

"Everyone is vaccinated before they start the drug," Brodsky said. "The risk of *Neisseria* meningitides on this drug is about 0.5% per year. But if you have a 20-year-old woman on it, and she will be on it for the rest of her life, over the next 60 years she probably has a 30% chance of coming down with *Neisseria* meningitides."

FAST FACTS

Issues at Hand

1 Prior to the approval of eculizumab, patients diagnosed with paroxysmal nocturnal hemoglobinuria had few treatment options available to them and often had to deal with severe symptoms such as lethargy, erectile dysfunction and thrombosis for 10 to 15 years.

2 Eculizumab was approved in March 2007 based on the results of the TRIUMPH trial, which indicated that eculizumab helped patients achieve stabilization of hemoglobin levels, reduced intravascular hemolysis and improved quality of life.

3 Although eculizumab dramatically improves symptoms of PNH, it does not cure the disease. Physicians who are prescribing eculizumab to patients with PNH should still be aware of a patient's risk for *Neisseria* meningitides, thrombosis and extravascular hemolysis.

Questions unanswered

In addition to considering the possible pitfalls of prescribing eculizumab, there

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are other questions that physicians should consider when prescribing the drug.

"Eculizumab is not right for everyone with PNH and does require judgment on the part of the prescribing physician to identify the appropriate patient for treatment," Parker said.

"In patients with small PNH clones who don't have much hemoylsis, their main clinical problems are related to bone marrow failure. This is typically seen in the setting of some other bone marrow failure syndrome, particularly aplastic anemia and the refractory anemia variant of myelodysplasia," Parker said. "In those cases the focus of treatment is really on the bone marrow failure component of the disease."

In addition, a patient with a small proportion of abnormal cells probably does not need the medicine because their symptoms are not incapacitating, Rosse said.

The role of anticoagulants once a patient is started on eculizumab is also unclear, Parker added. Many patients with PNH are assigned an anticoagulant to prevent either first or recurrent thrombosis. However, according to Parker, there are little data to address whether or not to continue an anticoagulant in combination with eculizumab.

"In my opinion, anyone who has had a prior thromboembolic complication should remain on anticoagulation," Parker said. "You could probably make a better case for discontinuing anticoagulation in a patient who has never had a thromboembolic complication once they start eculizumab, but again that issue has not been addressed by appropriate clinical studies."

Physicians should also be aware that patients with PNH are at risk for both intravascular and extravascular hemolysis, according to Parker. "In patients who are treated with eculizumab, the intravascular hemolytic process is ameliorated almost completely by the drug, but there is another part of hemolysis ,called extravascular hemolysis, that is not blocked by eculizumab."

These patients will typically still require some transfusion and possibly other modification of their treatment to maintain an adequate hemoglobin level, according to Parker. "It is important for physicians to be aware that there are a

Samsung Bioepis Exhibit No. 1002
Page 11765

high percentage of patients that do continue to have ongoing hemolysis, although it is almost exclusively extravascular. As we use the drug more, we are seeing more of these patients.

"One thing that is important to understand is that eculizumab does not treat the underlying clonal proliferative disease in PNH. It only treats the hemolysis by blocking complement. Ultimately, the issue is that the drug is really just treating the symptoms rather than the underlying disease. We still need to understand the pathophysiology better so that we can eventually develop an approach to cure the disease, as opposed to just ameliorating the symptoms," Parker said. – *by Leah Lawrence*

POINT / COUNTER

Should patients remain on an anticoagulant after being assigned to eculizumab?

For more information:

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Samsung Bioepis Exhibit No. 1002
Page 11766

APPENDIX F

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Paroxysmal nocturnal hemoglobinuria

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare bone marrow failure disorder that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias. The absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, leads to uncontrolled complement activation that accounts for hemolysis and other PNH manifestations. GPI anchor protein deficiency is almost always due to somatic mutations in phosphatidylinositol glycan class A (*PIGA*), a gene involved in the first step of GPI anchor biosynthesis; however, alternative mutations that cause PNH have recently been discovered. In addition, hypomorphic germ-line *PIGA* mutations that do not cause PNH have been shown to be responsible for a condition known as multiple congenital anomalies-hypotonia-seizures syndrome 2. Eculizumab, a first-in-class monoclonal antibody that inhibits terminal complement, is the treatment of choice for patients with severe manifestations of PNH. Bone marrow transplantation remains the only cure for PNH but should be reserved for patients with suboptimal response to eculizumab.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal hematopoietic stem cell disorder that manifests with hemolytic anemia, bone marrow failure, and thrombosis.[1–3] One of the earliest descriptions of PNH was by Dr Paul Strübing, who in 1882 described a 29-year-old man who presented with fatigue, abdominal pain, and severe nocturnal paroxysms of hemoglobinuria.[4] Strübing deduced that the hemolysis was occurring intravascularly as the patient's plasma turned red following severe attacks of hemoglobinuria. Later reports by Marchiafava and Micheli led to the eponym, Marchiafava-Micheli syndrome, but it was Enneking, in 1925, who introduced the term paroxysmal nocturnal hemoglobinuria.[5] In 1937, Thomas Ham reported that PNH erythrocytes were hemolyzed when incubated with normal, acidified serum.[7] This seminal discovery resulted in the first diagnostic test for PNH, the acidified serum (Ham) test. The cell lysis following acidified serum appeared to be complement dependent because heat inactivation abrogated the reaction; however, it was not until 1954, with the discovery of the alternative pathway of complement activation, that complement was formally proven to cause the hemolysis of PNH red cells. In the 1980s, it was discovered that PNH cells display a global deficiency in a group of proteins affixed to the cell surface by a glycosylphosphatidylinositol (GPI) anchor. Two of the missing GPI anchored proteins (CD55 and CD59) regulate complement. A few years later, a genetic mutation (phosphatidylinositol glycan class A

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[*PIGA*]) responsible for the GPI anchor protein deficiency was discovered,[8-11] and most recently, a humanized monoclonal antibody that inhibits terminal complement activation has been shown to ameliorate hemolysis and thrombosis and improve quality of life in PNH patients.[12]

Pathophysiology

Hemolysis in PNH is complement mediated and is a direct result of PNH cells acquiring a deficiency of complement regulatory proteins. The disease begins with the expansion of a hematopoietic stem cell that has a severe deficiency or absence for GPI, a glycolipid moiety that anchors >150 different proteins to the cell surface (Figure 1). GPI anchor deficiency in virtually all PNH cases is the result of a somatic mutation in *PIGA*, an X-linked gene whose product is required for the first step in GPI anchor biosynthesis. This results in the deficiency of complement inhibitory proteins CD55 and CD59 that leads to chronic complement-mediated hemolysis of the GPI-deficient erythrocytes, as well as activation of platelets, monocytes, and granulocytes. There are >12 GPI-anchored proteins (GPI-APs) on hematopoietic cells, including blood group antigens, adhesion molecules, and complement regulatory proteins. GPI-APs also serve as receptors for proaerolysin, a pore-forming bacterial toxin secreted by *Aeromonas hydrophila*[13,14]; however, it is the absence of CD55 and CD59 that accounts for most of the clinical manifestations of PNH.[15,16] CD59 is a 19 000-Da glycoprotein that directly interacts with the membrane attack complex (MAC) to prevent lytic pore formation by blocking the aggregation of C9.[16] CD55, a 68 000-Da glycoprotein, functions to accelerate the rate of destruction of membrane-bound C3 convertase.[17] Hence, CD55 reduces the amount of C3 that is cleaved, and CD59 reduces the number of MAC that is formed (Figure 2). Central to these mechanisms is the alternative pathway of complement activation. In this pathway, C3 protein spontaneously hydrolyzes and leads to the formation of C3 convertase (this process is also known as tick-over). Hemolysis in PNH is chronic because of a continuous state of complement activation through tick-over, but paroxysms resulting in brisk hemolysis coincide with increases in complement activation triggered by surgery, infection, or inflammation. The mechanism of intravascular hemolysis begins with the increased activity of C3 convertases on the surface of PNH erythrocytes as a result of the lack of CD55. This leads to activation of C3, C5, and the terminal pathway of complement culminating in the formation of the MAC. Under normal conditions, formation of the MAC is under the regulation of CD59. The absence of CD59 on PNH erythrocytes leads to uncontrolled formation of the MAC resulting in complement-mediated intravascular hemolysis. Extravascular hemolysis in PNH begins with increased opsonization of PNH erythrocytes by complement fragments (mostly C3d). This is the result of the lack of CD55. Opsonized erythrocytes are cleared and destroyed by cells of the reticulo-endothelial system.[18] Extravascular hemolysis is often inconspicuous in the untreated PNH patient because signs and symptoms of intravascular hemolysis dominate. However, extravascular hemolysis can become the primary mechanism of hemolysis in patients treated with the terminal complement inhibitor, eculizumab (Figure 2).

Genetics

PIGA mutations that lead to PNH

GPI biosynthesis is a post-translational event that occurs in the endoplasmic reticulum.[19] There are >10 steps and ≥26 gene products required. The PIGA gene product is 1 of 7 proteins involved in the first step of GPI anchor biosynthesis. Theoretically, a mutation of any gene in the pathway could lead to PNH; however, until recently *PIGA* was the only mutated gene found in PNH patients.[8,10,11,20] This is because *PIGA* is on the X chromosome; thus, a single somatic mutation in a hematopoietic stem cell is sufficient to produce a PNH phenotype (men have a single X chromosome and women have only one active X chromosome due to lyonization). The remaining known genes in the GPI anchor biosynthethic pathway are on autosomes; thus, 2 hits disrupting function on both alleles would be necessary to interrupt GPI anchor synthesis. The 16-kb-long *PIGA* gene (mendelian inheritance in man [MIM] #311770) is located at

Samsung Bioepis Exhibit No. 1002

Xp22.1; it encodes for a protein that contains 484 amino acids (60 kDa).[9] An intronless pseudogene has been found on chromosome 12q21.[21] Numerous somatic mutations throughout the coding region of the *PIGA* gene have been described in PNH patients. There are no mutational hot spots, although exon 2, which contains almost half of the coding region, is the exon where most mutations occur. Most *PIGA* mutations are small insertions or deletions, usually 1 or 2 bp, which result in a frameshift in the coding region and consequently a shortened, nonfunctional product.[22] Although PIGA function is usually abolished by these frameshift mutations, missense mutations, have also been described where the product of the mutated *PIGA* gene has some residual activity.

PNH stem cell and bone marrow failure

To cause PNH, *PIGA* mutations must occur in a self-renewing, hematopoietic stem cell and must achieve clonal dominance.[23,24] The mechanisms leading to the clonal expansion and dominance of PNH stem cells remain a topic of continued investigation. Any hypotheisis must also account for the close pathophysiologic relationship between PNH and acquired aplastic anemia, a T cell-mediated autoimmune disease characterized by depletion of hematopoietic stem cells. The leading hypothesis is that PNH stem cells have a conditional survival advantage in the setting of an autoimmune attack (eg, aplastic anemia) that targets the bone marrow.[25-27] One hypothesis involves natural killer group 2, member D (NKG2D) -mediated immunity, which is activated by the expression of ligands such as major histocompatibility complex class I chain-related peptides A and B (MICA/B) and cytomegalovirus UL-16 binding proteins (ULBPs).[28,29] MICA/B are transmembrane proteins, but the ULBPs are GPI linked. NKG2D is a common receptor for MICA/B and the ULBPs. It is expressed on natural killer cells and $CD8^+$ cytotoxic T cells. Engagement of NKG2D with its ligands (MICA/B and ULBPs) promotes cell death of the NKG2D ligand-expressing cells by the $NKG2D^+$ effectors; thus, PNH cells would be relatively spared from effector cell-mediated killing because they lack GPI-anchored ULBPs. Recently, it has been proposed that CD1d-restricted, GPI-specific T cells might be responsible for the immune killing in PNH.[30] Under this scenario, PNH cells would be spared immune-mediated killing because CD1d has been shown to associate with GPI. Others have shown that mutations that confer a survival advantage to the PNH clone can contribute to clonal outgrowth.[31]

Other mutations that cause PNH

The absence of CD59 is most responsible for the clinical manifestations in PNH. Accordingly, rare cases of inherited mutations in CD59 leading to loss of CD59 on the cell surface have been well documented.[32,33] The phenotype of these patients mimics PNH in that they manifest with chronic intravascular hemolysis with paroxysmal flares of hemolysis and a propensity for thrombosis. Unlike PNH patients, those with inherited CD59 deficiency also present with relapsing immune-mediated peripheral neuropathy. In classical PNH, the CD59 deficiency is only found on the blood cells; in patients with germ-line CD59 mutations, CD59 is deficient in all cells in the body. These data suggest that germ-line CD59 deficiency is associated with demyelination via activation of terminal complement.

Recently a 44-year-old man with paroxysms of hemolysis, abdominal pain, fatigue, and headache was found to have GPI-AP-deficient blood cells in multiple lineages but wild-type *PIGA*. Ultradeep genomic sequencing revealed that the patient was born with a heterozygous germ-line splice site mutation in phosphatidylinositol glycan class T (*PIGT*) and later acquired a somatic 8-MB deletion involving the other *PIGT* allele in a myeloid stem cell.[34] PIGT is a component of the transamidase complex that is responsible for the attachment of the preassembled GPI anchors to proteins.[35,36] The second hit abolished *PIGT* function in myeloid stem cell, resulting in loss of GPI and clinical manifestations of PNH. The hemolysis in patients with inherited CD59 deficiency and the patient with the compound heterozygous mutation in *PIGT* responded to terminal complement inhibition with eculizumab.[34,37]

Samsung Bioepis Exhibit No. 1002
Page 11770

PIGA mutations that do not cause PNH

Somatic *PIGA* mutations arising from hematopoietic cells can be found at low frequency (~1 in 50 000 granulocytes) in healthy control subjects.[24,38] These mutations arise from colony-forming cells. Because normal and *PIGA* mutant colony-forming cells do not self-renew and only survive for 3 to 4 months, these cells cannot contribute to disease. PNH granulocytes (0.01-5%) can also be found in up to 25% of patients with myelodysplastic syndromes (MDS); however, unlike acquired aplastic anemia, it is extremely rare for PNH to evolve from MDS patients.[39-41] These small PNH populations in MDS appear not to be clinically relevant because the *PIGA* mutations in MDS are transient and also arise from colony-forming cells rather than hematopoietic stem cells.[42] In contrast, *PIGA* mutations in PNH patients and patients with acquired aplastic anemia arise from a multipotent hematopoietic stem cell and are found in all lineages, including T lymphocytes.[42]

Germ-line *PIGA* loss-of-function mutations were thought to be embryonic lethal.[43,44] Indeed, generation of *piga* knockout mice was unsuccessful. Targeted disruption of *PIGA* in human-induced pluripotent stem cells results in a block in embryonic development before mesoderm differentiation due to perturbed signaling through bone morphogenic protein 4.[45] Although germ-line *PIGA* null mutations are embryonic lethal, hypomorphic *PIGA* mutations are responsible for the X-linked form of a recently recognized syndrome known as multiple congenital anomalies–hypotonia-seizure syndrome 2 (MIM 300818).[46-49] Children born with hypomorphic *PIGA* mutations present with severe intellectual disability, dysmorphic facial features, seizures, and early death. Hypomorphic GPI-AP deficiency is most conspicuous on granulocytes. The red cells from these patients have little to no GPI anchor deficiency and no hemolysis; however, the severe phenotype associated with partial deficiency of GPI-APs demonstrates that 1 or more GPI-APs is critical in early development.

Diagnosis and classification of PNH

PNH is a clinical diagnosis that should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-APs on ≥2 lineages.[50,51] Loss of GPI-APs is detected after staining cells with monoclonal antibodies and a reagent known as fluorescent aerolysin (FLAER).[52] FLAER is a fluorescein-tagged proaerolysin variant that binds the glycan portion of the GPI anchor. Consensus guidelines for detecting GPI anchor-deficient blood cells that use FLAER in combination with several monoclonal antibodies have been published.[53] A classification scheme, proposed by the International PNH Interest Group, includes 3 main categories of PNH: (1) classical PNH, which includes hemolytic and thrombotic patients; (2) PNH in the context of other primary bone marrow disorders, such as aplastic anemia or myelodysplastic syndrome; and (3) subclinical PNH, in which patients have small PNH clones but no clinical or laboratory evidence of hemolysis or thrombosis.[54] This classification scheme has resulted in some confusion because varying degrees of bone marrow failure underlie virtually all cases of PNH; thus, the distinction between 3 categories may be difficult in some cases.

Clinical manifestations

Anemia

Anemia in PNH is often multifactorial and may result from a combination of hemolysis and bone marrow failure. Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in lactate dehydrogenase (LDH) is common in classical PNH. Patients with classical PNH often have a high (>50%) percentage of PNH granulocytes. PNH in the context of other primary marrow disorders usually refers to acquired aplastic anemia.[55] The anemia in these patients is primarily due to bone marrow failure; thus, these patients frequently have hypocellular bone marrows, more severe thrombocytopenia, small PNH clones, lower reticulocyte counts, and modest or no elevation in LDH levels. Thrombosis may occur but is less common than in patients with classical PNH. Patients with subclinical

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PNH are by definition asymptomatic with normal or near normal blood counts and few (usually <10%) PNH granulocytes. Often these patients have a diagnosis of mild aplastic anemia or have recovered hematopoiesis after treatment of acquired aplastic anemia.[56] Expansion of the PNH clone and PNH symptoms may accompany relapse of their aplastic anemia.

Thrombosis

Thrombosis leads to severe morbidity and is the most common cause of mortality in PNH.[57] Thrombosis in PNH may occur at any site; however, venous thrombosis is more common than arterial. For unclear reasons, common sites include intraabdominal (hepatic, portal, mesenteric, splenic, etc) and cerebral (sagittal and cavernous sinus) veins, with hepatic vein thrombosis (Budd-Chiari syndrome) being the most common site of thrombosis in PNH. Deep venous thrombosis, pulmonary emboli, and dermal thrombosis are also relatively common.

Thrombophilia in PNH is multifactorial. The absence of GPI-anchored complement regulatory proteins (CD55 and CD59) on PNH platelets leads to prothrombotic microparticles.[58] High levels of free hemoglobin leads to scavenging of nitric oxide (NO), which has been implicated in contributing to platelet activation and aggregation.[59] Complement activation also contributes to the prothrombotic tendency of PNH patients. Specifically, C5a may result in proinflammatory and prothrombotic processes by generating inflammatory cytokines such as interleukin-6, interleukin-8, and tumor necrosis factor-α.[60] Last, defective fibrinolysis resulting from deficiency or absence of GPI-linked proteins such as urokinase-type plasminogen antivator receptor,[61] heparan sulfate, and a GPI anchored coreceptor for tissue factor pathway inhibitor[62] have been speculated to contribute to the thrombophilic state in PNH. It is unclear which of these mechanisms contribute most to thrombosis in PNH; however, complement inhibition is the most effective strategy to stop thrombosis in PNH.[63,64] Thrombosis may occur in any PNH patient, but those with a large percentage of PNH cells (>50% granulocytes) are at greatest risk.[4,65] Anticoagulation and eculizumab are indication for acute thrombotic events; however, primary prophylactic anticoagulation has not been proven to be beneficial in PNH.[57] It is also unclear as to whether lifelong anticoagulation is necessary for secondary prophylaxis in PNH patients who are well controlled on eculizumab.[66]

Smooth muscle dystonia

Abdominal pain, esophageal spasm, dysphagia, and erectile dysfunction are common symptoms associated with classical PNH and are a direct consequence of intravascular hemolysis and the release of free hemoglobin.[59,65] Free hemoglobin is normally cleared by haptoglobin, CD163, and hemopexin. These clearing mechanisms are overwhelmed in PNH and lead to accumulation of high levels of free hemoglobin in the plasma and consequently depletion of NO. Free hemoglobin is a potent NO scavenger; the 2 molecules undergo a fast and irreversible reaction that results in the production of nitrate and methemoglobin. Normally, NO is synthesized by endothelial cells and functions to maintain smooth muscle relaxation and inhibit platelet activation and aggregation. The deficiency of NO as a result of scavenging by free hemoglobin contributes to deregulation of smooth muscle tone and platelet activation. Acccordingly, smooth muscle dystonias are more common in patients with a large PNH clone size.[65]

Other manifestations

PNH patients have a greater than sixfold increased risk of chronic kidney disease.[67] Renal tubular damage is caused by microvascular thrombosis and accumulation of iron deposits. Mild to moderate pulmonary hypertension is more common that previously recognized.[68,69] Raised pulmonary pressures and reduced right ventricular function caused by subclinical microthrombi and hemolysis-associated NO scavenging contribute to symptoms of fatigue and dyspnea.

Samsung Bioepis Exhibit No. 1002
Page 11772

Treatment

Terminal complement inhibition with eculizumab and allogeneic bone marrow transplantation (BMT) are the only widely effective therapies for patients with classical PNH. Corticosteroids can improve hemoglobin levels and reduce hemolysis is some PNH patients, but the long-term toxicity and limited efficacy limits enthusiasm for these agents.

Eculizumab

Eculizumab is a humanized monoclonal antibody that blocks terminal complement by binding to C5 and is the only US Food and Drug Administration-approved therapy for PNH.[12,70-72] The drug is administered intravenously every 7 days for the first 5 weeks and then biweekly thereafter. Eculizumab inhibits the formation of the MAC and in doing so compensates for the CD59 deficiency of PNH patients (Figure 1). It does not compensate for the CD55 deficiency; thus, eculizumab is highly effective in abrogating the intravascular hemolysis in PNH, but most PNH patients on eculizumab will continue to experience mild to moderate extravascular hemolysis due to C3d deposition on the PNH red cells.[18] This explains why >50% of PNH patients treated with eculizumab develop a positive direct antiglobulin test (C3 positive but IgG negative) in conjunction with a mild to moderate anemia and elevated reticulocyte count.[73] A common side effect of eculizumab, headache, appears to be a consequence of acutely increasing NO levels and is experienced by up to 50% of patients with the first dose.[74] Headache is rarely reported after the first several doses. The most serious risk of terminal complement blockade is life-threatening *Neisserial* infections (roughly 0.5%/year or 5% after 10 years). Thus, all patients treated with eculizumab should be vaccinated against *Neisseria.* In severe PNH cases, especially those with concomitant thrombosis, administration of eculizumab and vaccination can be performed on the same day. In such cases, 2 weeks of prophylactic therapy with ciprofloxacin is recommended. Penicillin prophylaxis is also advocated by some investigators, especially in younger patients, but this has not been formally studied.

Despite the limitations described above, eculizumab is highly effective in treating PNH and has changed the natural history of the disease.[63,71,72,75] The efficacy and safety of eculizumab has been demonstrated in 2 multinational phase 3 trials and a multinational extension study. The drug is highly effective in stopping intravascular hemolysis, eliminating or decreasing the need for red cell transfusions, improving quality of life, and reducing the risk of thrombosis, the leading cause of mortality from PNH. It has also been shown to improve renal function and to reduce prothrombotic and proinflammatory markers in PNH patients.[64,67] Unfortunately, the long-term outcome (median follow-up >7 years) of the phase 3 multinational studies has not been published; thus, we still do not know what percentage of these patients remain on the drug, have breakthrough hemolysis, and remain transfusion independent beyond 5 years.

Eculizumab is expensive and must be administered indefinitely for a sustained response; thus, patients with mild or no symptoms should be followed with watchful waiting. Severe anemia, thrombosis, frequent pain paroxysms, debilitating fatigue, worsening renal insufficiency, or dyspnea are good indications to initiate therapy.[51] Therapeutic decisions should not be based solely on the PNH clone size; however, patients with a large clone (>50% PNH granulocytes and >10% PNH red cells) coupled with a markedly elevated LDH (indicator of intravascular hemolysis) and a robust reticulocyte count (indicator of adequate bone marrow reserve) are most likely to benefit. Eculizumab does not alleviate bone marrow failure. Patients with ongoing bone marrow failure from aplastic anemia (hypocellular bone marrow, severe thrombocytopenia, and a relatively low reticulocyte count) are less likely to derive benefit from eculizumab. For these patients, therapy should address the underlying bone marrow failure.

The majority of classical PNH patients will respond to eculizumab; however, the hemoglobin response is highly variable and may depend on underlying bone marrow failure, concurrent inflammatory conditions, genetic factors, and the size of the PNH red cell clone following therapy.[76] In fact, 25% to 35% of patients continue to require red cell transfusions despite treatment with eculizumab. The most common reason for

Samsung Bioepis Exhibit No. 1002
Page 11773

continued transfusions is extravascular hemolysis. An increase in the percentage of PNH red cells after eculizumab therapy correlates with response but also with extravascular hemolysis. The PNH red cells that are protected by eculizumab are CD55 deficient and thus are susceptible to opsonization by C3 and premature removal in the spleen.[18] This explains why >50% of PNH patients (Coombs negative at diagnosis) become Coombs positive (IgG^- and $C3^+$) after treatment with eculizumab. Interestingly, up to 10% of PNH patients treated with eculizumab have a decrease in the percentage of PNH erythrocytes despite a large percentage of PNH granulocytes.[76] These patients achieve normal hemoglobin levels without the aid of transfusions. Pharmacogenetics has also been shown to influence response to therapy. Polymorphisms in the complement receptor 1 (*CR1*) gene are associated with response to eculizumab. CR1, through binding C3b and C4b, enhances the decay of the C3 and C5 convertases.[77] The density of CR1 on the surface of red cells modulates binding of C3 fragments to the GPI-negative red cells when C5 is inhibited. PNH patients with polymorphisms in *CR1* that lead to low CR1 levels (L/L genotype) are more likely to be suboptimal responders to eculizumab than patients with intermediate (H/L genotype) or high (H/H genotype) levels of CR1.

More recently, it has been discovered that a single missense C5 heterozygous mutation, c.2654G→A, prevents binding and blockade by eculizumab while retaining the functional capacity to cause hemolysis.[78] The polymorphism accounts for the poor response to eculizmumab in patients carrying the mutation. The c.2654G→A mutation is present in 3.5% of the Japanese population and has not yet been described in other ethnic groups.

Monitoring the PNH patient on eculizumab

Patients on eculizumab should be monitored with a complete blood count, reticulocyte count, LDH, and biochemical profile weekly for the first 4 weeks and then at least monthly thereafter (Table 1). A direct antiglobulin test should be obtained in patients with evidence of persistent hemolysis, and PNH flow cytometry should by obtained yearly because the PNH clone size may fluctuate over time. The LDH usually returns to normal or near normal within days to weeks after starting eculizumab; however, the reticulocyte count usually remains elevated and the hemoglobin response is highly variable. The reticulocyte count often remains elevated because most PNH patients on eculizumab continue to have some extravascular hemolysis due to deposition of C3 fragments on the PNH red cells. The hemoglobin response is largely dependent on the degree of extravascular hemolysis and the amount of underlying bone marrow failure.

In classical PNH patients who are transfusion dependent, a marked decrease in red cell transfusions is observed in most patients, with >70% achieving transfusion independence. Breakthrough intravascular hemolysis and a return of PNH symptoms occurs in <5% of PNH patients treated with eculizumab. This typically occurs 1 or 2 days before the next scheduled dose and is accompanied by a spike in the LDH level. If this occurs on a regular basis, the interval between dosing can be shortened to 12 or 13 days or the dose of eculizumab can be increased. It is also important to recognize that increased complement activation that accompanies infections (eg, influenza or viral gastroenteritis) or trauma can also result in transient breakthrough hemolysis. These single episodes of breakthrough hemolysis do not require a change in dosing because patients usually return to their baseline hemoglobin once the infection or inflammation has resolved.

BMT

BMT should not be offered as initial therapy for patients with classical PNH given the risks of transplant-related morbidity and mortality.[79,80] Exceptions are PNH patients in countries where eculizumab is not available. BMT is also a reasonable option for patients who do not respond to eculizumab therapy due heterozygous c.2654G→A mutations in C5 or the rare patient where eculizumab does not entirely block

Samsung Bioepis Exhibit No. 1002
Page 11774

intravascular hemolysis due to persistent inflammation.[76] Patients meeting criteria for severe aplastic anemia with PNH clones continue to be good candidates for BMT if they are young and have a suitable donor. A myeloablative conditioning regimen is not required to eradicate the PNH clone. Allogeneic BMT following non-myeloablative conditioning regimens can cure PNH.[81,82] Whether or not there is an advantage to the non-myeloablative approach will require further study; however, non-myeloablative regimens may be preferable in young patients seeking to maintain fertility or patients with moderate organ dysfunction who may not tolerate a myeloablative regimen. Because BMT is the only curative therapy available for PNH, continued use and investigation of this approach in selected patients is reasonable. Recent advances in mitigating graft-versus-host disease such as post-transplant high-dose cyclophosphamide may particularly effective in nonmalignant hematopoietic diseases such as PNH.[83,84]

Conclusions

Improved knowledge of the molecular and cellular underpinnings of PNH over the last 2 decades has resulted in greater understanding of the biology and natural history of PNH. Recent studies with the monoclonal antibody, eculizumab, demonstrate that terminal complement inhibition controls most of the symptoms and life-threatening complications of PNH. A large international PNH registry has been established. Data from this registry should help define the natural history of PNH since the introduction of therapy that inhibits terminal complement.[85] In the coming years, novel inhibitors of the alternative pathway of complement[86,87] and complement inhibitors with extended half-lives are likely to further improve quality of life for PNH patients.

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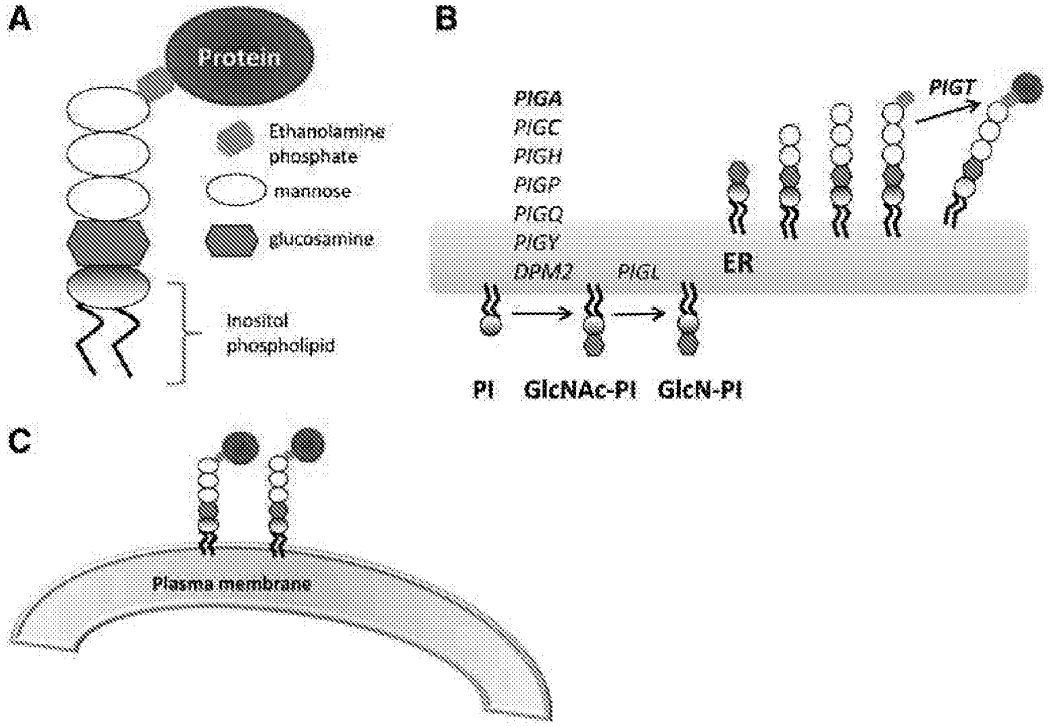
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Figures and Tables

Samsung Bioepis Exhibit No. 1002

Figure 1

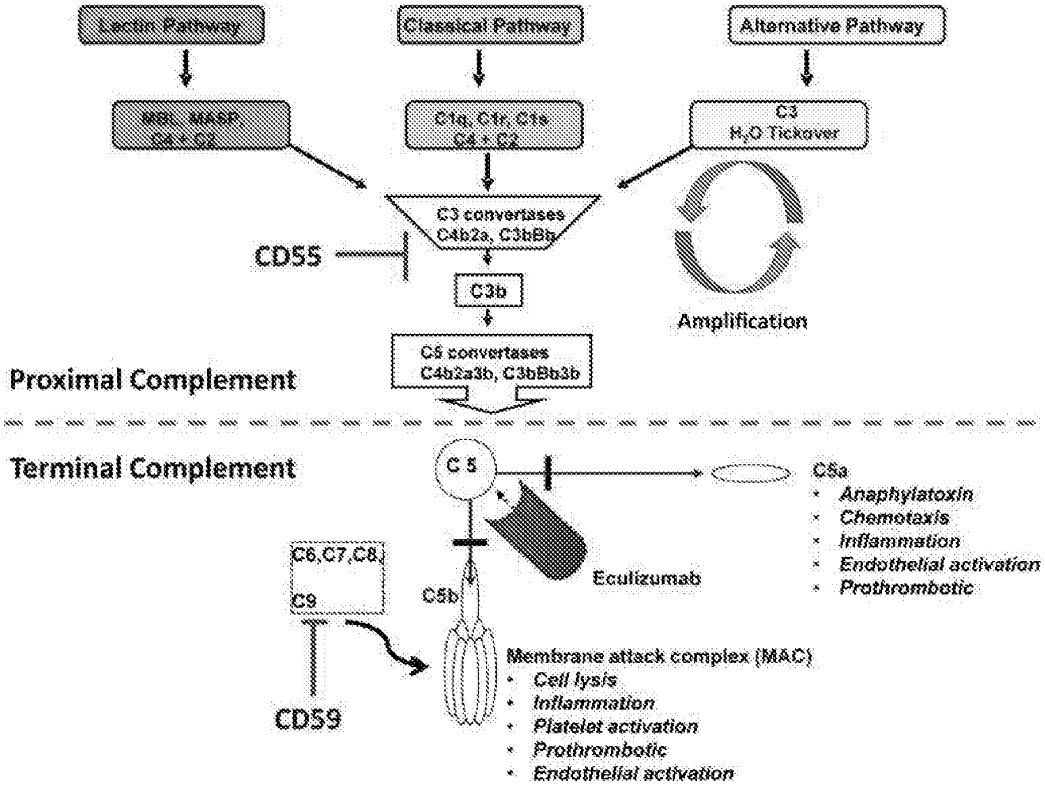


Open in a separate window

GPI anchor biosynthesis. (A) Core structure of the GPI anchor. The inositol-phospholipid (PI) is anchors into the lipid bilayer of the plasma membrane. The glycan core consists of a molecule of *N*-glucosamine, 3 manose molecules (Man), and a molecule of ethanolamine phosphate. The protein is covalently attached through an amide bond to an ethanolamine on the terminal mannose. (B) GPI anchor biosynthesis takes place in the endoplasmic reticulum. *PIGA* is 1 of 7 subunits involved in the first step of GPI anchor biosynthesis. There are ≥10 additional steps and >25 genes involved. After the protein is attached to the GPI anchor, the mature GPI-anchored protein goes to the Golgi, where fatty acid remodeling occurs and (C) eventually the GPI anchored protein is transported to the plasma membrane.

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Figure 2



Open in a separate window

Complement regulation and eculizumab. The lectin, classical, and alternative pathways converge at the point of C3 activation. In PNH, hemolysis is usually chronic because the alternative pathway is always in a low-level activation state through a process known as tick-over. Terminal complement begins with cleavage of C5 to C5a and C5b. C5b oligomerizes with C6, C7, C8, and multiple C9 molecules to form the MAC. CD55 inhibits proximal complement activation by blocking the formation of C3 convertases; CD59 inhibits terminal complement activation by preventing the incorporation of C9 into the MAC. The absence of CD55 and CD59 on PNH cells leads to hemolysis, inflammation, platelet activation, and thrombosis. Eculizumab inhibits terminal complement activation by binding to C5 and preventing generation of C5a and C5b.

Samsung Bioepis Exhibit No. 1002
Page 11783

Table 1

Monitoring the PNH patient on eculizumab

Monthly (draw tests before drug infusion)	Yearly
Complete blood count	PNH flow cytometry
Reticulocyte count	
Serum bilirubin	
Serum LDH	
If evidence of extravascular hemolysis (anemia and elevated reticulocyte count)	
Direct antiglobulin test	

Articles from Blood are provided here courtesy of **The American Society of Hematology**

Samsung Bioepis Exhibit No. 1002
Page 11784

APPENDIX G

MEET BILL

Diagnosed with PNH at 28 years old







In 1985, Bill had already been living with aplastic anemia for 10 years when chronic bouts of fatigue during exercise landed him in the hospital, where he was diagnosed with paroxysmal nocturnal hemoglobinuria (PNH). At the time, very little was known about PNH, an ultra-rare, life-threatening blood disorder in which uncontrolled activation of complement, a component of the normal immune system, leads to chronic hemolysis (destruction of the red blood cells).[1,2] In fact, Bill was only the second patient at his hospital to be diagnosed with the disease.

In addition to severe fatigue, Bill experienced stomach pain, kidney pain, dark urine, and dysphagia (difficulty swallowing). His symptoms made it difficult to eat and sleep. Soon, Bill became dependent on regular blood transfusions, which made day-to-day life all the more challenging. Still, as a married father of three with a demanding job, he pushed through each day and did his best to live life without focusing on his illness.

After years of managing his symptoms as best he could with blood transfusions—and periodic hospitalizations—Bill learned about Soliris® (eculizumab), a then investigational therapy that was undergoing clinical trials. He successfully enrolled in one of the trials in 2005, and soon began to see improvements in his symptoms. Specifically, Bill was able to stop receiving blood transfusions. He remains on treatment today.

Bill and his wife Nancy are now enjoying their retirement years and looking forward to what life with their three grown children will bring. As Bill says, "I've got one life to live and I'm going to live it to the fullest."

See Important Safety Information for Soliris below

View Soliris Prescribing Information (PDF)

References:

1. Hill A, Richards SJ, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2007 May;137(3):181-92.
2. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995 Nov 9;333(19):1253-8.

APPENDIX H

MEET JOE

Diagnosed with PNH at 24 years old







Joe was completing his Master's degree, engaged to be married, and on his way to becoming a professional mixed martial arts competitor when the symptoms began: unexplained fatigue, dark urine, back and stomach pain. After six weeks of numerous blood tests, Joe was referred to a hematologist who diagnosed him with paroxysmal nocturnal hemoglobinuria (PNH) – an ultra-rare, life-threatening blood disorder in which uncontrolled activation of the complement system leads to the chronic destruction of red blood cells.[1] Historically, approximately one-third of patients with PNH do not survive more than five years from the time of diagnosis.[2]

When Joe was diagnosed, he says that he felt like his dreams were nearly shattered. He was worried that he would not have a future with his fiancée and was told he would never be able to compete in contact sports again. With this news, Joe could have simply thrown in the towel, but he didn't. Instead, he made it his mission to educate himself and his family about PNH. Fortunately for Joe, his doctors were able to manage his PNH.

"I've never been one to back down in a fight, but when I was diagnosed with PNH, the prognosis was overwhelming. I had no choice but to view this disease as yet another challenge – one that I had to overcome. If anything, living with PNH has made me appreciate my time even more, and given me more drive to get back to doing what I love to do."

Today, Joe shares his story with other patients with PNH to give them hope for the future. Joe is living his life on his own terms; he married his college sweetheart, welcomed the birth of two daughters, and is back in his routine.

See Important Safety Information for Soliris below

View the Soliris Prescribing Information (PDF)

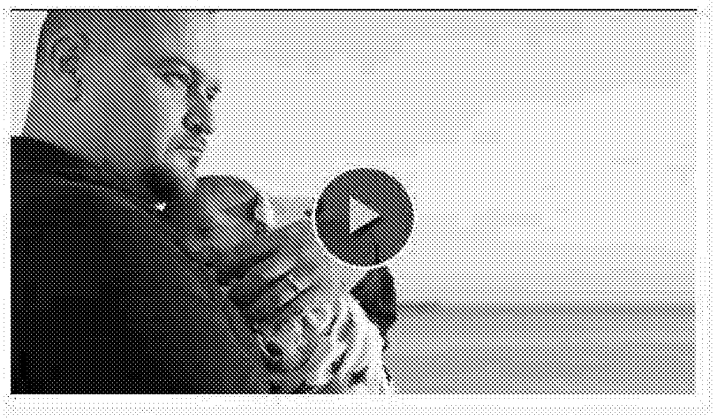
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2. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995 Nov 9;333(19):1253-8.

APPENDIX I

MEET VICTOR

Diagnosed with PNH at 27 years old







Victor worked in the concert security industry and was planning a future with his fiancé when he started experiencing unexplained bruising, fatigue and abdominal pain. A visit to his doctor led to a month-long stay in the hospital, where he was diagnosed with aplastic anemia. He continued to have symptoms such as dark urine, difficulty swallowing and back pain. After trying unsuccessfully for two years to treat his anemia, his doctor referred him to a specialist, who diagnosed him with paroxysmal nocturnal hemoglobinuria (PNH) – an ultra-rare, life-threatening blood disorder in which uncontrolled activation of the complement system leads to the chronic destruction of red blood cells.[1,2]

When he was first diagnosed in his mid-twenties, Victor says he was devastated and felt as if he had crawled into a cave. He was getting blood transfusions monthly, had little energy and was told he might only have 10 more years to live. The most difficult thing about having PNH was missing out on activities with friends and family, and the toll it took on him mentally. He became depressed. "People were doing things without me and I felt like I wasn't a part of normal society," he says. "I didn't want to talk to people."

Victor and his doctor discussed options and he began appropriate management of his PNH. He also joined a support group at his wife's suggestion, which radically changed his outlook.

"When I went to the first meeting and shared my story, I realized it's important to know you are not alone and that there is hope," Victor says. "It gave me a sense of comfort and encouragement. Now I know that others can benefit from my experience and I want to be an inspiration to them."

See Important Safety Information for Soliris below

View the Soliris Prescribing Information (PDF)

References:

1. Hill A, Richards SJ, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2007 May;137(3):181-92.
2. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995 Nov 9;333(19):1253-8.

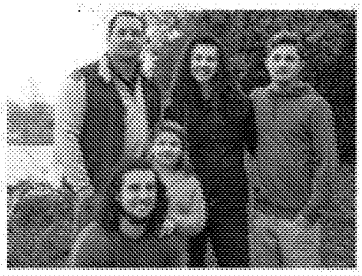
APPENDIX J

MEET RUTHIE

Diagnosed with PNH at 28 years old







Ruthie was a typical college senior at the University of Georgia in 1996 when she began experiencing chronic fatigue and frequent headaches. She initially chalked it up to long nights and not getting enough sleep, but eventually visited the campus clinic when her symptoms became severe. After reviewing her lab results, the clinic advised her to see an oncologist at a local hospital in Athens.

At first, Ruthie was misdiagnosed with leukemia and then with aplastic anemia. She initially received treatment for aplastic anemia, but her condition deteriorated over the next few months. Finally, in 1999, Ruthie was diagnosed with paroxysmal nocturnal hemoglobinuria (PNH)—an ultra-rare blood disorder in which uncontrolled activation of complement, a component of the normal immune system, leads to chronic hemolysis (destruction of the patient's red blood cells).[1,2]

By then, Ruthie was married with a newborn son, and she and her husband were scared to learn that PNH was a life-threatening illness that at the time had no approved treatments. Ruthie first learned about Soliris® (eculizumab) while it was in clinical trials, and began treatment shortly after it was approved by the U.S. FDA in 2007. Today, Ruthie continues to receive treatment, and has the energy to be an engaged and involved mother to three active kids.

As her husband David notes, "In the beginning, we didn't know how long Ruthie would be around, but today I'm excited for our children and for our future."

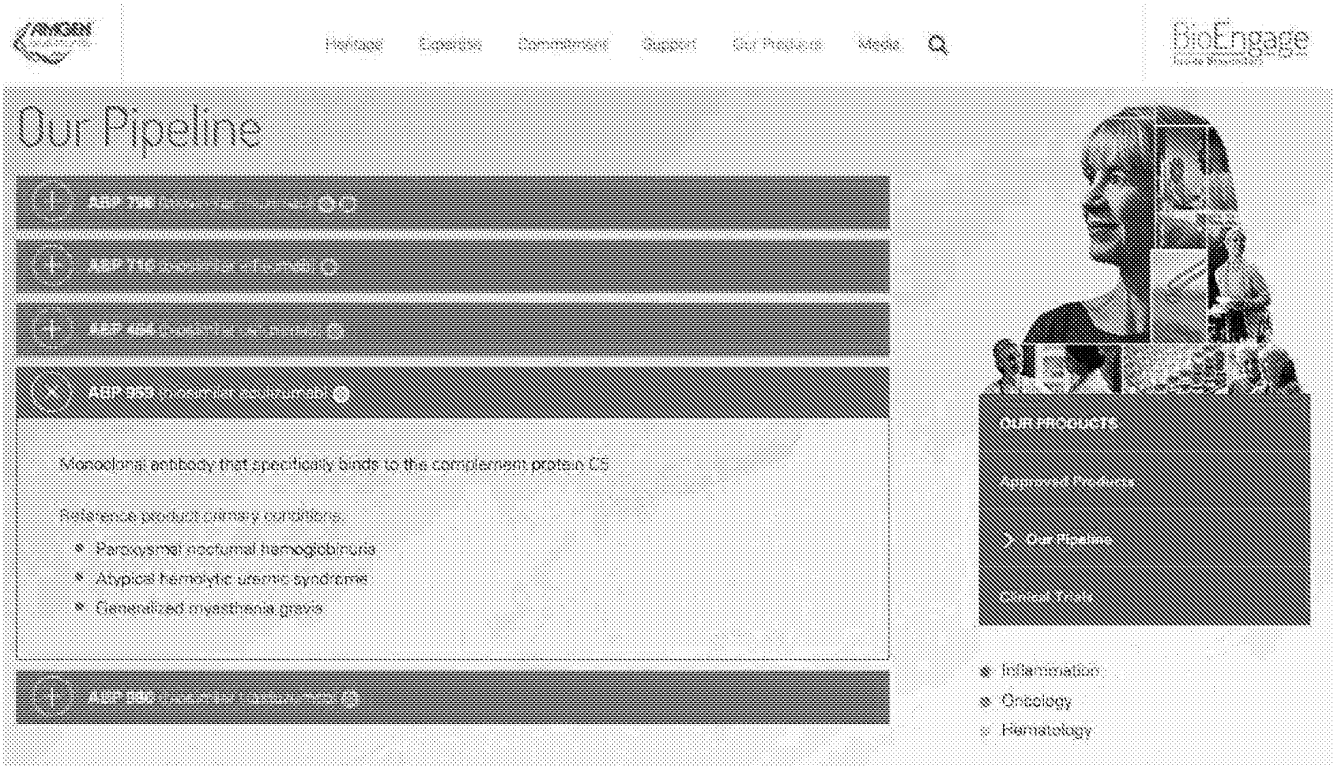
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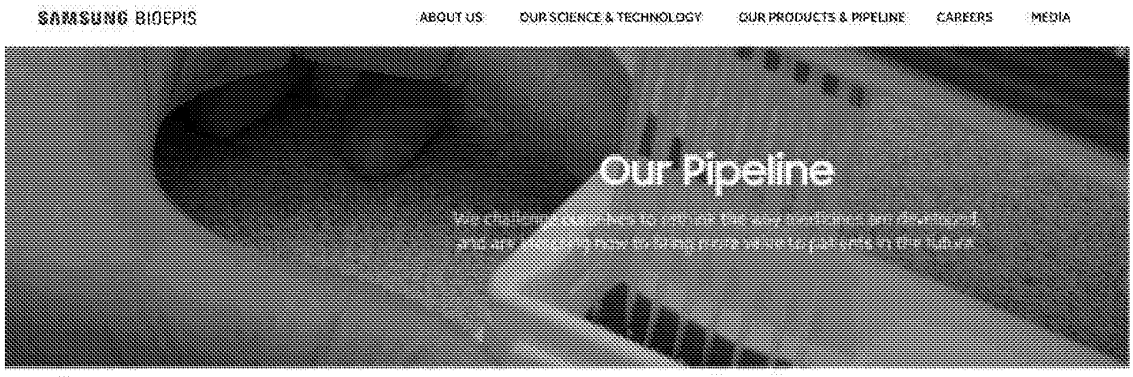
References:

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2. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995 Nov 9;333(19):1253–8.

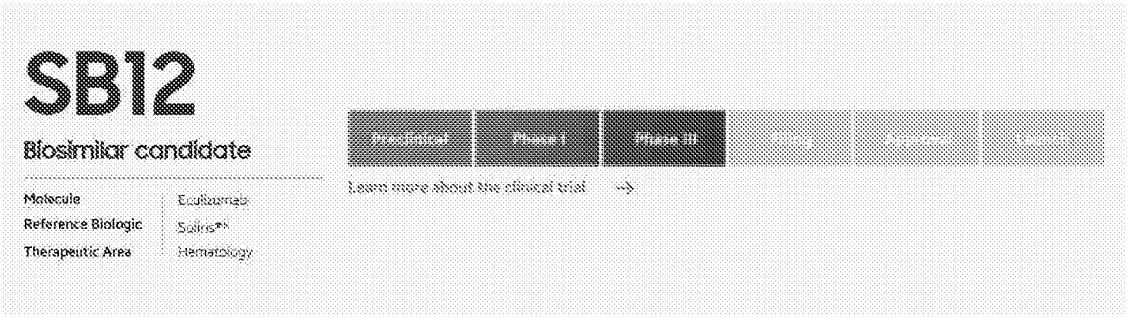
APPENDIX K


Heritage
Expertise
Commitment
Support
Our Products
Media
BioEngage
Our Pipeline
ABP 710
ABP 798
ABP 959
Monoclonal antibody that specifically binds to the complement protein C5
Reference product clinical conditions:
Paroxysmal nocturnal hemoglobinuria
Atypical hemolytic uremic syndrome
Generalized myasthenia gravis
ABP 885
OUR PRODUCTS
Approved Products
Our Pipeline
Clinical Trials
Inflammation
Oncology
Hematology

APPENDIX L



We strive for constant innovation and we are putting our passion and expertise to work in new areas including ophthalmology, gastroenterology, and hematology.



APPENDIX M

U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies
About Studies
Submit Studies
Resources
About Site

Trial record **1 of 2** for: sb12

Previous Study | Return to List | Next Study

A Study to Compare SB12 (Proposed Eculizumab Biosimilar) to Soliris in Subjects With Paroxysmal Nocturnal Haemoglobinuria

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04058158

Recruitment Status : Recruiting
First Posted : August 15, 2019
Last Update Posted : September 30, 2019

See Contacts and Locations

Sponsor:
Samsung Bioepis Co., Ltd.

Information provided by (Responsible Party):
Samsung Bioepis Co., Ltd.

Study Details | Tabular View | No Results Posted | Disclaimer

Samsung Bioepis Exhibit No. 1002
Page 11802

How to Read a Study Record

Study Description

Go to

Brief Summary:

This is a randomised Phase III, double-blind, multicentre, cross-over study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB12 and Soliris® in subjects with PNH.

Condition or disease	Intervention/treatment	Phase
Paroxysmal Nocturnal Hemoglobinuria	Drug: SB12 (proposed eculizumab biosimilar) Drug: Soliris (eculizumab)	Phase 3

Detailed Description:

Subjects will be randomised in a 1:1 ratio to either treatment sequence. Subjects randomly assigned to treatment with SB12 or Soliris® will receive 600 mg of eculizumab IV every week for first 4 weeks (initial phase) and 900 mg for the fifth week, followed by 900 mg every 2 weeks until Week 52. Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® and subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26.

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	50 participants
Allocation:	Randomized
Intervention Model:	Crossover Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Phase III Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics, and Immunogenicity Between **SB12** (Proposed Eculizumab Biosimilar) and Soliris® in Subjects With Paroxysmal Nocturnal Haemoglobinuria
Actual Study Start Date :	August 7, 2019

Samsung Bioepis Exhibit No. 1002
Page 11803

Estimated Primary Completion Date : May 2021
Estimated Study Completion Date : July 2021

Resource links provided by the National Library of Medicine

NIH NLM

Genetics Home Reference related topics:
Paroxysmal nocturnal hemoglobinuria

Drug Information available for: Eculizumab

Genetic and Rare Diseases Information Center resources:
Paroxysmal Nocturnal Hemoglobinuria Myelodysplastic Syndromes

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Treatment Sequence I Subjects who are randomised to initially receive SB12 will be switched to receive Soliris® at Week 26	Drug: SB12 (proposed eculizumab biosimilar) 600 mg IV every week for first 4 weeks and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter Drug: Soliris (eculizumab) 600 mg IV every week for first 4 weeks and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter
Experimental: Treatment Sequence II Subjects who are randomised to initially receive Soliris® will be switched to receive SB12 at Week 26	Drug: SB12 (proposed eculizumab biosimilar) 600 mg IV every week for first 4 weeks and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter Drug: Soliris (eculizumab)

Samsung Bioepis Exhibit No. 1002
Page 11804

Arm	Intervention/treatment
	600 mg IV every week for first 4 weeks and 900 mg for the fifth week, followed by 900 mg every 2 weeks thereafter

Outcome Measures

Go to

Primary Outcome Measures :

1. Hemolysis as measured by Lactate dehydrogenase (LDH) [Time Frame: Week 26]

   Parallel comparison

2. Hemolysis as measured by LDH [Time Frame: Week 52]

   Crossover comparison

Eligibility Criteria

Go to

Information from the National Library of Medicine NIH NLM

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Samsung Bioepis Exhibit No. 1002
Page 11805

Inclusion Criteria:

- Male or female aged 18 or older
- Eculizumab-naïve patients with PNH
- Presence of the PNH white blood cell (WBC) clone ≥ 10%
- Documented LDH level ≥ 1.5 x ULN at Screening
- History of transfusion for anaemia within 12 months prior to Screening or having PNH-related symptoms at Screening
- Subjects must be vaccinated against Neisseria meningitides

Exclusion Criteria:

- Previous treatment with any complement pathway inhibitors
- ANC ≤ 500/mm3 or Platelet count < 70,000/mm3
- History of meningococcal disease
- History of bone marrow transplantation
- Known or suspected active bacterial/viral/fungal infection within 30 days
- Stable use of erythropoietic, corticosteroids, heparin, warfarin before randomisation

Contacts and Locations

Go to

Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT04058158***

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Locations

Samsung Bioepis Exhibit No. 1002
Page 11806

India

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Gurgaon, Haryana, India, 122002

Korea, Republic of

Samsung Medical Center
Seoul, Korea, Republic of

Seoul National University Hospital
Seoul, Korea, Republic of

Taiwan

Tri-Service General Hospital
Taipei, Taiwan

Ukraine

Vinnytsia Regional Clinical Hospital n.a. M.I.Pyrohov
Vinnytsia, 'Vinnyts'ka Oblast, Ukraine, 21018

Municipal Institution Cherkasy Regional Oncology Dispensary of Cherkasy Regional Cour
Cherkasy, Ukraine, 18009

Communal Non-profit Enterprise Regional Center of Oncology
Kharkiv, Ukraine

Poltava Regional Clinical Hospital n.a. M.V. Sklifosovskyi
Poltava, Ukraine

Sponsors and Collaborators

Samsung Bioepis Co., Ltd.

More Information

Go to

Responsible Party:	Samsung Bioepis Co., Ltd.
ClinicalTrials.gov Identifier:	NCT04058158 History of Changes
Other Study ID Numbers:	SB12-3003
First Posted:	August 15, 2019 Key Record Dates
Last Update Posted:	September 30, 2019
Last Verified:	September 2019

Samsung Bioepis Exhibit No. 1002
Page 11807

Studies a U.S. FDA-regulated Drug Product: No
Studies a U.S. FDA-regulated Device Product: No

Additional relevant MeSH terms:

Hemoglobinuria	Signs and Symptoms
Hemoglobinuria, Paroxysmal	Anemia, Hemolytic
Proteinuria	Anemia
Urination Disorders	Hematologic Diseases
Urologic Diseases	Myelodysplastic Syndromes
Urological Manifestations	Bone Marrow Diseases

Samsung Bioepis Exhibit No. 1002
Page 11808

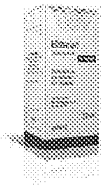
APPENDIX N

Generium

Elizaria®

INN: Eculizumab

A humanized monoclonal antibody that binds to the human complement protein C5 and inhibits the activation of complement-mediated cytolysis.



Elizaria® inhibits the activation of the terminal complement complex in humans, restores the regulation of complement activity in the blood.

Elizaria® prevents intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH), as well as excessive activation of the terminal complement complex in patients with atypical hemolytic uremic syndrome (aHUS).

Eculizumab treatment in patients leads to a significant decrease in hemolysis, frequency of thrombosis, dependence on blood transfusion in patients with paroxysmal nocturnal hemoglobinuria, and also significantly improves renal function in patients with atypical hemolytic uremic syndrome.

Indications for use:

- Paroxysmal nocturnal hemoglobinuria (PNH)
- Atypical hemolytic uremic syndrome (aHUS)

GENERIUM is the only company in the world that has developed and manufactured a biosimilar of Eculizumab.

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Tel: +7 495 988-47-84
Generium@Generium.ru

About

Careers

Our products

Ceagil-VIII®
Octofactor®
Immunofactor®
Blankitest®
Infibeta®
T-SPOT® TB
Tiperase®
Elizerie®
Glurazyme®
Revelase®

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Site development — AGIMA Tech support — Techart

APPENDIX O

BIOCAD
Biotechnology Company

CLINICAL STUDY PROTOCOL

Protocol Title:	A Double-blind, Randomized Clinical Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity of Single Intravenous Doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in Healthy Volunteers
Protocol ID:	BCD-148-3
Protocol Date:	13-Jun-2018
Protocol Amendment:	N/A
Date of Protocol Amendment:	N/A
Protocol Version:	1.0
Study Sponsor:	JSC BIOCAD, Russia Legal address: 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, Russian Federation, 198515 Mailing address: Petrovo-Dalneye, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 Tel.: +7(495) 992-66-28; Fax: +7 (495) 992-82-98
Sponsor's Contact Person Responsible for Signing the Protocol and Protocol Amendments:	Roman Alekseevich Ivanov, Vice President Research & Development Address: Petrovo Dalneye, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 E-mail: ivanov@biocad.ru Tel.: + 7 (495) 992-66-28 (ext. 154)
Sponsor's Responsible Medical Officer:	Arina Valerievna Zinkina-Orikhan, Medical Expert, Category III 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, Russian Federation, 198515 E-mail: zinkina@biocad.ru Tel.: +7 (812) 380-49-33 (ext. 744)

The information presented in this document is confidential and intended to be used solely by investigators, ethics committee members, and health care authorities. This information may not be transferred to any third party without prior written permission from JSC BIOCAD, except when necessary for obtaining subject's consent to participate in the study. These requirements come into effect upon signature of the Protocol.

Samsung Bioepis Exhibit No. 1002
Page 11812

TABLE OF CONTENTS

SIGNATURE PAGE....8
ABBREVIATIONS....9
TERMS AND DEFINITIONS....11
DOCUMENT HISTORY....13
SYNOPSIS....15
1. STUDY RATIONALE....24
1.1. Introduction....24
1.1.1. Complement system....24
1.1.2. Paroxysmal nocturnal hemoglobinuria....25
1.1.3. Atypical hemolytic uremic syndrome....27
1.1.4 Current treatment options for aHUS and PNH....28
1.1.5. Brief overview of the study product and its advantages....28
1.2. Name and description of the investigational product....28
1.2.1. Test drug....28
1.2.2. Reference drug:....29
1.2.3. Labeling of the study and reference products in this study....29
1.2.4. Posology and route of administration....30
1.3. Relevant non-clinical and clinical aspects....32
1.3.1. Non-clinical studies....32
1.3.1.1. Physicochemical properties and potency....34
1.3.1.2. Cytokine release by peripheral blood mononuclear cells in response to BCD-148....40
1.3.1.3. Potency of BCD-148 in murine intravascular hemolysis model....40
1.3.1.4. Single-dose IV toxicity and PK study of BCD-148 in cynomolgus monkeys....42
1.3.1.5. *In vitro* activity of BCD-148....43
1.3.1.6. Cross-reactivity study....44
1.3.1.7. Cross-reactivity study....44
1.3.2. Clinical studies....45
1.3.2.1. Overview of clinical methodology....45
1.3.2.2. Discussion of pharmacokinetic results....46
1.3.2.3. Discussion of pharmacodynamic results....49

Samsung Bioepis Exhibit No. 1002
Page 11813

1.3.2.4. Discussion of the safety results 52
1.3.2.5. Discussion of the Phase I study results 55
1.4. Summary of the known and potential risks and benefits to human subjects, if any (risk/benefit balance) 57
1.4.1. Benefit assessment 57
1.4.2. Risk assessment 57
1.5. Description and justification of route of administration, doses, and dosing regimen 62
1.5.1 Description and justification of the study design 62
1.5.2. Description and justification of the route of administration, doses, and dosage regimen 64
1.6. Clinical study compliance with regulatory requirements 64
1.7. Study population 65
1.8. References 65
2. STUDY PURPOSE AND OBJECTIVES 67
2.1 Study purpose 67
2.2 Study objectives 67
3. STUDY HYPOTHESIS 67
4. STUDY DESIGN 67
4.1. Primary and secondary outcome measures to be assessed in the study 67
4.1.1 PK endpoints 67
4.1.2 PD endpoints 68
4.1.3. Safety endpoints: 70
4.1.4. Immunogenicity endpoints 70
4.2. Study Design 70
4.3. Measures to minimize/eliminate bias 78
4.3.1. Inclusion of subjects in the study and assigning the screening and study IDs 78
4.3.2. Stratification procedure 78
4.3.3. Randomization procedure 79
4.3.4. Blinding 79
4.4. Description of the study treatment, dose and dosing regimen for the investigational product(s). Pharmaceutical form, packaging, and labeling of investigational products 79

Samsung Bioepis Exhibit No. 1002
Page 11814

4.1.4. Description of the study treatment, dose, and dosing regimen for the investigational product(s) 79
4.4.2. Pharmaceutical form, packaging, and labeling of investigational products 79
4.4.2.1. Test drug 79
4.4.2.2. Reference drug 79
4.4.2.3. Meningococcal vaccine 80
4.5. Expected duration of the study and subjects' participation in the study 81
4.6. Study periods 81
4.6.1 Study visits and procedures 81
4.6.2. Procedures by visits 84
4.6.3. Description of individual clinical, laboratory, and instrumental tests 89
4.6.3.1. Physical examination 93
4.6.3.2. Clinical data, demographics, and medication history 93
4.6.3.3. Vital signs 94
4.6.3.4. Hematology, chemistry, coagulation test, and urinalysis 94
4.6.3.5. Blood tests for infection markers 95
4.6.3.6. Eculizumab assay, hemolytic complement activity assay, and immunogenicity assessment 95
4.6.3.6.1. Eculizumab assay in the serum 103
4.6.3.7. Chest X-ray and fluorography 103
4.6.3.8. ECG 103
4.6.3.9. Urine test for psychotropic and recreational drugs, psychoactive medications 103
4.6.3.10. Saliva alcohol test 103
4.6.3.11. Unscheduled visits 104
4.7. Stop rules and criteria for premature withdrawal for study subjects, study periods, and study as a whole 105
4.8. Drug accountability 105
4.1.8. Handling of investigational products 106
4.9. Procedure for code keeping and unblinding 106
4.10. Data entered directly into the CRF (i.e. no prior written or electronic record of data) and considered as source data 107
5. ELIGIBILITY AND EXCLUSION OF STUDY SUBJECTS 107
5.1. Inclusion criteria 107

Samsung Bioepis Exhibit No. 1002
Page 11815

5.2 Exclusion criteria 108
5.3. Withdrawal criteria 109
5.3.1. Replacing drop-outs 109
5.4 Follow-up of subjects withdrawn from the study or subjects who discontinued the study treatment but remain in the study for follow-up 110
5.4.1. Follow-up of subjects who received at least one dose of BCD-148/Soliris® 110
6. Administration of the investigational product 110
6.1 Route of administration used in the study 110
6.2. Dose modification for the study drug 110
6.3. Overdose 110
6.4. Concomitant therapy, medications allowed and prohibited by the Protocol 111
6.5. Compliance with study procedures 111
6.6. Compliance 112
7. PK AND PD ASSESSMENT 112
7.1. List of pharmacokinetic parameters 112
7.2. List of pharmacodynamics parameters 113
8. SAFETY ASSESSMENT 113
8.1 List of safety endpoints 113
8.2 Definitions 113
8.2.1 Adverse events 113
8.2.2 Serious adverse events 114
8.2.3. Unexpected adverse drug reaction 115
8.3 Methods and time of assessment, recording and analysis of safety parameters 115
8.3.1 Time windows for analysis of safety parameters 115
8.3.2 Methods and timeframes for assessment and recording of safety parameters 116
8.4 Requirements for reports. Documenting and reporting AEs and completing AE Report Forms 117
8.4.1 Documenting AEs/SAEs 117
8.4.2 AE/SAE reporting 117

Samsung Bioepis Exhibit No. 1002
Page 11816

8.5 Information concerning the method and duration of follow-up for study subjects after the onset of AE/SAE 120
9. STATISTICAL METHODOLOGY 121
9.1 Calculation of PK and PD parameters 121
9.1.1. PK parameters 121
9.1.2. PD parameters 122
9.2. Statistical methods 123
9.3. Justification of sample size, including reasoning or calculations to justify statistical power and clinical justification of the study 124
9.4. Statistical analysis steps and timelines for reports 126
9.5. Study termination criteria 127
9.6. Handling of missing, unevaluable or uncertain data 127
9.7. Reporting any deviations from the initial statistical plan 127
9.8 Selection of subjects for analysis 127
10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 128
11. QUALITY CONTROL AND QUALITY ASSURANCE 128
11.1. Data quality assurance 128
11.2. Investigator adherence to the Protocol 128
11.3. Investigator responsibility to comply with the Protocol 129
11.4. Study monitoring 129
11.5. Data management and quality control 130
11.6. Study termination 130
12. ETHICS 131
12.1. Ethical aspects of the study 131
12.2. Confidentiality of study subjects 131
13. DATA HANDLING AND RECORD KEEPING 132
13.1. Record keeping at the study site 132
13.2. Confidentiality of data 132
13.3. Collection of data 133

Samsung Bioepis Exhibit No. 1002
Page 11817

14. FINANCE AND INSURANCE.....133

Samsung Bioepis Exhibit No. 1002
Page 11818

SIGNATURE PAGE

To Protocol v. #1.0 of 13-Jun-2018: A Double-blind, Randomized Clinical Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity of Single Intravenous Doses of BCD-148 (JSC BIOCAD, Russia) And Soliris® in Healthy Volunteers

I, the undersigned, agree with the following:

1. I have read the Protocol, I agree with all the provisions of the Protocol, and I will conduct the study as outlined in this Protocol, the ICH GCP, Russian National Standard GOST R 52379-2005, and regulations of the state authorities.
2. I will ensure no deviations from the Protocol to take place without prior written agreement from the Sponsor and documented approval from the Council for Ethics or the local ethics committee, except where necessary to eliminate an immediate hazard to the study participants.
3. I confirm that all staff members are appropriately qualified for the study conduct, the study site has all necessary equipment, and I, the study investigator, have sufficient time to conduct this study in accordance with the Protocol.
4. I will take all due measures to ensure that all staff members involved in the conduct of this study are informed about their obligations in accordance with this Protocol.
5. I agree to fully cooperate with audits and inspections conducted in accordance with the rules established by the Sponsor and the state regulatory authorities.
6. I understand that the text of this Protocol and all other materials and results of this study are confidential and proprietary to the Sponsor. I agree not to disclose any of this information to a third party except unless required to do so by the law of the Russian Federation.

Principal Investigator:

_____
Signature

_____
Full Name

_____
Date

R.A. Ivanov, Vice President R&D JSC BIOCAD

_____
Signature

_____
Date

Samsung Bioepis Exhibit No. 1002
Page 11819

ABBREVIATIONS

ABEC	The area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h.
AE	Adverse event
aHUS	Atypical hemolytic uremic syndrome
AlkPh	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the Concentration *vs*. Time curve
AUMC	Area under the first moment curve
BAbs	Binding antibodies
BCD-148	A monoclonal antibody developed by JSC BIOCAD to target the complement component C5.
BP	Blood pressure
C_{max}	Maximum drug concentration in the serum
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee

Samsung Bioepis Exhibit No. 1002
Page 11820

Ig	Immunoglobulin
IMU	Instruction for Medical Use
INN:	International non-proprietary name
JSC	Joint Stock Company
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MABEL	Minimal Anticipated Biological Effect Level
MBEDL	Minimal Biological Effect Dose Level
MP	Medicinal product
MTD	Maximum tolerated dose
NAb	Neutralizing antibodies
NBEDL	No Biological Effect Dose Level
NOAEL	The No Observed Adverse Effect Level
PD	Pharmacodynamics
PK	Pharmacokinetics
PNH	Paroxysmal nocturnal hemoglobinuria
RAMS	Russian Academy of Medical Sciences
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard Operating Procedure
$T_{½}$	Elimination half-life
TD	Test drug
Th	T-helper cells
ULN	Upper limit of normal
WHO	World Healthcare Organization
TMA	Thrombotic microangiopathy

Samsung Bioepis Exhibit No. 1002
Page 11821

TERMS AND DEFINITIONS

Term	Definition
Investigational product	This term includes the test drug, comparator, or placebo. A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use
Study/test product/drug	A pharmaceutical forms the properties of which are investigated in this clinical trial.
Comparator/reference product/drug	An active control being tested as a control in the clinical study to reduce the bias of assessments, keep the study therapy blind, and assess the internal validity of the study and/or comparative effects of the study product.
Case Report Form (CRF)	A printed or electronic document designed to record all the protocol-required information to be reported to the Sponsor on each study subject.
Investigator's Brochure	A compilation of the clinical and non-clinical information on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.
Subject identification code / subject ID |__|__|-|__|__|__|	A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data. Usually, the subject ID is a five-digit code where the first two digits are the site number and the last three digits are assigned sequentially to each participant as he/she enters the study.
Screening ID |__|__|-|__|__|	A unique code assigned to each study subject who have signed the informed consent. The first two digits are the site number, and the last two digits are assigned sequentially to each subject as he/she gets enrolled at this particular study site.
Assessment	The procedure of obtaining the data that have to be gathered in this trial.
Enrollment in the study	A time point when the subject signs the informed consent.
Other therapy used in the study	Any medications other than the investigational product that are used to perform the study procedures. This includes, for example, the drugs used as part of the combination therapy.
Premature withdrawal	The time point when the subject stops participation in the study before the planned investigational treatment is completed and/or assessments

Samsung Bioepis Exhibit No. 1002
Page 11822

Term	Definition
	are performed. No further assessments are performed beyond this point except for monitoring of the survival and/or disease progression in certain trials. If the subject discontinues the study due to an event planned by the Protocol (for example, a complete response), he/she is considered a dropout anyway.
End-of-study	The time point when the subject attends his/her last study visit.
Study therapy	Any medication or a combination of medications used in any arm as part of study procedures, including concomitant medications and introductory therapy before the active medication.
Concomitant therapy	Therapy with any drugs included in the study therapy, except for the test drug and reference drug. For example, drugs used for combination therapy, pre-medication etc.
Discontinuation of study therapy	The time point when the investigational therapy is terminated regardless of what caused the termination. It does not necessarily coincide with subject's withdrawal from the study.
Variable	An identifier used for the data analysis and derived directly or indirectly from the protocol-specified assessments at pre-determined time points.

Samsung Bioepis Exhibit No. 1002
Page 11823

DOCUMENT HISTORY

N/A.

Samsung Bioepis Exhibit No. 1002
Page 11824

Names/positions of investigators responsible for the study conduct. Contacnt information of the study sites

#	Title of the study site (center)	Address	Phone	Full name of the PI	Job Title of the PI
1.	Limited Liability Company Research Center Eco-Bezopasnost (OOO Research Center Eco-Bezopasnost)	65, Pr. Yurija Gagarina, St. Peterburg, Russian Federation, 196143	+7 812-500-52-03, +7 812-325-03-05, +7 812-500-52-03	Konstantin Anatolievich Zakharov	Deputy Director

Name, job title, address and telephone number of the qualified physician responsible for taking medical decisions

N/A.

Names and addresses of clinical or other medical and/or technical services and/or organizations involved in the study

#	Institution, role in the study	Address	Phone	Full name of responsible person	Job Title of responsible person
1.	Bioanalytical Laboratory, Analytical Development Department, JSC BIOCAD PK, PD, and IG study	34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, Russian Federation, 1985155	+7(812) 380-49-33	Aleksander Valerievich Novikov	PhD, Analytical Development Director at JSC BIOCAD

Samsung Bioepis Exhibit No. 1002
Page 11825

SYNOPSIS

SYNOPSIS	
Protocol ID:	BCD-148-3
Study Title	A Double-blind, Randomized Clinical Study to Compare the Pharmacokinetics, Pharmacodynamics, Safety, and Immunogenicity of Single Intravenous Doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in Healthy Volunteers
Study Phase:	Phase I
Study Sponsor:	JSC BIOCAD Mailing address: Petrovo-Dalneye, Krasnogorskiy District, Moscow Region, Russian Federation, 143422 Tel.: (495) 992 66 28 (ext.193), fax: +7 (495) 992 82 98. Legal address: 34-A, Ul. Svyazi, Strelna, Petrodvortsoviy District, St. Petersburg, Russian Federation, 198515
Test Drug:	BCD-148 (INN: eculizumab), concentrate for solution for infusion
Reference Drug:	Soliris® (INN: eculizumab), concentrate for solution for infusion
Study Purpose and Objectives:	**Purpose:** To perform a comparative assessment of the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of a single intravenous infusion of BCD-148 and Soliris® in healthy volunteers. **Study objectives:** 1. To determine and compare the PK parameters of BCD-148 and Soliris®, each given as a single intravenous infusion 2. To determine and compare the PD parameters of BCD-148 and Soliris®, each given as a single intravenous infusion 3. To determine and compare the adverse event profile with a single infusion of BCD-148 and Soliris® 4. To evaluate and compare the proportion subjects positive for binding and neutralizing anti-drug antibodies in the BCD-148 and Soliris® arms after a single drug infusion
Study Population	Healthy male volunteers aged from 18 to 45 years (inclusive)
Planned Sample Size	78 healthy volunteers (39 in each trial arm)
Study Design	This is a double-blind, randomized clinical study to compare

Samsung Bioepis Exhibit No. 1002
Page 11826

SYNOPSIS	
	the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of single intravenous doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in healthy volunteers. The suggested double-blind randomized parallel-group design that utilizes a drug with demonstrated efficacy (reference drug) as an active control is aimed at proving pharmacokinetic equivalence of a biosimilar BCD-148 (test drug) and Solaris® (reference drug) in terms of the key PK parameters. This is a common approach in the development of biosimilars, which complies with the Russian[1] and international[2] regulations. The EMA[3,4] guidelines state that for long half-life products (such as eculizumab) a parallel-group study design is preferred to crossover. **Randomization** It is planned to randomize 78 adult healthy volunteers who then will be assigned at a 1:1 ratio to one of the two treatment arms: 39 subjects in the BCD-148 arm and 39 subjects in the Soliris® arm. During the study, each volunteer will receive a single IV infusion of 900 mg BCD-148 (test drug) or 900 mg Soliris® (reference drug). Before enrollment, all volunteers will be given all the information about this clinical study, its purpose, and the risks associated with study participation. After signing the informed consent form (ICF), each subject will undergo a screening examination (no longer than 20 days), which is to find out whether the subject meets the eligibility criteria. **Study periods** 1. Screening period will include 2 visits and 1 phone call. • *Screening Visit 1/ Days -20 to -18* ICF signing and eligibility assessment (interview, history taking, physical examination, and laboratory and instrumental investigations). • *Visit 2/ Day -17* It has been shown that patients treated with eculizumab may have increased susceptibility to infections caused by encapsulated bacteria, especially to meningococcal infection. Therefore, all subjects

[1] A.N. Mironov, V.G. Kukes, V.I. Petrov, A.L. Kuznetsov, D.V. Goryachev, R.R. Niyazov, A.B. Prokofyeva, S.V. Nedogoda, M.Yu.Frolov, A.Shnayder. Bioequivalence evaluation for generic medicinal products // Guidance on evaluation of medicinal products Vol. I – M.: Grif and K, 2013.
[2]Rules for investigation of biologics (Eurasian Economic Commission)
https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78
[3]Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010, 2012.
[4]Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)

Samsung Bioepis Exhibit No. 1002
Page 11827

SYNOPSIS	
	who are considered eligible for the study will be preventively vaccinated against *Neisseria meningitidis* to ensure their safety. • *Screening phone call / Day -15* The study team member interviews the subject by phone to monitor for any post-vaccination complications. • *Screening Visit 3/ Days -3 to -1* This visit occurs at least 14 days post-vaccination. This time is enough for a subject to develop post-vaccination immunity. During this visit, each subject will be re-evaluated for eligibility based on their clinical and laboratory results. Hematology and chemistry tests will be performed, and the subjects will be assessed for any post-vaccination complications that may interfere with further participation in the study. 2. Main study period The duration of the main study period is 59 days, including the day of the BCD-148/Soliris® infusion. During this period, multiple blood collections will be performed for assessment of PK/PD, safety, and immunogenicity of eculizumab. Because of multiple blood collections and the necessity of monitoring the safety and tolerability of eculizumab, each subject will stay in a hospital for the first 48 h post-infusion. Blood samples will be collected from study subjects for the PK study (assessment of eculizumab concentration in the serum) and PD study (hemolytic complement activity CH50). All blood collections will be performed according to the study procedure schedule: – 5 min before the infusion of BCD-148/Soliris® – 5 min, 4 h (±5 min), 8 h (±10 min), 12 h (±15 min), and 24±1 h post-infusion – 2 days (48±1 h), 3 days (72±2 h), 5 days (120±3 h), 8 days (192±4 h), 11 days (264±4 h), 15 days (360±4 h), 22 days (528±4 h), 29 days (696±4 h), 36 days (864±4 h), 43 days (1032±4 h), 50 days (1200±4 h), and 58 days (1392±4 h) post-infusion. The immunogenicity assessment is a mandatory part of the drug safety monitoring and will be performed prior to the infusion of eculizumab, 29 days post-infusion, and upon completion of the main study period (Day 59). The study results will be used to test the hypothesis of pharmacokinetic equivalence (in terms of the primary endpoint $AUC_{(0-\infty)}$ of eculizumab following a single IV infusion) of the biosimilar BCD-148 and the reference drug Soliris® and to assess the PD, safety, and immunogenicity of the test drug versus the reference drug. In total, the planned visits are as follows: 3 visits and 1 phone

Samsung Bioepis Exhibit No. 1002
Page 11828

SYNOPSIS	
	call during the screening period and 12 visits in the main study period.
Test Drug/ Reference Drug and Dosing Regimen	In this clinical study, each healthy volunteer will get one infusion of either the test drug BCD-148 or the reference drug Soliris®, depending on the study arm to which the subject is randomized. Both eculizumab products (BCD-148/Soliris®) will be administered as a single 900 mg drip infusion given over 25-45 min. The drug will be infused at the study site.
Total Study Duration:	The study is expected to last for 2 years, which includes subject recruitment, the treatment and follow-up period, and statistical processing of results. Expected duration of study participation for each particular subject is 82 days from the moment the subject signs the ICF. This includes the screening period (20 days maximum), a maximum of 3 days from randomization to Visit 1/ Day 1, and the main study period (59 days).
Inclusion Criteria:	1. Signed ICF for participation in the study 2. Men from 18 to 45 years old (inclusive) at the time of signing the ICF 3. BMI within the normal limits (18.0 to 30.0 kg/m^2) 4. The subject is able to follow the Protocol procedures (in the investigator's opinion) 5. The subject is verified as "Healthy" according to the results of standard clinical, laboratory, and instrumental tests 6. Normal hemodynamic parameters: systolic BP from 90 mmHg to 130 mmHg; diastolic BP from 60 mmHg to 90 mmHg; HR from 60 bpm to 90 bpm 7. The subject and his sex partner of childbearing potential consent to implement reliable contraceptive methods from the moment the subject signs the ICF and until the subject completes the study. This requirement does not apply to those subjects who had undergone surgical sterilization. Reliable contraception methods mean one barrier method in combination with one of the following: spermicides, intrauterine device and/or oral contraceptives used by the subject's partner. 8. The subject agrees not to drink alcohol for 24 h prior to the infusion of the test/reference drug and for the entire period while he is in the study.
Exclusion Criteria:	1. Psychiatric disorders or other conditions that can affect the ability of the subject to follow the study protocol

Samsung Bioepis Exhibit No. 1002
Page 11829

SYNOPSIS	
	2. Acute infections within 4 weeks before signing the ICF 3. Results of laboratory and/or instrumental tests are outside the site's normal range 4. Any surgery done within 30 days before the screening or planned within 30 days after the subject completes the study 5. Impossibility to insert an intravenous catheter for blood collection (e.g., because of a skin condition at the venipuncture site) 6. A history of allergies 7. Known hypersensitivity to any component of BCD-148 or Soliris®, murine proteins or other drug components; hypersensitivity to any component of the meningococcal vaccine 8. The subject had used any medications that significantly affect hemodynamics, liver function, etc. (barbiturates, omeprazole, cimetidine, etc.) within 30 days before signing the ICF and/or the subject needs any medications (other than the study drugs) to be taken during the entire study period 9. The subject had previously used eculizumab and/or other therapeutic monoclonal antibodies against complement C5 10. Regular use (oral or parenteral) of any drugs, including OTC products, vitamins or biologically active supplements within 14 calendar days before signing the ICF 11. A history of recurrent/chronic hemorrhages or any hemorrhage within 30 days prior to signing the ICF 12. Acute or chronic infections or other diseases that, in the investigator's opinion, may affect the PK, PD or safety of the study products 13. HIV, HCV, HBV infection, syphilis 14. Meningococcal infection in the past (documented or mentioned verbally by the subject) 15. Vaccination within 4 weeks before the planned infusion date, except for vaccination against *Neisseria meningitidis* given to all subjects in the screening period 16. The subject refuses to get a vaccination against *Neisseria meningitidis* during the screening period[5] 17. The subject smokes more than 10 cigarettes per day 18. The subject consumes more than 10 units of alcohol per week (1 unit equals to 0.5 L of beer, 200 mL of wine or 50 mL of a

[5] Except for cases when the subject has a documented evidence that he received a tetravalent meningococcal vaccine (serogroups A, C, Y, and W-135) within 2 years before signing the informed consent form If the previous vaccination was perform not with the tetravalent vaccine, the subject has to be re-vaccinated.

Samsung Bioepis Exhibit No. 1002
Page 11830

SYNOPSIS	
	strong alcohol beverage) or has a history of alcohol, recreational drug or medication abuse, or tests positive for alcohol and/or psychoactive substances during the screening examination 19. Donation of ≥ 450 mL of blood or plasma within 60 calendar days before signing the ICF 20. Participation in any drug clinical studies within 30 calendar days prior to signing the informed consent form and through the entire period of study participation.
Study Hypothesis:	This study is to test the hypothesis that the test drug BCD-148 and the reference drug Soliris® have equivalent pharmacokinetics. The equivalence hypothesis will be tested for the primary PK endpoint – $AUC_{(0-\infty)}$ of eculizumab after a single IV infusion of BCD-148/Soliris®. BCD-148 will be proved equivalent to Soliris® if the limits of the two-sided 95% CI for the ratio of the geometric means of eculizumab $AUC_{(0-\infty)}$ values after a single IV infusion of BCD-148 and Soliris® fall within 80.00-125.00%.
Pharmacokinetics / Pharmacodynamics Assessments	Pharmacokinetic assessment will be based on the concentration of eculizumab (monoclonal antibodies to complement C5) measured in the serum of healthy volunteers. Pharmacodynamics will be investigated by measuring the hemolytic complement activity in the serum (CH50), where one unit of hemolytic activity is the reciprocal of the serum dilution which causes a 50% hemolysis. ***Blood sampling for PK/PD study:*** – 5 min before the infusion of BCD-148/Soliris® – 5 min, 4 h (±5 min), 8 h (±10 min), 12 h (±15 min), and 24±1 h post-infusion – 2 days (48±1 h), 3 days (72±2 h), 5 days (120±3 h), 8 days (192±4 h), 11 days (264±4 h), 15 days (360±4 h), 22 days (528±4 h), 29 days (696±4 h), 36 days (864±4 h), 43 days (1032±4 h), 50 days (1200±4 h), and 58 days (1392±4 h) post-infusion. Because of multiple blood collections and the necessity for monitoring the safety and tolerability of eculizumab, each subject will stay in a hospital for the first 48 h post-infusion.
PK Endpoints:	**The primary endpoint for PK assessment after a single infusion of BCD-148/Soliris®:** • $AUC_{0-\infty}$ of eculizumab (the area under the *Concentration vs. Time* curve from 0 to infinity).

Samsung Bioepis Exhibit No. 1002
Page 11831

SYNOPSIS	
	The secondary endpoints for PK assessment after a single infusion of BCD-148/Soliris®: • C_{max} of eculizumab (maximum drug concentration in the serum). • T_{max} of eculizumab (time to C_{max}) • AUC_{0-1392} of eculizumab (area under the *Concentration vs. Time* curve from 0 to 1392 h post-infusion) • $T_{1/2}$ of eculizumab (half-life) • Vd of eculizumab (steady-state volume of distribution) • K_{el} of eculizumab (elimination constant) • Cl of eculizumab (clearance)
PD Endpoints:	**The secondary endpoints for PD assessment after a single infusion of BCD-148/Soliris®:** • $ABEC_{(0-1392)}$ CH50 (the area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h). • $AUEC_{(0-1392)}$ CH50 ((area under the *Time vs. Effect* curve from 0 to 1392 h) • E_{min} CH50 (minimum hemolytic complement activity from 0 to 1392 h) • T_{min} CH50 (time to minimum hemolytic complement activity within the period from 0 to 1392 h).
Safety Endpoints:	• The proportion of subjects who develop AEs/SAEs that, in the Investigator's opinion, are related to eculizumab • The proportion of subjects who develop CTCAE v. 4.03 grade 3/4 AEs that, in the Investigator's opinion, are related to eculizumab, by study arms.
Immunogenicity Endpoints	• The proportion of BAb- and NAb-positive subjects ***Time points for immunogenicity blood collections:*** – 5 min before the infusion of BCD-148/Soliris® – 29 days after the infusion of BCD-148/Soliris® – Completion of the main study period (Day 59 of the study).
Statistical Analysis	**Determination of sample size** BCD-148 will be proved equivalent to Soliris® if the limits of the two-sided 95% CI for the ratio of the geometric means of eculizumab $AUC_{(0-\infty)}$ values after a single IV infusion of BCD-148 and Soliris® fall within 80.00-125.00%.

Samsung Bioepis Exhibit No. 1002
Page 11832

SYNOPSIS	

The sample size sufficient for testing the equivalence of eculizumab $AUC_{(0-\infty)}$ was calculated. The calculations were based on the $AUC_{(0-\infty)}$ data available in the literature[6,7].

Type I error was set as 5% (α=0.05); type II error was set as 20% (β=0.2); the test power was 80%.

It was shown that to get the full and valid data for testing the hypothesis of PK equivalence (the primary PK endpoint of $AUC_{(0-\infty)}$) 70 subjects have to be enrolled in total (35 subjects in each arm).

Variable	The ratio of mean values	CV	Sample size (N)	Power
$AUC_{(0-\infty)}$	$\frac{\mu_T}{\mu_C} = 0.95$	0.288	$N_{AUC\,0-\infty} = 70$ subjects (35 subjects/arm)	80.01%

This sample size will be sufficient to demonstrate, with the 80% power and 0.05 significance level, that the two-sided CI for the $AUC0_{(0-\infty)}$ ratio between BCD-148 and Soliris® falls within the range from 80.00% to 125.00%. The expected dropout rate due to reasons not related to the study drugs is approximately 10%. Therefore, 8 more volunteers will be enrolled to compensate for the premature withdrawal of randomized subjects. Thus, the overall number of study participants will be 78 subjects (39 in each study arm).

Methods of analysis

Statistical methods for other variables will be chosen according to the type of initial data and their distribution. The normally distributed quantitative data will be compared using the following tests: the two-tailed Student's *t*-test, Welch's *t*-test, and ANOVA. The non-normally distributed quantitative data will be compared by using the Mann-Whitney test, Wilcoxon test, Kruskal-Wallis test, and Friedman's test. The categorical data will be processed using the frequency tables, exact Fisher's test, χ^2 test, and Cochran-Mantel-Haenszel test.

PK/PD analysis:

The PK/PD analysis will include data from all subjects who received the test drug/ reference drug. However, subjects who had two or more PK/PD blood samples missed/lost/spoiled will be removed from the analysis.

[6] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000791/WC500054212.pdf

[7] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_ClinPharmR.pdf (table 1, page 10)

Samsung Bioepis Exhibit No. 1002
Page 11833

SYNOPSIS	
	To obtain valid results, individual concentration values will be excluded from analysis if a technical issue occurs during the concentration analysis due a human error (e.g., a whole biospecimen is compromised because a wrong reagent or wrong amount of an appropriate reagent was added; a sample was re-frozen after thawing; a sample was contaminated with foreign substances, etc.) or due to an unexpected technical problem, and it is impossible to retest the sample. If, with the inappropriate sample excluded from the analysis, a subject has two or more blood samples missed/lost/spoiled over the entire study period, this volunteer will be completely removed from the PK assessment. **Safety analysis** The safety analysis will include all subjects dosed with BCD-148/Soliris®. **Immunogenicity analysis** The immunogenicity analysis will include data from all subjects who received BCD-148/Soliris®, except for those whose pre-infusion sample and at least one post-infusion sample are missed/lost/spoiled.

Samsung Bioepis Exhibit No. 1002
Page 11834

1. STUDY RATIONALE

1.1. Introduction

1.1.1. Complement system

The complement system is a system of serum proteins consisting of nine main and three inhibitory proteins. The complement system is a part of the innate immune system and activates through an enzyme cascade pathway, where the product from the previous reaction is a catalyst in the subsequent reaction.

Complement triggers the following immune functions: promotes phagocytosis by releasing certain substances that cover pathogens or immune complexes; promotes inflammation by regulating the expression of biologically active substances by basophils; promotes cytotoxicity through the formation of the membrane attack complex (MAC) from terminal complement components [1].

There are three pathways through which complement can be activated: the classical, lectin, and alternative pathways. The classical and lectin pathways are triggered when antibodies (classical pathway) or pattern-recognition molecules (pentraxins and C1q in the classical pathway and lectins and ficolins in the lectin pathway) recognize pathogens or damage on the cell surface. Both classical and lectin pathways lead to the cleavage of C4 resulting in the formation of the C4bC2a C3 convertase complex on the target surface. The C4bC2a is an enzymatic complex that cleaves C3 into the anaphylatoxin C3a and C3b. The alternative pathway is activated as a result of the spontaneous generation of fluid-phase C3b (C3 tick-over). C3b accumulates on the surface of pathogens or self-cells and, together with the activated factors D and B, forms the C3-convertase enzyme complex of the alternative pathway (C3b/Bb), which triggers additional C3 cleavage, thus creating a positive feedback loop. It is important that, after C3b is generated, the alternative C3-convertase further promotes complement activation by triggering other activation pathways. C3b accumulates on the surface of a pathogen and binds to specific receptors on white blood cells, which induces phagocytosis of cells labeled by complement enzymes. Attachment of C3b to C3-convertase converts this enzyme into C 5-convertase, an enzyme that cleaves C5 into C5a and C5b. C5a is a pro-inflammatory and pro-thrombotic protein, while C5b initiates the terminal complement pathway with the formation of the terminal complement complex C6-C9. Finally, the C5b-9 complex (MAC) is formed on the surface of the target cells. The MAC causes hemolysis, stimulates the production of pro-coagulant micro particles, and activates platelets [1].

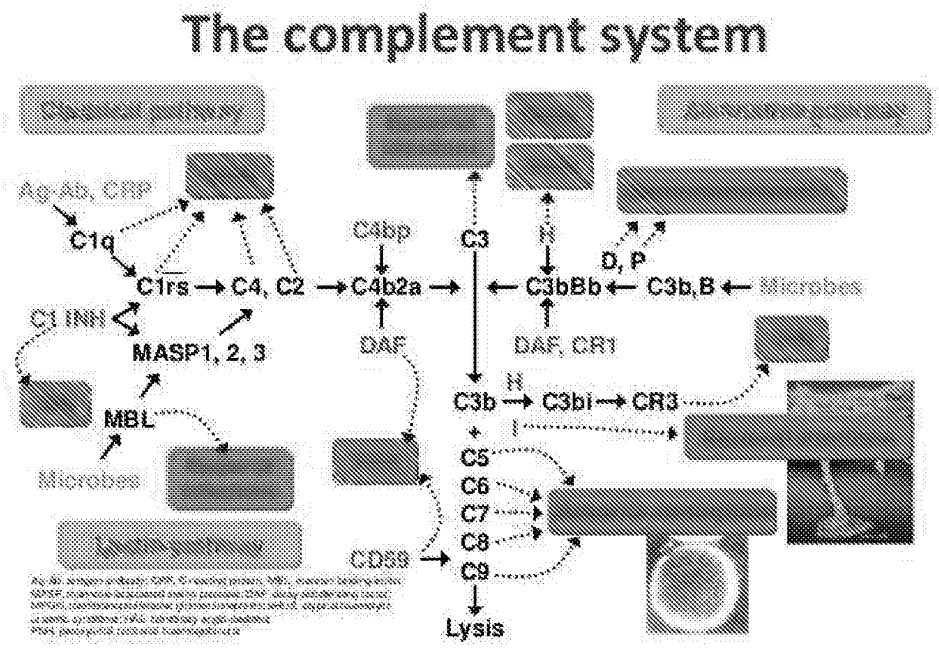
The complement activation is regulated by certain complement control molecules - membrane receptors (MCP (membrane cofactor protein), CD55 (DAF), CD59 (MIRL), and THBD

Samsung Bioepis Exhibit No. 1002
Page 11835

(thrombomodulin)) and soluble molecules (e.g., CFH (complement factor H)). These control molecules may cause C3b cleavage into inactive forms and dissociation of C3- and C5-convertases or may prevent MAC assembly.

The complement system imbalance resulting from certain genetic disorders is one of the key components in the mechanism of the atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH).

Figure 1. The complement system



1.1.2. Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired, clonal disease of the blood. The disease is characterized by chronic intravascular hemolysis, impaired bone marrow function, high risk of blood clots, kidney disease, and pulmonary hypertension. A somatic mutation in the X-linked gene encoding phosphatidylinositol glycan A (PIG-A) leads to the deficiency of glycosyl phosphatidylinositols (GPI) anchors that attach a number of proteins to blood cell membranes (e.g. certain complement system control molecules such as CD55/DAF, HRF, and CD59). Normally, these proteins interact with complement components, particularly with C3b and C4b, thus inducing dissociation of the convertase complexes and slowing down the accelerating activation of the complement. The lack of these proteins on the cell membrane in subjects with PNH results in cells

Samsung Bioepis Exhibit No. 1002
Page 11836

(primarily erythrocytes) becoming hypersensitive to complement-induced lysis, intravascular hemolysis, and anemia. Released free hemoglobin partially binds to haptoglobin in the serum, but the concentration of plasma hemoglobin in PNH exceeds the capacity of haptoglobin. Thus, hemoglobin binds irreversibly to nitric oxide, which is a physiological vasodilator. Depletion of nitric oxide induces vasospasm, pulmonary hypertension, impaired renal blood flow, and GI smooth muscle spasm. Excretion of free hemoglobin into urine results in tubular necrosis and renal impairment. Moreover, PNH is frequently associated with thrombotic complications, which may be due to the higher platelet aggregation caused by the deficiency of the membrane CD59 and due to elevated plasma pro-coagulant activity. Typically, the clinical onset of PNH occurs in people from 20 to 40 years old; the median survival based on historical data is about 10 years. [2].

The worldwide prevalence of PNH is approximately 13 cases per 1 000 000 people [3] with the incidence of about 1 case per 1 000 000 people per year. Large-scaled epidemiological studies have shown that 35% of PNH patients lose their lives within 5 years from the date of diagnosis and their 10 years mortality reaches approximately 50% despite supporting therapy. Thrombotic events are responsible for 40-67% of deaths [2, 3, 4, 5, 6, 7, 8]. Other causes of morbidity and mortality can be listed as renal failure, pulmonary hypertension, erectile dysfunction and dysphagia [9].

Allogeneic bone marrow transplantation is the only potentially curative treatment for PNH, however, it is associated with high mortality. In one of the PNH studies, the 10-year survival rate was 42%. Regardless of the indication, the frequency of complications with allogenic bone marrow transplantation remains very high. The average incidence of graft versus host disease has been observed as 42-54%.

Patients with complement-mediated hemolysis may be candidates for eculizumab therapy. According to literature, eculizumab therapy in PNH patients significantly reduces hemolysis, decreases the frequency of thrombosis and transfusion dependence, and alleviates the severity of symptoms such as dyspnea, fatigue, and pulmonary hypertension. Eculizumab also improves the renal function and quality of life. Long-term use of eculizumab increases survival up to the level of general population in the same age group. Eculizumab is not a curative treatment but long-term eculizumab treatment has a good safety profile and reduces complications and the risk of death significantly. Eculizumab should be prescribed based on clinical and laboratory signs. For patients diagnosed with PNH, Eculizumab treatment indications are available in the following cases:

– Presence of thrombotic event
– Presence of organ damage due to chronic hemolysis
– Transfusion dependence

Samsung Bioepis Exhibit No. 1002
Page 11837

– If PNH patient is pregnant.

For patients who had thrombotic complications in the past, eculizumab is indicated to prevent further thrombosis. For patients with high LDH activity (>1.5 of the normal limit), PNH complications including life-threatening cases increased significantly. For this reason, eculizumab should be used in the treatment of patients having LDH activity > 1.5 of the normal, which is associated with chronic hemolysis – for example, thrombosis, anemia, acute and chronic renal failure, pulmonary hypertension, smooth muscle dystonia (e.g., abdominal pain, dysphagia, erectile dysfunction etc.). Eculizumab treatment is also indicated to transfusion-dependent patients with chronic hemolysis. Eculizumab blocks hemolysis and significantly decreases the number of transfusions [2]

1.1.3. Atypical hemolytic uremic syndrome

Atypical hemolytic uremic syndrome (aHUS) is a chronic systemic genetic disease caused by uncontrolled activation of the alternative pathway in the complement system. The disease is characterized by generalized thrombotic microangiopathy (complement-mediated TMA). This is an orphan disease with the prevalence of 2 to 7 subjects per 1 000 000 people.

The atypical hemolytic uremic syndrome can manifest at any age; however, children and young adults are affected more often than other categories. Approximately 60% of aHUS cases are diagnosed in children versus 40% in adults. The disease affects males and females in equal numbers. In adulthood, females are affected more often than males.

Atypical HUS is caused by genetic defects in the regulation of the alternative pathway of the complement system, which results in its uncontrolled activation. It is believed that aHUS patients have mutations in the genes encoding certain regulatory proteins (CFH, CFI, MCP, THBD). By causing the deficiency or, more often, dysfunction of these proteins, such mutations deteriorate the defense mechanism against complement-induced endothelial cell activation. This results in increased liberation of MAC at the endothelial surface, causing additional endothelial cell damage with exposure of the subendothelial matrix, conversion of athrombotic phenotype into prothrombotic, and subsequent thrombus formation. The complement activation on the platelet surface, which triggers the platelet functional activity, is an additional factor contributing to the thrombus formation in aHUS patients with factor H mutations.

Besides improving survival in aHUS patients, aHUS therapy aims at inhibiting the uncontrolled complement activation, alleviating clinical and laboratory signs/symptoms of TMA, preserving and improving damaged organ functions (e.g. preventing terminal renal failure, taking

Samsung Bioepis Exhibit No. 1002
Page 11838

patients off from dialysis, preventing damage of visceral organs other than kidneys) and providing better quality of life.

The aHUS therapy includes fresh frozen plasma infusions, plasma exchange, and heparin therapy if indicated. According to the national guidelines, eculizumab therapy is indicated to adult aHUS patients who do not respond to plasma therapy, have adverse events, have recurrent disease, or have a family history of aHUS.

1.1.4 Current treatment options for aHUS and PNH

Treatment options for aHUS and PNH include eculizumab (Soliris®), a humanized monoclonal antibody binding to the complement protein C5. This inhibits C5 cleavage to C5a and C5b and thereby prevents the generation of pro-inflammatory cytokines (via C5a) and MAC (via C5b).

Clinical studies and further clinical practice have shown that eculizumab therapy in PNH patients significantly reduces hemolysis, decreases the frequency of thrombosis and transfusion dependence, and alleviates the severity of symptoms such as dyspnea, fatigue, and pulmonary hypertension. Eculizumab also improves the renal function and quality of life. Long-term use of eculizumab increases survival up to the level of general population in the same age group. Thus, eculizumab therapy significantly reduces the mortality and incidence of complications, although it is not a curative treatment [2].

In aHUS patients, eculizumab reverses the TMA effect and/or prevents further kidney damage. Although eculizumab suppresses the terminal complement system, the proximal complement system, responsible for opsonization of microorganisms and clearance of immune complexes, remains intact [10].

1.1.5. Brief overview of the study product and its advantages

JSC BIOCAD (Russia) develops BCD-148 as a biosimilar to Soliris®. This is a drug to treat PNH and aHUS.

Eculizumab is a humanized monoclonal antibody that specifically binds to the complement protein C5. Binding C5, eculizumab prevents its cleavage to C5a and C5b and, therefore, inhibits the generation of the membrane attack complex (MAC).

1.2. Name and description of the investigational product

1.2.1. Test drug

Invented name: Not applicable

Samsung Bioepis Exhibit No. 1002
Page 11839

Internal code: BCD-148

International non-proprietary name: eculizumab

Dosage form: Concentrate for solution for infusion

Composition: 1 mL of solution contains

Active ingredient: eculizumab 10 mg

Excipients: Sodium acetate trihydrate 0.436 mg, trehalose dihydrate 100 mg, poloxamer 188 0.2 mg, glacial acetic acid ad pH 5.0, water for injection ad 1.0 mL.

Manufacturer: JSC BIOCAD, Russia.

Shelf life: 2.5 years.

Storage and transportation conditions: At 2 to 8 °C, protect from light. Do not freeze. Keep out of the sight and reach of children.

Packaging: 30 mL of the drug product in a vial (grade I colorless neutral glass) with a rubber stopper and a seal (aluminum cap) with plastic closure. Each vial has a self-adhesive label. One vial in a carton.

1.2.2. Reference drug:

Invented name: Soliris®

International non-proprietary name: eculizumab

Dosage form: Concentrate for solution for infusion

Marketing Authorization Holder: Alexion Pharma GmbH[8]

Composition:

1 mL of solution contains

Active ingredient: eculizumab 10 mg

Excipients: sodium dihydrogen phosphate monohydrate 0.46 mg, sodium hydrogen phosphate 1.78 mg, sodium chloride 8.77 mg, polysorbate-80 0.22 mg, water for injection ad 1.0 mL.

Shelf life: 2.5 years. Do not use after the expiry date which is stated on the carton.

Storage and transportation conditions: At 2 to 8 °C, protect from light. Keep out of the sight and reach of children.

Packaging: This is a marketed drug. The package is in accordance with the approved specification.

1.2.3. Labeling of the study and reference products in this study

This study is blind, so the investigational products will be labeled identically.

[8] If the product is not available or difficult to purchase in the Russian Federation, it will be purchased in other countries.

Samsung Bioepis Exhibit No. 1002
Page 11840

Labeling: The secondary package contains the following information (printed in the easily readable font):

- Name of the test/ reference drug
- Dosage
- Date of manufacture
- Shelf life
- Investigational product lot number.
- Dosage form

The secondary package will contain the following information (printed in the easily readable font):

- Name of the test/ reference drug
- Dosage
- Manufacturer/MAH
- Investigational product lot number
- Date of manufacture
- Shelf life
- Route of administration
- Dosage form
- Storage conditions
- Cautionary labeling
- Protocol ID.

The investigator will also put the following information on the secondary package: Protocol ID, study site number, and Subject ID.

Both primary and secondary package will also have the following labeling: "For Clinical Trials Only".

1.2.4. Posology and route of administration

In this clinical study, each healthy volunteer will get one infusion of either the test drug BCD-148 or the reference drug Soliris®, depending on the study arm to which the subject is randomized. Both eculizumab products (BCD-148/Soliris®) will be administered as a single 900 mg drip infusion given over 25-45 min. The infusion will be given at the study site.

The subject should be warned not to smoke for 1 h before the infusion of BCD-148/Soliris® and for 3 h following the infusion.

Route of administration:

Samsung Bioepis Exhibit No. 1002
Page 11841

The infusion of BCED-148/Soliris® will be given at the study site. Subjects will stay at the study site for monitoring for 48 h post-infusion. The study site where the infusion is given and the following monitoring is performed must have all the necessary equipment for emergency care.

Instructions for reconstitution of the test/reference drug solution

Take care to ensure aseptic handling when you prepare the infusion.

According to the storage conditions, vials with BCD-148/Soliris® should be stored at 2 to 8 °C protected from light (in a refrigerator).

Before administration, inspect the solution in the vial for particulate matter or discoloration.

Take the vials with BCD-148/Soliris® from the refrigerator and allow to warm to room temperature (not higher than 25°C) for 30 minutes before administration.

Dilute BCD-148/Soliris® to a final concentration of 5 mg/mL with sodium chloride 9% solution for infusion. To do so, remove excessive sodium chloride 9% solution for infusion from the infusion bag/vial. The volume of solution remaining in the infusion bag/vial should be 90 mL.

Use a sterile syringe with a needle to transfer the contents of 3 vials with BCD-148 / Soliris® to the vial containing the solution for infusion.

The final volume of a 5 mg/mL diluted BCD-148 / Soliris® solution is 180 mL for 900 mg doses (refer to Table 1).

Samsung Bioepis Exhibit No. 1002
Page 11842

Table 1. Solution reconstitution for certain doses

Dosage of BCD-148/Soliris® to be transferred to the infusion bag/vial	Volume (mL) of BCD-148/Soliris® solution to be transferred to the infusion bag/vial	Required number of vials of BCD-148/Soliris®	Volume (mL) of 0.9% sodium chloride solution for infusion	Final volume of 5 mg/mL BCD-148/Soliris® solution for infusion to be administered to a subject
900 mg	90 mL	3 vials (take the contents of all three vials to the syringe)	90 mL	180 mL

The final solution should be clear and colorless. Do not use the solution if it is colored or has any visible particles. Administer the infusion immediately after preparation. In exceptional circumstances, the solution can be stored for not more than 24 h at a temperature from 2 to 8 °C. Before giving an infusion, gently agitate the infusion bag containing the diluted solution to ensure thorough mixing of the product and diluent. There is no need to protect the reconstituted solution from light during the infusion. During the infusion, the temperature of the solution should be 20–25 °C.

BCD-148/Soliris® is administered only as an intravenous infusion. BCD-148/Soliris® must not be administered as an intravenous push or bolus injection!

When the infusion is completed, add 5 mL of normal saline to the catheter to rinse it and remove any remaining drug.

If any adverse events develop during the infusion, the infusion rate may be reduced or the infusion can be stopped at the discretion of the investigator. If reducing the infusion rate, make sure that the overall duration of BCD-148/Soliris® infusion does not exceed 2 h.

The subjects will stay at the study site and will be monitored by the medical team for 2 days after the infusion.

1.3. Relevant non-clinical and clinical aspects

1.3.1. Non-clinical studies

According to ICH M3(R2)[9], clinical studies of single subtherapeutic doses or doses of the anticipated therapeutic range should rely on non-clinical pharmacology, safety, single-dose toxicokinetics, and mutagenicity studies. As BCD-148 is a biological medicinal product with its non-clinical development regulated by ICH S6(R1)[10], no mutagenicity assessment is required.

[9]Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2)
[10]ICH harmonized tripartite guideline preclinical safety evaluation of biotechnology-derived pharmaceuticals S6(R1)

Samsung Bioepis Exhibit No. 1002
Page 11843

The experiments showed that BCD-148 blocks only human complement component C5[11], so there is no relevant animal model for its non-clinical assessment. In this case, ICH S6 (R1) recommends an abridged non-clinical development program with alternative approaches:

As described in ICH S6, when no relevant species can be identified because the biopharmaceutical does not interact with the orthologous target in any species, use of homologous molecules or transgenic models can be considered.

A similar approach is presented in WHO Guideline for medicinal products prepared by recombinant DNA technology[12].

When no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins should be considered.

If C5 transgenic animals are used, the drug will bind only to human protein in serum and will not affect the endogenous level of C5 in experimental animals. Because such models have overexpression of the human protein and background levels of the murine protein, they will not allow demonstrating any toxicity mediated through specific binding of the drug to its ligand. In this case, the only relevant approach for evaluating drug properties is to use an orthologous drug.

The *in vivo* non-clinical development program of BCD-148 involved potency and toxicokinetic studies. Potency was evaluated using an experimental approach modeling hemolytic-uremic syndrome and paroxysmal nocturnal hemoglobinuria[13]. Mice were administered with antibodies to erythrocyte surface antigens and human serum containing complement component C5. Both BCD-148 and Soliris® decreased serum levels of free hemoglobin and prevented animals' death. As there are no relevant animal species to assess the safety of BCD-148, JSC BIOCAD initiated a Phase I clinical trial with stepwise dose escalation in healthy volunteers. The starting dose for the Phase I trial of BCD-148 was chosen on the basis of available non-clinical data and potency data[14].

The cross-reactivity study[15] showed that there are no relevant animal species. This is also true for eculizumab (Soliris®), which is specific for the same target. The toxicokinetics study[16] was performed in cynomolgus monkeys because the Fc-fragment of BCD-148 has an affinity to

[11]Report: Cross-reactivity of BCD-148 (JSC BIOCAD) in Heterologous RBC Lysis Assay
[12]Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology. WHO, 2013
[13]Report: Potency of BCD-148 in Murine Intravascular Hemolysis Model
[14]Report: Potency of BCD-148 in Murine Intravascular Hemolysis Model
[15]Report: Cross-reactivity of BCD-148 (JSC BIOCAD) in Heterologous RBC Lysis Assay
[16]Report: Single-dose Subcutaneous Toxicity and Pharmacokinetics of BCD-148 in Cynomolgus Monkeys (Macaca Fascicularis)

Samsung Bioepis Exhibit No. 1002
Page 11844

neonatal Fc receptor (FcRn) of cynomolgus monkeys[17]. This determines the mean residence time of the drug in the serum of experimental animals and reflects its pharmacokinetic properties.

The study of physicochemical and biological properties was conducted in accordance with ICH requirements and European requirements for biotechnology-derived products and monoclonal antibodies[18]. Quality parameters to be studied were selected on the basis of available information about the originator Soliris®.

The assessment of structure as part of comparability exercise involved a thorough comparative analysis of the primary, secondary and higher order structures, post-translation modifications and charged forms profile. Special attention was paid to a comparison of purity and content of impurities in both drugs. These parameters were tested using several methods (an orthogonal approach). If there were any differences between BCD-148 and the reference drug, they were assessed for their impact on biological activity *in vitro*.

Biological properties of eculizumab were studied by evaluating its binding to complement fragment C5 by means of ELISA. Purity and homogeneity were evaluated by SDS-PAGE under reducing and non-reducing conditions, size-exclusion HPLC, and capillary gel electrophoresis under reducing and non-reducing conditions. The glycan profile of the eculizumab molecule was investigated by NP HPLC.

Over 20 analytical methods were used to found any potential structural and functional differences between BCD-148 and Soliris®. The quality parameters and analytical procedures chosen are recommended for studies of protein products by ICH Q6B and European Medicines Agency[19].

1.3.1.1. Physicochemical properties and potency

BCD-148 has been developed by JSC BIOCAD as a biosimilar of Soliris®. Eculizumab is a humanized monoclonal antibody that specifically binds to complement fragment C5. JSC BIOCAD has conducted comparative studies of structural, physicochemical and biological properties of BCD-148 (eculizumab biosimilar by BIOCAD) and the originator Soliris®[20]. The study involved the assessment of the following characteristics:

1. Physicochemical properties

[17]Report: Analysis of Affinity Constant for Binding of Soliris® and BCD-148 to Human and Cynomolgus Monkey's FcRn receptors using Forte Bio OctetRed96
[18]Report: Experimental Investigation of Structural, Physicochemical and Biological Properties of Eculizumab Biosimilar (BCD-148) (JSC BIOCAD, Russia) and reference drug Soliris®.
[19]EMA/CHMP/BWP/247713/2012
[20]Report: Experimental Investigation of Structural, Physicochemical and Biological Properties of Eculizumab Biosimilar (BCD-148) (JSC BIOCAD, Russia) and Reference Drug Soliris®.

Samsung Bioepis Exhibit No. 1002
Page 11845

2. Functional characteristics.

The following parameters were studied as part of the physicochemical evaluation:

- Structural characteristics
- Charged forms profile
- Purity and impurities
- Content of bacterial endotoxins
- Glycosylation profile
- Content of monosaccharides
- Content of protein.

The following parameters were studied as part of the biological evaluation:

- Potency
- Affinity to antigen.

N-terminal and C-terminal sequences of the light and heavy chains of BCD-148 were found to agree with those of Soliris®. This demonstrates the biosimilarity of the drugs in terms of this parameter. The amino acid sequences of the light chains of BCD-148 and the reference drug Soliris® were confirmed vs. the theoretical sequence (both 100%). The amino acid sequences of the heavy chains of BCD-148 and Soliris® were also confirmed vs. the theoretical sequence (99% and 100%, respectively). The results obtained by other methods confirmed that the structures of eculizumab (JSC BIOCAD) and originator agreed with the theoretical data, thus further demonstrating the biosimilarity of the drugs.

Purity and homogeneity were evaluated by SDS-PAGE under reducing and non-reducing conditions, size-exclusion HPLC, and capillary gel electrophoresis under reducing and non-reducing conditions.

Heterogeneity of eculizumab was evaluated by reversed-phase HPLC (isoaspartic acid residues, monosaccharides), reversed-phase HPLC with MS-detection (oxidized and deamidated forms) and normal-phase HPLC (glycan profile). In addition, functional characteristics of eculizumab were evaluated: potency and affinity for antigen (complement fragment C5) and FcRn receptor.

A comparison of physicochemical and biological properties of BCD-148 (JSC BIOCAD, Russia) and the originator Soliris® showed the comparability of their quality.

Data obtained in comparative physicochemical and functional studies of BCD-148 and originator are summarized in the tables below.

Samsung Bioepis Exhibit No. 1002
Page 11846

Table 2. Comparative assessment of physicochemical and structural characteristics of BCD-148 and Soliris®

Quality attribute	Method	Measured parameter	Criticality of quality attribute by three factors	Approach to biosimilarity assessment	Results for BCD-148	Assessment criteria for Soliris®
Primary structure	RP UPLC-MS/MS	Verification of amino acid sequence of light chain	High – Medium	Tier 3	100% of the amino acid sequence identified	100% of the amino acid sequence identified
Primary structure	RP UPLC-MS/MS	Verification of amino acid sequence of heavy chain	High – Medium	Tier 3	99% of the amino acid sequence identified	100% of the amino acid sequence identified
Primary structure	RP UPLC-MS/MS	Identification of N-terminal peptides	High – Medium	Tier 3	N-terminal sequences confirmed	
Primary structure	RP UPLC-MS/MS	Identification of C-terminal peptides	High – Medium	Tier 3	C-terminal sequences confirmed	
Primary structure	RP UPLC-MS/MS	Peptide map	High – Medium	Tier 3	The peptide map of the biosimilar corresponded to that of the originator	
Molecular weight	MALDI-TOF-TOF	Molecular weight of glycosylated protein, Da	High – Medium	Tier 2	[148529;148541]	[148172;148769]
		Molecular weight of deglycosylated protein, kDa			[145893;146179]	[145558;146240]
Higher order structure	Sulfhydryl groups by Ellmann's method	Content of free SH-groups	Middle	Tier 3	The biosimilar and comparator did not contain free sulfhydryl groups, which corresponds to literature data.	
Higher order structure	RP UPLC-MS/MS	Number of disulfide bonds	Middle	Tier 3	The number of disulfide bonds was found to be 18, which agrees with the theoretical data.	
Higher order structure	Spectral profile by UV-spectroscopy	Absorption maxima and minima	Middle	Tier 3	The spectral profile of the biosimilar corresponds to that of the originator	
Higher order structure	Spectral profile by far and near UV circular dichroism spectra	Secondary and tertiary structure	High – Medium	Tier 3	The spectral profile of the biosimilar corresponds to that of the originator	
Higher order structure	Fluorescence spectroscopy	Tertiary structure	High – Medium	Tier 3	The spectral profile of the biosimilar corresponds to that of the originator	
Thermal stability of structure	Differential scanning calorimetry	Thermal transition temperature, °C	Medium – Low	Tier 2	[76.31;76.47]	[63.75;80.39]
Oxidized forms	RP UPLC-MS/MS	Methionine M48 of heavy chain	High – Medium	Tier 2	[2.00;3.04]	[1.75;2.99]
		Methionine M81 of heavy chain			[3.69;5.11]	[2.25;5.22]
		Methionine M253 of heavy chain			[9.88;11.86]	[4.20;14.16]
		Methionine M359 of heavy chain			[3.85;4.07]	[0.55;5.25]

Samsung Bioepis Exhibit No. 1002
Page 11847

Quality attribute	Method	Measured parameter	Criticality of quality attribute by three factors	Approach to biosimilarity assessment	Results for BCD-148	Assessment criteria for Soliris®
		Methionine M429 of heavy chain			[5.18;5.24]	[2.85;5.50]
		Methionine M4 light chain			[4.60;6.04]	[0.00;8.44]
Deamidated forms	RP UPLC-MS/MS	Glutamine Q312 of heavy chain	High – Medium	Tier 2	[0.44;0.57]	[0.43;0.59]
		Asparagine N362 of heavy chain			[1.00;1.10]	[0.49;1.22]
		Asparagine N435 of heavy chain			[0.63;1.07]	[0.42;1.19]
Isoaspartyl forms	RP-HPLC	Isoaspartyl forms, %	High – Medium	Tier 2	[3.71;4.45]	[0.00;32.26]
Isoforms	Capillary zone electrophoresis	Charged forms profile	High – Medium	Tier 3	Charged forms profile of the biosimilar corresponds to that of the originator	
Purity	SDS-PAGE under reducing conditions	Sum of (L + H) chains, %	High – Medium	Tier 2	[92.55;97.81]	[91.29;100.00]
Purity	SDS-PAGE under reducing conditions	Impurities, %	High – Medium	Tier 2	[2.19;7.45]	[0.00;8.71]
Purity	SDS-PAGE under non-reducing conditions	Major band, %	High – Medium	Tier 2	[91.41;92.73]	[90.18;96.37]
Purity	SDS-PAGE under non-reducing conditions	Impurities, %	High – Medium	Tier 2	[7.27;8.59]	[3.63;9.82]
Purity	Size-exclusion HPLC	Monomer, %	High – Medium	Tier 2	[99.23;99.35]	[96.54;100.00]
Purity	Size-exclusion HPLC	Aggregates, %	High – Medium	Tier 2	[0.28;0.30]	[0.00;2.86]
Purity	Size-exclusion HPLC	Impurities, %	High – Medium	Tier 2	[0.65;0.77]	[0.00;3.46]
Purity	Capillary electrophoresis under reducing conditions	Sum of (L + H) chains, %	High – Medium	Tier 2	[96.86;98.16]	[89.11;100.00]
Purity	Capillary electrophoresis under reducing conditions	Non-glycosylated heavy chain, %	High – Medium	Tier 2	0.43	[0.73;0.98]
Purity	Capillary electrophoresis under non-reducing conditions	Monomer, %	High – Medium	Tier 2	[96.39;97.73]	[95.87;99.73]
Purity	Capillary electrophoresis under non-reducing conditions	LMW impurities, %	High – Medium	Tier 2	[2.28;3.62]	[0.27;4.13]
Process-related impurities	Bacterial endotoxins (LAL-test)	Bacterial endotoxins, EU/mg	Middle	Tier 2	0.03	[0.00;0.42]
Glycosylation profile	NP HPLC	Oligosaccharide groups: Galactosylated, %	High – Medium	Tier 2	[19.16;19.60]	[11.87;20.68]

Samsung Bioepis Exhibit No. 1002
Page 11848

Quality attribute	Method	Measured parameter	Criticality of quality attribute by three factors	Approach to biosimilarity assessment	Results for BCD-148	Assessment criteria for Soliris®
		Afucosylated (not accounting for mannoses), %			[2.31;2.53]	[4.24;4.64]
		Sialylated, %			[0.98;1.00]	[1.01;2.03]
		Mannosylated, %			[1.40;1.52]	[3.91;7.42]
Content of monosaccharides	RP-HPLC	D-mannose, %	High – Medium	Tier 2	[32.50;32.62]	[32.46;34.51]
		Glucosamine, %			[51.62;51.94]	[48.95;53.65]
		D-galactose, %			[2.37;2.53]	[1.65;2.99]
		D-fucose, %			[13.03;13.39]	[11.13;14.66]
Assay	RP-HPLC	Protein content, mg/mL	High – Medium	Tier 2	[9.80;10.72]	[9.29;10.59]

Samsung Bioepis Exhibit No. 1002
Page 11849

Table 3. Comparative assessment of functional characteristics of BCD-148 and Soliris®

Quality attribute	Method	Measured parameter	Criticality of quality attribute by three factors	Approach to biosimilarity assessment	(Mean ± SD) for BCD-148	Quality range for the originator Soliris®
Potency	ELISA	Relative potency, %	High	Tier 1	[93.38;97.62]	[93.00;124.00]
Affinity for C5 antigen	Biolayer interferometry	KD (M)	High	Tier 1	$[1.97;2.91] \cdot 10^{-10}$	$[1.93;3.09] \cdot 10^{-10}$
	Surface plasmonic resonance	KD (M)	High	Tier 1	$[1.27;1.65] \cdot 10^{-10}$	$[1.09;1.70] \cdot 10^{-10}$
Affinity for FcRn receptor	Biolayer interferometry	KD (M)	Middle	Tier 2	$[3.03;3.57] \cdot 10^{-8}$	$[2.10; 3.54] \cdot 10^{-8}$

Samsung Bioepis Exhibit No. 1002
Page 11850

The experimental data show that the amino acid sequence of BCD-148 agrees with that of eculizumab (Soliris®). Comparative assessment of BCD-148 and Soliris® in terms of potency *in vivo*[21] and *in vitro*[22] showed similar results.

The similar structure and antigen specificity (both drugs bind the same epitope of complement component C5)[23], the comparable activity of BCD-148 and Soliris® allow using the data obtained during the non-clinical studies of the orthologous drug BB5.1 for the evaluation of BCD-148. No safety pharmacology studies of BCD-148 are required in support of Phase I clinical trials, and no multiple-dose toxicity, reproductive toxicity or carcinogenicity studies are required in support of clinical trials of later phases. 4-week and 26-week toxicity studies in mice were performed with the orthologous drug.

Thus, the non-clinical studies of BCD-148 and data obtained with the orthologous drug BB5.1 during the assessment of Soliris® allow a thorough assessment of the efficacy and safety of BCD-148. BCD-148 can be recommended for clinical development.

1.3.1.2. Cytokine release by peripheral blood mononuclear cells in response to BCD-148

The study aimed to assess whether BCD-148 is able to induce healthy volunteers' mononuclear cells to release major pro-inflammatory cytokines *in vitro*[24].

Concentrations of major anti-inflammatory cytokines (IL-2, IL-4, IL-10, TNFα, IFNγ, IL-17A, IL-6) were studied by ELISA after 20-h incubation of the PBMC culture. Anti-CD3/CD28 antibodies were used as a control. When added to the culture of healthy volunteers' mononuclear cells, BCD-148 did not increase concentrations of IL2, IL4, IL10, TNFα, IFNγ, IL17A, IL-1β, or IL6 vs. control. This shows that BCD-148 is not associated with a risk of so-called cytokine storm.

1.3.1.3. Potency of BCD-148 in murine intravascular hemolysis model

The non-clinical development of BCD-148 included a study of its potency in a complement-dependent hemolysis model[25].

The study involved 88 male Balb/c mice. The animals were distributed into 11 groups of 8 males each. At time point 0, the animals received normal human serum 0.5 mL/mouse intraperitoneally. In 10 min after this, they received intravenous BCD-148 or Soliris® (1

[21]Report: Potency of BCD-148 in Murine Intravascular Hemolysis Model
[22]Report: In Vitro Activity of BCD-148 (JSC BIOCAD, Russia)
[23]Report: Superimposing of Epitopes Binding BCD-148 and Eculizumab on the Surface of Protein C5 using Forte Bio Octet RED
[24]Report: Release of Cytokines by Peripheral Blood Mononuclear Cells in Response to BCD-148 Drug Product, Batch 295011116P (JSC BIOCAD, Russia)
[25]Report: Potency of BCD-148 in Murine Intravascular Hemolysis Model

Samsung Bioepis Exhibit No. 1002
Page 11851

mg/animal, 0.1 mg/animal, 0.01 mg/animal or 0.001 mg/animal). Animals of the control group received an isotonic solution of sodium chloride (the same volume and by the same mode as in the test groups). In 10 min after this, all animals received anti-murine RBC antibodies. The animals were examined every hour during the first 6 hours of the study and then in 1 day after the beginning of the study.

BCD-148 and Soliris® were associated with decreases in intravascular hemolysis. Both BCD-148 and Soliris® reduced levels of serum hemoglobin vs. positive control group, where animals received placebo (isotonic sodium chloride). This can show that both drugs bound to complement component C5 and inhibited RBC destruction. With BCD-148 and Soliris® 1.0, 0.1 and 0.01 mg/animal, serum levels of hemoglobin significantly decreased vs. positive control group. Serum hemoglobin levels in the animals on the minimal dose (0.001 mg/animal) did not differ from those in the positive control group, thus showing that neither BCD-148 0.001 mg/animal nor Soliris® 0.001 mg/animal exhibited potency. There were no differences between the groups in serum Hb levels when BCD-148 and Soliris® were administered at doses of 0.01 mg/animal, 0.1 mg/animal, and 1.0 mg/animal. The values were comparable and did not have any significant differences.

Taking into account no potency with BCD-148 0.001 mg/animal, this dose was considered the No Biological Effect Dose Level.

The effect was not dose-dependent, so Hb level could not be used to choose the Minimal Anticipated Biological Effect Level (MABEL) and the maximum effective dose.

The doses of 0.001 mg/animal and 0.01 mg/animal were not associated with increased survival vs. positive control group. In all of the groups, all animals died. BCD-148 0.1 mg/animal was associated with the minimal protective effect: 25% survival (1 animal out of 4). A similar result was shown for Soliris®. The maximal dose of the drugs (1.0 mg/animal) was associated with a 75% survival (3 animals out of 4).

Considering no direct dose-dependent effect of BCD-148 on Hb in murine serum, it was decided to use only survival to establish the minimal anticipated biological effect level (MABEL) and maximum effective dose. The minimal activity of BCD-148 was shown with the dose of 0.1 mg/animal. With lower doses, 100% of animals died. In this case, 0.1 mg/animal can be considered the minimum anticipated biological effect level (MABEL). The highest survival was shown with BCD-148 1.0 mg/animal, so this dose can be considered the dose with the highest activity.

The starting dose in the clinical Phase I study BCD-148-1 was calculated using the No Biological Effect Dose Level (NBEDL) established in the above-mentioned study of potency in human C5 complement component model – 0.001 mg/animal.

Samsung Bioepis Exhibit No. 1002
Page 11852

1.3.1.4. Single-dose IV toxicity and PK study of BCD-148 in cynomolgus monkeys

The study was to evaluate the toxicokinetics of BCD-148 in laboratory animals[26].

BCD-148 upon single-dose administration was studied in cynomolgus monkeys (*Macaca fascicularis*) weighed 3.10-4.25 kg. A total number of animals used in the study: 12 monkeys.

The animals were divided into 4 groups (3 males per group) according to their body weight. Animals in each group received a certain dose of BCD-148. BCD-148 was given as an IV infusion at 3 dose levels (25 mg/kg, 50 mg/kg, and 100 mg/kg, solution in sterile buffer saline). The infusion volume was 10 mL/kg. Animals in the control group received the buffered saline at the same volume and by the same mode as those used in test groups. All study animals were monitored for 30 days. The maximum dose of the test drug used in this study (100 mg/kg) is equivalent to 10 × max efficacy dose determined in the hemolysis model potency study, which complies with Russian[27] and international[28,29] recommendations

The toxicological profile of BCD-148 was assessed by using common experimental methods recommended for non-clinical studies[30].

Throughout the study, the following parameters were assessed: motor activity, general health state and behavior, body weight, appetite, stool, excretory system function, body temperature, and peripheral blood cell populations. In addition, the study assessed the effects of BCD-148 on major blood chemistry markers (AST, ALT, LDH, total bilirubin, protein, and glucose) and urinary system function (urinalysis results).

Single IV doses of BCD-148 did not result in animal deaths. The animals tolerated the drug well and showed no clinical signs of toxicity throughout the entire observation. It was technically impossible to inject doses needed to determine the LD50.

The single IV administration of BCD-148, regardless of the dose, did not produce any toxic effects in cynomolgus monkeys (*Macaca fascicularis*). A single subcutaneous administration of BCD-148 to the primates did not affect the RBC and WBC counts or the urinalysis results. Ascending doses of BCD-148 (25 mg/kg, 50 mg/kg and 100.0 mg/kg) did not affect the total protein, glucose, bilirubin, or LDH, AST, or ALT serum levels in the primates.

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[26]Report: A Single-Dose IV Toxicity and Pharmacokinetics Study of BCD-148 in cynomolgus monkeys (Macaca fascicularis)

[27]Guidance on evaluation of medicinal products// M. - 2014.

[28]Addendum to ICH S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals. – 2009.

[29]World Health Organization. Guidelines on the quality, safety, and efficacy of biotherapeutic protein products prepared by recombinant DNA technology. 2013

[30]Preclinical safety evaluation of biotechnology-derived pharmaceuticals S6. – 1997.

Samsung Bioepis Exhibit No. 1002
Page 11853

For PK study, blood samples were collected from animals of groups 1, 2, and 3 dosed with BCD-148. Blood collections were as follows: before the infusion, and then 5min, 15 min, 30 min, 1 h, 3 h, 6 h, 24 h, 30 h, 48 h, 72 h, 96 h, 120 h, 144 h, 168 h, 240 h, 312 h, 384 h, 480 h, 600 h, and 696 h post-injection.

The key PK parameters calculated for each group are shown in Table 3.

Table 3. PK parameters for ascending doses of BCD-148 (10 mg/kg, 50 mg/kg, 100 mg/kg)

Dose, mg/kg		25		50		100	
		Xmean		Xmean		Xmean	
C_{max}	(µg/mL)	344.26	57.89	661.97	129.43	2349.91	425.82
$AUC_{(0-696)}$	(µg/mL*h)	46219.67	15180.88	72933.63	29675.35	218032.33	84030.61
$AUC_{(0-\infty)}$	(µg/mL*h)	55980.33	24887.76	97551.97	61288.20	289787.33	164839.21
K_{el}	(1/h)	0.0032	0.0013	0.0030	0.0019	0.0032	0.0021
$T_{1/2}$	(h)	244.32	104.85	303.06	173.05	287.07	162.16
MRT	(h)	336.98	148.06	413.78	246.62	418.12	236.19
Clearance	mL/kg*h	0.58	0.16	0.75	0.25	0.50	0.16
Vd	mL/kg	179.17	38.01	274.72	87.10	190.75	82.77
C_{max}/AUC		0.0070	0.0021	0.0096	0.0019	0.0115	0.0032

The PK study has shown that the C_{max} and $AUC_{(0-696)}$ are directly proportional to the dose of BCD-148, while the $T_{1/2}$, Cl, k_{el}, MRT, and Vd are not dose-dependent. These data suggest that pharmacokinetics of BCD-148 is linear.

1.3.1.5. *In vitro* activity of BCD-148

This *in vitro* study aimed to assess the ability of BCD-148 to block the lysis of heterologous erythrocytes in alternative complement pathway[31]. The potency of BCD-148 was studied the following way: human serum was used as a complement pool to form a lytic complex. Rabbit erythrocytes were isolated for analysis of lysis in the alternative complement pathway. Before the assessment of the impact of BCD-148 on hemolysis in the serum, it was shown that complement components in the serum resulted in lysis of heterologous erythrocytes. Isolated heterologous erythrocytes were washed; a 5% solution was prepared and applied in wells of a 96-well plate. Absorbance at 800 was measured every 20 sec in APC buffer.

To rule out non-specific response, intravenous normal human immunoglobulin (IVIG) was used as an additional control. In the IVIG group, normal human immunoglobulin was applied instead of the test drug.

In the samples without the drug (a negative control and a negative control with IVIG), significant hemolysis was seen demonstrated by absorbance. Decreases in absorbance were seen

[31]Report: *In Vitro* Activity of BCD-148 (JSC BIOCAD, Russia)

Samsung Bioepis Exhibit No. 1002
Page 11854

at all time points of the study. Changes in absorbance over time were similar in both groups. In samples with BCD-148, absorbance decreased much more slowly than in the negative control groups.

The experimental data confirmed the ability of BCD-148 to block the formation of the terminal lytic complex.

1.3.1.6. Cross-reactivity study

The study aimed to evaluate the cross-reactivity of BCD-148.

The study assessed the ability of BCD-148 to block the cleavage of C5 into C5a and C5b and the formation of the terminal lytic complex[32].

Blood serum was obtained from a panel of candidate animals (rabbits, guinea pigs, hamsters, rats, minipigs, dogs, cynomolgus monkeys). This serum was used as a complement pool to form a lytic complex. Rabbit and human erythrocytes were isolated for analysis of lysis in the alternative complement pathway. Complement components in the serum of candidate animals triggered the cascade of lytic complex formation for lysis of heterologous erythrocytes. If BCD-148 bound to complement fragment C5 of candidate animals, no hemolysis was observed.

When heterologous rabbit erythrocytes were added to human serum, hemolysis increased. In the presence BCD-148 hemolysis significantly slowed down. Total human immunoglobulins (IVIG) were used as an additional control to assess the effect of immunoglobulins on non-specific hemolysis.

BCD-148 did not change the rate of hemolysis caused by the addition of heterologous rabbit erythrocytes to serum samples taken from a guinea pig, a hamster, a rat, a mini pig, a dog, and a cynomolgus monkey. This demonstrates that BCD-148 did not bind to complement component C5 of these animal species.

Thus, the study of cross-reactivity of BCD-148 by heterologous RBC lysis assay with the alternative complement pathway did not show any relevant species except for humans.

1.3.1.7. Cross-reactivity study

The study aimed at evaluating the cross-reactivity of BCD-148 by immunohistochemical (IHC) staining in frozen normal human tissues[33].

The frozen normal human tissues consisted of autopsy material. Samples of 35 human tissues were used: pituitary, stomach, peripheral blood cell, cerebral cortex, skin, lung, lymph

[32]Report: Cross-reactivity of BCD-148 (JSC BIOCAD, Russia) in Heterologous RBC Lysis Assay
[33]Report: Cross-reactivity of BCD-148 (JSC BIOCAD, Russia) in Frozen Normal Human Tissues

Samsung Bioepis Exhibit No. 1002
Page 11855

node, uterus, tonsil, cerebellum, mammary gland, urine bladder, ureter, adrenal gland, peripheral nerve, parotid gland, salivary gland, parathyroid gland, liver, pancreas, striated muscle, kidney, prostate, spleen, testicle, heart, spinal cord, large intestine, small intestine, fallopian tube, thyroid gland, vascular endothelium, testis and ovary tissue.

A suspension of HEP-G2 cells expressing C5 antigen was used as a positive control. HEP-G2 is a stable cell line with overexpression of C5.

With BCD-148, specific anti-C5 IHC staining was observed for the HEP-G2 cells comprising the C5 gene.

Specific anti-C5 staining with BCD-148 was seen in myoepithelial cell of mammary gland acini; cells of smooth muscles from various organs, including vascular wall; epithelium of kidney tubules; stroma of pituitary gland, ovary, parathyroid gland; mucous membrane of stomach; connective tissue of tonsil, spleen and heart; submucosal membrane of fallopian tube; proper substance of cornea; suprarenal cortex; Hassall's bodies.

No specific IHC staining of C5 with BCD-148 was found in samples of skin, peripheral blood cells, brain cortex, amygdala, cerebellum, peripheral nerve, salivary gland, striated muscle, spinal marrow, thyroid gland, and testis.

Non-specific IHC staining of C5 with BCD-148 was found in hepatocytes and samples from the mucous membrane of the colon and small intestine.

Cross-reactivity of BCD-148 was demonstrated in the samples of the human proper substance of cornea, suprarenal cortex, and Hassal's bodies.

1.3.2. Clinical studies

1.3.2.1. Overview of clinical methodology

Currently, a Phase I clinical study was performed in healthy volunteers. Results of this study provided a pilot estimate of the pharmacokinetics, pharmacodynamics, and safety of BCD-148. This was an open-label, single-center, non-randomized, dose-escalation clinical study of the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of BCD-148 in healthy volunteers (Phase I, '3+3' design).

The study utilized the '3+3' design with dose escalation across 8 cohorts of healthy volunteers. The first three cohorts included one subject each (a 'sentinel volunteer). From Cohort 4 and up, the study was had a traditional 3+3 design, i.e. three-patient cohorts were enrolled at each dose level.

Thus, the BCD-148-1 study involved 18 healthy volunteers in 8 cohorts:

1. Cohort 01: 1 subject received a single 30-minute IV infusion of 0.0007 mg/kg BCD-148.
2. Cohort 02: 1 subject received a single 30-minute IV infusion of 0.007 mg/kg BCD-148.

Samsung Bioepis Exhibit No. 1002
Page 11856

3. Cohort 03: 1 subject received a single 30-minute IV infusion of 50 mg BCD-148.
4. Cohort 04: 3 subjects, each received a single 30-minute IV infusion of 150 mg BCD-148.
5. Cohort 05: 3 subjects, each received a single 30-minute IV infusion of 300 mg BCD-148.
6. Cohort 06: 3 subjects, each received a single 30-minute IV infusion of 600 mg BCD-148.
7. Cohort 07: 3 subjects, each received a single 30-minute IV infusion of 900 mg BCD-148.
8. Cohort 08: 3 subjects, each received a single 30-minute IV infusion of 1200 mg BCD-148.

1.3.2.2. Discussion of pharmacokinetic results

One of the main objectives of the BCD-148-01 study was to investigate the pharmacokinetics of different doses of BCD-148 administered as a single IV infusion.

The PK was evaluated based on the BCD-148 concentration in the serum samples collected across the study.

Serum concentrations of the monoclonal antibody to the complement protein C5 were used to calculate the following PK parameters:

Main

- $AUC_{(0\text{-}1392)}$ and $AUC_{(0\text{-}\infty)}$ of BCD-148

Secondary:

- C_{max}
- T_{max}
- $T_{1/2}$
- K_{el}
- Cl
- Vd.

It has been shown that single IV infusions of ascending doses of BCD-148 result in a gradual increase of the study drug concentration in the serum.

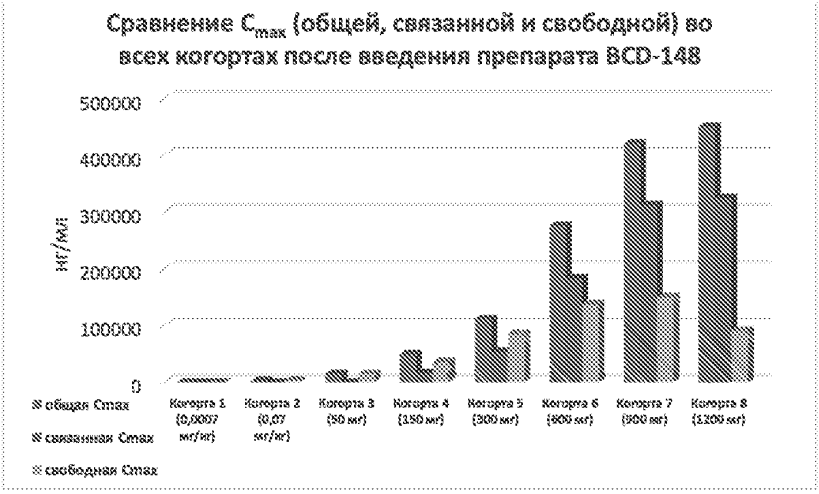
To better understand the distribution of BCD-148 in the serum, the concentrations of total anti-C5 monoclonal antibody (MAb) were measured along with the concentrations of free and conjugated anti-C5 MAb.

The highest serum concentrations of the anti-C5 MAb (C_{max}) following the IV infusion were 450796 ng/mL for the total eculizumab (conjugated + free), 325148 ng/mL for the free eculizumab, and 150928 ng/mL for the conjugated eculizumab (the numbers presented are the median values). The median time to the maximum concentration is 5 min post-infusion in all cohorts (measured for the total anti-C5 MAb concentrations).

Samsung Bioepis Exhibit No. 1002
Page 11857

The most meaningful results were obtained in cohorts 06, 07, and 08, where the subjects received a single IV infusion of 600 mg, 900 mg, and 1200 mg, respectively. In these cohorts, the level of free anti-C5 MAb during the first days post-infusion was higher than the level of conjugated anti-C5 MAb. At the same time, there was a trend towards the decrease in the free anti-C5 MAb concentration and increase in the conjugated MAb concentration, which indicates the gradual inhibition of the complement protein C5. At a certain moment, the concentration of the conjugated anti-C5 MAb started to decrease or entered a plateau phase (Cohort 07), and the concentration of the free anti-C5 MAb also decreased as expected.

Figure 2. The C_{max} (total, conjugated, and free) across all cohorts after the infusion of BCD-148



C_{max} of BCD-148 (total, conjugated, and free) across the cohorts								
ng/mL								
	Cohort 1 (0.0007 mg/kg)	Cohort 2 (0.07 mg/kg)	Cohort 3 (50 mg)	Cohort 4 (150 mg)	Cohort 5 (300 mg)	Cohort 6 (600 mg)	Cohort 7 (900 mg)	Cohort 8 (1200 mg)
Blue – C_{max} total Red – C_{max} conjugated Green – C_{max} free								

The total area under the *Concentration vs. Time* curve from 0 to 1392 h ($AUC_{(0-1392)}$) was also calculated for the total (conjugated + free), conjugated, and free concentrations of BCD-148. It has been shown that the area under the *Concentration vs. Time* tends to increase with dose escalation.

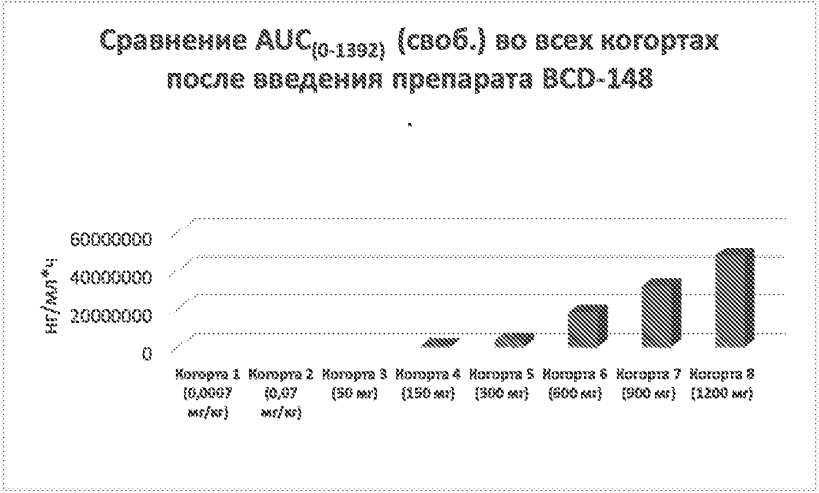
Samsung Bioepis Exhibit No. 1002
Page 11858

A slight decrease in $AUC_{(0-1392)}$, for the total BCD-148 concentration seen in Cohort 08 as compared to Cohort 07 is likely to be due to variations in the amount of the serum C5 between individual subjects.

The concentration of the free anti-C5 MAb in the subject's serum is the most important diagnostic indicator of the required BCD-148 dose.

The $AUC_{(0-1392)}$ values estimated for the concentrations of free BCD-148 in the serum demonstrate the dose-dependent pattern. The directly proportional relationship was most clearly observed in the 600 mg to 1200 mg dose range. The $AUC_{(0-1392)}$ in Cohort 06 (600 mg BCD-148) was 18069033 ng/mL*h; in Cohort 07 (900 mg BCD-148) it was 31744672.5 ng/mL*h; and in Cohort 09 (1200 mg BCD-148) it was 47613022.5 ng/mL*h.

Figure 3. $AUC_{(0-1392)}$ (free) following the BCD-148 infusion across the cohorts



$AUC_{(0-1392)}$ of BCD-148 (free) across the cohorts								
ng/mL*h								
	Cohort 1 (0.0007 mg/kg)	Cohort 2 (0.07 mg/kg)	Cohort 3 (50 mg)	Cohort 4 (150 mg)	Cohort 5 (300 mg)	Cohort 6 (600 mg)	Cohort 7 (900 mg)	Cohort 8 (1200 mg)

Similar results were revealed for the *Time vs. Concentration* curve in the time interval from 0 to infinity ($AUC_{0-\infty}$). Like it was for $AUC_{(0-1392)}$, the strongest tendency towards an increase in $AUC_{0-\infty}$ (free serum anti-C5 MAb) along with the dose increase was observed in cohorts 06, 07, and 08 (600 mg to 1200 mg dose range).

No clear relationship was seen between drug elimination and the dose given to the healthy subjects. The median half-life of the anti-C5 MAb varied from 93 h to 191 h (≈ 4 – 8 days).

Samsung Bioepis Exhibit No. 1002
Page 11859

Currently, Soliris® is the only approved monoclonal antibody to the complement protein C5. However, it was never studied in healthy subjects. The single-dose pharmacokinetics of Soliris® was investigated in two Phase I studies, one involving rheumatoid arthritis patients (C97-001-01) and another involving patients with systemic lupus erythematosus (SLE) (C97-002-01). In these trials, the drug was administered as single doses ranging from 0.1 mg/kg to 8 mg/kg. These studies produced similar results with AUC being directly proportional to the dose. The half-life of Soliris® was 92.94 h (≈ 4 days)[34].

1.3.2.3. Discussion of pharmacodynamic results

The PD effects of BCD-148 in a Phase I study BCD-148-1 were investigated by evaluating the hemolytic activity of the serum complement. One unit of the hemolytic complement (CH_{50}) is the amount of complement that results in 50% hemolysis of 0.5 mL standard suspended sensitized erythrocytes after a 45-min incubation at 37 °C[35].

Parameters calculated for the hemolytic complement activity in the serum were as follows:

- ABEC (the area between the baseline and effect curves)
- $AUC_{0\text{-}1392}$ (the area under the *Time vs. Concentration* curve from infusion to 1392 h (58 days post-infusion) and $AUC_{0\text{-}\infty}$ (from infusion to infinity)
- E_{max} (the maximum post-infusion effect)
- T_{max} (the time to E_{max}).

It was demonstrated that a single IV infusion of BCD-148 in ascending doses produced a significant reduction in the serum complement hemolytic activity (CH50) in healthy subjects.

The complement hemolytic activity was inversely proportional to the dose, thus suggesting the dose-dependent relationship.

The PD effect (inhibition of the serum hemolytic complement activity below the limit of detection) was seen 5 min post-infusion in all subjects starting from Cohort 04 and up (e.g. after a single IV infusion of 150 mg or more). The duration of the effect increased in direct proportion to the dose infused.

In general, the intensity of PD effects ($AUEC_{(0\text{-}1392)}$ for serum hemolytic complement activity) decreased inversely proportional to administered BCD-148 doses.

In general, the intensity of PD effects ($AUEC_{(0\text{-}1392)}$ for serum hemolytic complement activity) decreased inversely proportional to administered BCD-148 doses.

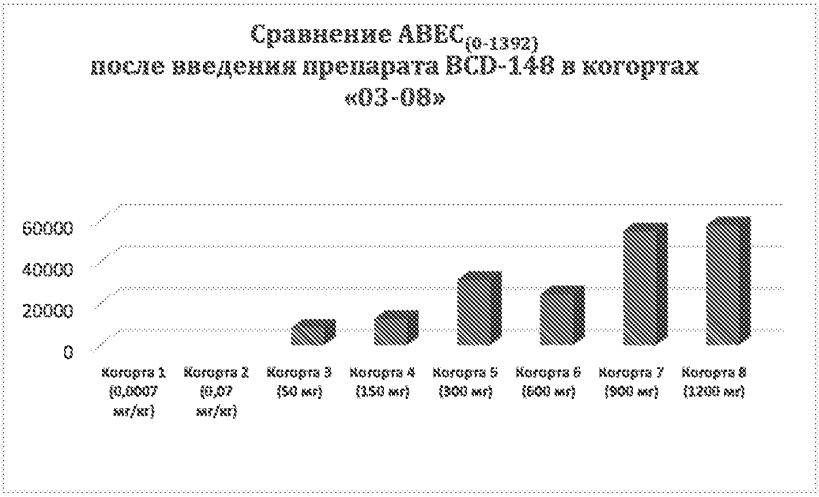
[34]http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000791/WC500054212.pdf
[35]Measuring the 50% Haemolytic Complement (CH50) Activity of Serum. Maurizio Costabile. J. of Vis. Exper. 37. 2010

Samsung Bioepis Exhibit No. 1002
Page 11860

Since the quantitative baseline (pre-infusion) level of hemolytic activity varies between subjects, the most relevant measure of the BCD-148 pharmacodynamics is the area between the baseline and effect curves (ABEC) from 0 to 1392 h. To account for baseline variations, the baseline (pre-infusion) values were subtracted from all subsequent measurements. The area was calculated using the absolute effect values that demonstrated a reduction of serum hemolytic complement activity from baseline. Therefore, the ABEC values are inverse to the $AUEC_{(0\text{-}1392)}$. It was considered unfeasible to use this parameter in the minimum dose cohorts (01 and 02) since individual CH50 values post-infusion in most cases did not change from baseline or sometimes were even higher. The analysis showed that the serum hemolytic complement activity changes directly proportional to the drug dose, which indicates the dose-dependent pharmacodynamics. Higher doses of BCD-148 produced more pronounced changes from baseline in hemolytic activity.

Samsung Bioepis Exhibit No. 1002
Page 11861

Figure 4. $ABEC_{(0-1392)}$ following the BCD-148 infusion in cohorts 03 to 08



$ABEC_{(0-1392)}$ of BCD-148 across cohorts 03-08								
	Cohort 1 (0.0007 mg/kg)	Cohort 2 (0.07 mg/kg)	Cohort 3 (50 mg)	Cohort 4 (150 mg)	Cohort 5 (300 mg)	Cohort 6 (600 mg)	Cohort 7 (900 mg)	Cohort 8 (1200 mg)

The longest PD effect of BCD-148 was seen in subjects from cohorts 06, 07, and 08 (600 mg, 900 mg, and 1200 mg, respectively), which matches the data obtained in the PK studies.

All three subjects in Cohort 06 (600 mg) showed complete inhibition of the serum hemolytic complement activity up to 264 h (11 days) post-infusion. Two of them had zero CH50 even 360 h (15 days) post-infusion.

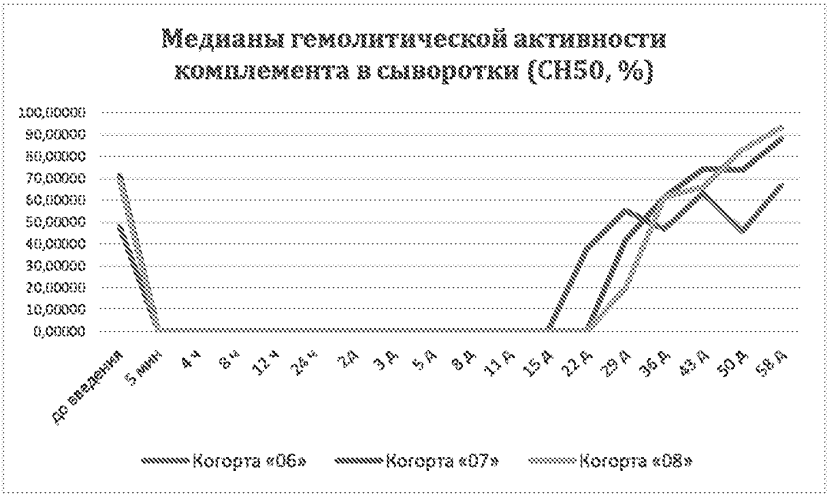
All three subjects in Cohort 07 (900 mg) showed CH50 inhibition through 528 h (22 days) after a single infusion of BCD-148.

All three subjects in the highest-dose Cohort 08 (1200 mg) also had CH50 inhibited for 22 days; in one subject this effect remained for 29 days post-infusion.

Thus, the study showed that the PD effect of BCD-148 increases in direct proportion with the dose.

Samsung Bioepis Exhibit No. 1002
Page 11862

Figure 5. Serum hemolytic complement activity in cohorts 06 to 08



Median hemolytic complement activity in the serum (CH50, %)																	
Pre-infusion	5 min	4 h	8 h	12 h	24 h	D2	D3	D5	D8	D11	D15	D22	D29	D36	D43	D50	D58
Blue – Cohort 06						Red – Cohort 07							Green – Cohort 08				

All cohorts demonstrated a reduction in the serum hemolytic complement activity immediately after the infusion of BCD-148. However, subjects in the first three cohorts received very low doses of the study drug, and the hemolytic activity reduction from baseline was insignificant. In subjects who received a single infusion of 150 mg to 1200 mg BCD-148 (cohorts 04-08), hemolytic activity was below the limit of detection 5 minutes after the infusion.

Thus, the duration of the PD effect is directly related to the dose of the investigational product and varied on an average from 11 to 22 days for 600 mg to 1200 mg BCD-148 dose range (cohorts 06-08). Further increase in the hemolytic complement activity was gradual, and in some subjects, the activity level measured 58 days after a single BCD-148 infusion did not exceed the pre-infusion baseline level.

1.3.2.4. Discussion of the safety results

In a Phase I study, BCD-148 showed a favorable safety profile and was well tolerated by subjects.

Adverse events following the infusion of BCD-148 were registered in 8 out of 18 subjects (44.44%) across all the cohorts. All AEs registered with BCD-148 were of grade 1 in severity (CTCAE 4.03), except for one event of grade 2 total bilirubin increased. According to the investigators, the majority of AEs were possibly related to the study drug. All registered AEs were

Samsung Bioepis Exhibit No. 1002
Page 11863

asymptomatic and did not require any medical measures to be taken. Since three subjects had more than one AE after a BCD-148 infusion, the total number of AEs in this study was 12. Of these 12 AEs, 10 were considered possibly related and 2 unlikely related to the study drug. All AEs resolved without any consequences by the time when each subject completed the study as scheduled.

Dose-limiting toxicity events (DLTs) were also captured in this study. DLTs were defined as any hematology and non-hematology AEs that could be potentially related to the study drug, occurred within 28 days post-infusion, and were of CTCAE 4.03 severity grade 3 or greater (acute infections were considered DLTs only if they were grade 4 or greater in severity). To provide the most comprehensive safety assessment, the study involved an Independent Data Monitoring Committee (IDMC) that reviewed the data on safety/tolerability and DLTs.

None of the subjects developed any AEs that could be considered a DLT.

No AEs of severity grade 3/4 (CTCAE 4.03) were registered in the study as well as no serious AEs.

All 18 subjects who were dosed with BCD-148 attended all scheduled visits, underwent all scheduled procedures, and completed the study as per protocol. Nobody dropped out due to AEs/SAEs or due to any other reasons. No deaths were reported in the study.

The table below shows assessment results for the safety endpoints in the overall population (n = 18) and in each cohort (01-08).

Samsung Bioepis Exhibit No. 1002
Page 11864

Table 4. Summary of BCD-148 safety for the overall population of healthy subjects (n = 18) and by cohorts (Cohort 01 is 0.0007 mg/kg; Cohort 02 is 0.07 mg/kg; Cohort 03 is 50 mg; Cohort 04 is 150 mg; Cohort 05 is 300 mg; Cohort 06 is 600 mg; Cohort 07 is 900 mg; and Cohort08 is 1200 mg)

Proportion of subjects who had	Cohorts								
	Overall population Cohorts 01 to 08 (n=18)	**Cohort 01: 0.0007 mg/kg (n = 1)**	**Cohort 02: 0.07 mg/kg (n = 1)**	**Cohort 03: 50 mg/kg (n = 1)**	**Cohort 04: 150 mg (n = 3)**	**Cohort 05: 300 mg (n = 3)**	**Cohort 06: 600 mg (n = 3)**	**Cohort 07: 900 mg (n = 3)**	**Cohort 08: 1200 mg (n = 3)**
any AE/SAE	8 (44.44%)	1 (100%)	0 (0.0%)	1 (100%)	1 (33.33%)	0 (0.0%)	2 (66.67%)	2 (66.67%)	1 (33.33%)
Therapy-related AEs/SAEs	8 (44.44%)	1 (100%)	0 (0.0%)	1 (100%)	1 (33.33%)	0 (0.0%)	2 (66.67%)	2 (66.67%)	1 (33.33%)
AEs grade 3/4 (including those related to BCD-148)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SAEs (including those related to BCD-148)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
DLTs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Early withdrawals due to AEs/SAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

The statistical significance of the difference in the AE incidence between the cohorts was not estimated due to the small number of subjects in each cohort, as these results would be not statistically valid. Although, no clear relationship between the dose and AE severity was seen as the dose increased.

Samsung Bioepis Exhibit No. 1002
Page 11865

All AEs captured after the infusion of BCD-148 were either laboratory abnormalities (abnormal results of hematology, chemistry, coagulation test, or urinalysis) or instrumental abnormalities (ECG), were short-term, transient, asymptomatic, and self-resolved without any consequences by the time the subject completed the trial.

- Blood and lymphatic system disorders: INR increased, WBC count decreased, neutrophil count decreased.
- Hepatobiliary disorders: AST increased, total bilirubin increased.
- Cardiovascular system disorders (judged based on the ECG): Sinus arrhythmia, conduction disturbance (short PR (PQ).)
- Renal and urinary disorders: Cloudy urine, urine crystals
- Metabolism and nutrition disorders: Total protein decreased, creatinine decreased.

Overall, the captured AEs were considered expected according to the safety information available for the authorized anti-C5 drug Soliris®, as described in the Summary of Product Characteristics effective at the time of the report[36].

As part of the drug safety monitoring, immunogenicity was evaluated before the drug infusion, on Day 30 (29 days post-infusion) and at the completion of the main study period on Day 59 (58 days post-infusion).

Immunogenicity was evaluated based on the presence or absence of binding (BAb) and neutralizing antibodies (NAb) against the anti-C5 MAb in the subjects' serum. Binding anti-drug antibodies were detected by ELISA.

No binding antibodies against the anti-C5 MAb were detected at any timepoint in any of the 18 subjects. Therefore, the testing for neutralizing antibodies was not performed.

Table 5. Immunogenicity cohorts (n = 18)

Endpoint	Cohorts 01-08 (n=18)	
	n	%
Proportion of BAb-positive patients at Day 59	0	0.00

Thus, all tested single IV doses of BCD-148 demonstrated a favorable safety profile in healthy subjects. The study results are consistent with the available information on the safety of an authorized therapeutic anti-C5 monoclonal antibody Soliris®.

1.3.2.5. Discussion of the Phase I study results

The Phase I BCD-148-1 study aimed at evaluating the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of single escalating IV doses of BCD-148 (a

[36]Soliris® Summary of Product Characteristics http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000791/WC500054208.pdf

Samsung Bioepis Exhibit No. 1002
Page 11866

monoclonal antibody targeting the complement protein C5; JSC BIOCAD, Russia) in healthy subjects. The results were used to establish the therapeutic dose range for BCD-148 for the further investigation of its clinical effects in the target population of PNH patients.

The study data analysis has clearly demonstrated the favorable safety profile of BCD-148 at doses from 0.0007 mg/kg to 1200 mg. No AEs of grade 3 or higher (CTCAE 4.03) or serious AEs were captured in this study as well as no DLTs.

In most cases, AEs were presented by individual laboratory abnormalities that resolved before the subject completed the study. The study results are consistent with the available information on the safety of an authorized therapeutic anti-C5 monoclonal antibody Soliris®.

No binding antibodies against the anti-C5 MAb were detected in any of the 18 subjects.

Results of the single-dose PK study of IV BCD-148 showed the dose-dependent pharmacokinetics: the C_{max} and AUC increased directly proportional to the dose. However, like for other therapeutic MAbs, the elimination characteristics were not dose-dependent.

The pharmacodynamic effect of BCD-148 increases in a dose-proportional manner. A reduction in the serum hemolytic complement activity was seen immediately after the infusion of BCD-148. The duration of response also increased with higher doses and varied on an average from 11 to 22 days: max 11 days for 600 mg BCD-148 and 22 days for 1200 mg BCD-148. Thus, the mean duration or response was approximately 2 weeks. Further increase in the hemolytic complement activity was gradual, and in some subjects, the activity level measured 58 days after a single BCD-148 infusion did not exceed the pre-infusion baseline level.

The correlative analysis of PK and PD results suggest the dose-dependent manner for both PK and PD of BCD-148. The most significant reduction in the complement C5 function was observed in subjects dosed with 600 - 1200 mg BCD-148. The concentration of anti-C5 MAb in the serum also increased in a dose-dependent way. A diagnostic factor essential for the determination of the required amount of BCD-148, the $AUC_{(0\text{-}1392)}$ estimated for free BCD-148 in the serum, was also dose-dependent. Most clearly this relationship was observed in a dose range from 600 mg to 1200 mg.

Considering the safety of all doses tested in this study, no immunogenic response to BCD-148, PK and PD profiles, and previously obtained potency data, the BCD-148 dose range recommended for further clinical development (studies of BCD-148 therapeutic effects) is from 600 mg to 1200 mg.

Thus, the Phase I study BCD-148-1 has characterized the PK, PD, and safety of BCD-148. It was demonstrated that 600 mg, 900 mg, and 1220 mg doses should be considered therapeutic as they result in optimal levels of anti-C5 MAb in the serum and produce a long-term effect (reduction

Samsung Bioepis Exhibit No. 1002
Page 11867

of the hemolytic complement activity). The reduction of the complement C5 function and, thus, inhibition of the complement hemolytic activity is a prognostic marker of the complement activity improvement. In this study, the mean duration of response for 600-1200 mg dose range was 2 weeks.

Results from this study are consistent with the current knowledge about the PK and PD of Soliris®, a drug similar to BCD-148 in its amino acid sequence and mechanism of action. Thus, it was assumed that the optimal BCD-148 dosing regimen ensuring the maximum benefit for patients is the same as that for Soliris® - the initial phase with weekly 600-1200 mg infusions followed by a maintenance phase with bi-weekly 600-1200 mg infusions.

Further clinical development of BCD-148 was considered feasible. The drug is expected to demonstrate a favorable risk/benefit balance in the target population of patients with a complement system disorder.

1.4. Summary of the known and potential risks and benefits to human subjects, if any (risk/benefit balance)

1.4.1. Benefit assessment

BCD-148 is a biosimilar to Soliris®.

The reference drug has been studied in multiple clinical trials proved effective and safe in PNH and aHUS patients.

The BCD-148-3 study is planned to investigate the PK, PD, safety, and immunogenicity of BCD-148 versus the reference drug Soliris®.

Study participants will not get any personal benefit other than a comprehensive physical examination and an anti-meningococcal vaccination required by the protocol. The data obtained at the study completion are to be of high scientific value and will potentially help to implement the biosimilar into clinical practice, thus making the treatment of such rare and severe diseases as PNH and aHUS more available to patients.

1.4.2. Risk assessment

The section below provides the risk assessment for BCD-148/Soliris®. The risk assessment is based on the known and anticipated adverse events that could occur due to the use of the therapeutic protein that selectively inhibits the complement component C5.

Since these drugs bind the complement C5, study subjects can possibly develop acute reactions caused by massive activation of immune cells and cytokine release. Because of the risk

Samsung Bioepis Exhibit No. 1002
Page 11868

of such complication, BIOCAD performed a non-clinical study to investigate the cytokine release by PBMC in response to BCD-148 in the cell culture obtained from healthy subjects. When added to the PBMC culture, BCD-148 did not increase concentrations of IL2, IL4, IL10, TNFα, IFNγ, IL17A, IL-1β, or IL6 vs. control. Thus, the same result is assumed to be seen in humans, and the risk of the cytokine release syndrome (CRS) is considered minimal. In the BCD-148-1 study, none of the subjects, including those in 900 mg and 1200 mg cohorts, had any adverse events that could be suggestive of the CRS. Therefore, the risk of the CRS in the subjects planned to be included in the BCD-148-3 is very low.

BCD-148 inhibits the cleavage of C5 to C5a and C5b and thereby prevents the generation of the terminal complement complex C5b-C9 and inhibits the complement-mediated intravascular hemolysis. It is known from clinical practice that repeated use of anti-C5 MAb increases patients' susceptibility to infections, especially with encapsulated bacteria (mainly meningococcal infection). Although a single infusion of BCD-148 given to a healthy subject is associated with a low risk of meningococcal infection, all study participants will receive a meningococcal conjugate vaccine (serotypes A, C, Y, and W135) at least 14 days before the planned infusion. This time is sufficient for a subject to develop immunity as the polysaccharide vaccine induces rapid (day 5 to day 14) increase in the antibody titer[37]. Thus, this vaccination allows reducing the risk of said infection to a minimum.

All subjects will be given a conjugated meningococcal vaccine (MCV-4). According to the publications, the immunogenicity and safety of this vaccine were investigated in a number of clinical studies with a 1-month follow up. The vaccine is generally characterized by a favorable safety profile and good tolerability. The most common post-vaccination adverse events in subjects from 18 to 55 years old were pain in the injection site, headache, and fatigue[38]. Based on the information on good tolerability and low incidence of post-vaccination complications, the risk of vaccine-associated adverse events in study subjects was estimated as low. During the screening period, a study team member will, in addition to scheduled visits, make a phone call to follow up with the patient regarding potential post-vaccination complications.

As there is a risk of latent infection re-activation associated with BCD-148, all subjects will be carefully checked at enrollment for any current acute/chronic infections or those in the past. Information for study participants provided in the Informed Consent Form will have a warning

[37]M.V. Nagibina, Yu.Ya. Vengerov, I.V. Shestakova Clinical Recommendations. Meningococcal Infection in Adults. Meningococcemia. 2015
[38]Menacra Instruction for Medical Use http://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=feb5d190-3f64-4061-ab27-a35af61dfbbb&t=

Samsung Bioepis Exhibit No. 1002
Page 11869

that if a subject develops high body temperature, headache with fever and/or stiffness in the neck, or photophobia, he should contact his doctor immediately as these could be signs of meningococcal infection. Diagnosing this hypothetically possible complication early allows take prompt therapeutic actions and minimize any adverse consequences.

This protocol has specific inclusion/exclusion criteria aimed at minimizing the risk of any undesirable effects and the procedure for continuous clinical and laboratory monitoring of the subjects.

Since there is a risk of latent infection re-activation, there will be a mandatory testing for HIV, chronic viral hepatitis, and tuberculosis. All subjects will also be checked for indirect signs of inflammation (hematology, chemistry and urine tests). During the study, the safety monitoring will be implemented including but not limited to capturing any infections.

BCD-148 is a pro, therefore there is a hypothetical risk of allergic reactions. To minimize this risk, subjects with a history of allergies, including anaphylaxis, as well as subjects with hypersensitivity to murine proteins and/or any components of BCD-148 and/or Soliris® will not be enrolled in this study. In addition, to monitor the subject's health and manage any acute conditions that may occur, the subjects will stay in the study center for the first two days (48 h) after the infusion.

The amino acid sequence of BCD-148 is the same as the one of Soliris® (eculizumab). Therefore, the nature and frequency of adverse events seen with BCD-148 may be similar to those with Soliris®. In clinical studies where aHUS and PNH patients received multiple doses of eculizumab, the headache was the most frequent adverse event. If the study participant develops a headache, it can be treated symptomatically. The risk that this adverse event becomes clinically significant is very low.

Patients treated with eculizumab frequently developed leukopenia and thrombocytopenia. Thus, this study will include subjects with normal baseline hematology results (tested during the screening) and with no clotting disorders. The main hematology components will be monitored throughout the study, and appropriate measures will be taken if any abnormalities are revealed.

The adverse events described blow were seen in clinical practice with the long-term use of eculizumab in PNH and aHUS patients. Each subject involved in this study will receive a single dose of BCD-148/Soliris®, which does not put him at significant risk of developing any of the adverse events registered in PNH and aHUS patients. Healthy subjects by definition have no clinically significant co-morbidities that might increase the risk of any certain disorder (e.g. cardiovascular, GI, hepatobiliary, or urinary disorder) following a single infusion of BCD-148/Soliris®.

Samsung Bioepis Exhibit No. 1002
Page 11870

Below it is a summary of adverse reactions reported in clinical trials and during the postmarketing use of eculizumab in PNH and aHUS patients, as presented in the Soliris® Instruction for Medical Use. Adverse events are listed by MedDRA system/organ classes and by incidence according to the WHO classification: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10000, <1/1000); and very rare (<1/10000)[39].

Blood and lymphatic system disorders: Common: leukopenia, thrombocytopenia, and hemolysis. Uncommon: coagulopathy, red blood cell agglutination, abnormal clotting, anemia, lymphopenia.

Neoplasms benign, malignant and unspecified: Uncommon: myelodysplastic syndrome, melanoma.

Cardiac disorders: Uncommon: palpitation.

Vascular disorders: Common: BP decreased. Uncommon: hematoma, BP increased, accelerated hypertension, hot flush, vein disorder.

Ear and labyrinth disorders: Uncommon: tinnitus, vertigo.

Endocrine disorders: Uncommon: hyperthyroid.

Eye disorders: Uncommon: conjunctival irritation, blurred vision.

Gastrointestinal disorders: Common: abdominal pain, constipation, diarrhea, dyspepsia, nausea, vomiting. Uncommon: abdominal distension, gastroesophageal reflux disease, gingival pain, peritonitis.

Metabolism and nutrition disorders: Common: loss of appetite. Uncommon: anorexia.

Hepatobiliary disorders: Uncommon: jaundice.

Nervous system disorders: Very common: headache. Common: dizziness, dysgeusia. Uncommon: syncope, tremor, paresthesia.

Respiratory, thoracic and mediastinal disorders: Common: cough, nasal congestion, oropharyngeal pain, dyspnea, rhinorrhea. Uncommon: hemoptysis, throat irritation.

Psychiatric disorders: Uncommon: abnormal dreams, anxiety, depression, insomnia, mood swings, and sleep disorder.

Renal and urinary disorders: Uncommon: hematuria, renal impairment, and dysuria.

Skin and subcutaneous tissue disorders: Common: alopecia, pruritus, rash. Uncommon: urticaria, dermatitis, erythema, petechia, skin depigmentation, hyperhidrosis, dry skin.

[39] https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=06cf0b20-6e76-4225-842b-18eb02976ac3&t=32d7d8df-4025-4f04-93e5-e800ca43cdd7

Samsung Bioepis Exhibit No. 1002
Page 11871

Musculoskeletal and connective tissue disorders: Common: arthralgia, back pain, myalgia, neck pain, pain in extremity, bone pain, muscle spasm. Uncommon: joint swelling, trismus.

Infections and infestations: Common: upper respiratory tract infections, urinary tract infections (including viral infections), nasopharyngitis, bronchitis, oral herpes, meningococcal sepsis, bacterial arthritis, aspergillus infection. Uncommon: lower respiratory tract infection, GI infection, cystitis, sinusitis, tooth and gingival infection, abscess, cellulitis, fungal infection, influenza, Neisseria and Hemophilus infections, impetigo, meningococcal meningitis, sepsis, septic shock, pneumonia.

Immune system disorders: Common: anaphylactic reaction. Uncommon: hypersensitivity.

Reproductive system and breast disorders: Uncommon: menstrual disorder, spontaneous penile erection.

General disorders and administration site conditions: Common: chest discomfort, chills, fatigue, edema, pyrexia, asthenia, influenza-like illness. Uncommon: chest pain, paresthesia, infusion site hemorrhage and pain, feeling hot.

Investigations: Common: Coombs test positive. Uncommon: AST increased, ALT increased, GGT increased, hemoglobin decreased, hematocrit decreased.

Injury, poisoning and procedural complication: Uncommon: administration site conditions.

In all clinical trials, including PNH and aHUS clinical trials, the most severe adverse reaction was meningococcal septicemia. Antibodies to Soliris® were detected in 2% of treated PNH patients and 3% of aHUS patients, thus the drug was qualified as low-immunogenic.

Cases of haemolysis have been reported in the setting of missed or delayed Soliris® dose in PNH clinical trials.

Clinical signs of thrombotic microangiopathy have been reported in the setting of missed or delayed Soliris® dose in aHUS clinical trials.

Safety information from other clinical studies Supportive safety data were obtained in 11 completed clinical studies that included 716 patients exposed to Soliris® in other disease populations other than PNH and aHUS. The cumulative analysis of these data revealed 1 case of meningococcal meningitis in an un-vaccinated patient diagnosed with idiopathic membranous glomerulonephropathy.

The analysis of safety data obtained in all double-blind, placebo-controlled trials in patient populations other than PNH (526 patients dosed with Soliris® and 221 patients dosed with placebo) showed that the following adverse events were reported with the incidence of 2% or greater: upper respiratory tract infection, rash, and infusion reactions.

Conclusions

Samsung Bioepis Exhibit No. 1002
Page 11872

Given the mechanism of action, eculizumab is considered safe with regard to the health and wellbeing of the study participants.

The risks for study subjects will be minimized through the protocol-specified inclusion/exclusion criteria and procedures. A single dose of BCD-148/Soliris® is not expected to cause any severe adverse events. The study participants will be monitored for 59 days, which covers five Soliris® half-life periods (the mean half-life of Soliris® is 11.3 days, hence 11.3 x 5 $T_{1/2}$ = 56.5 days).

No medical benefit is expected for the study participants other than a comprehensive medical examination and immunization (development of bactericidal antibodies) against meningococcus serotypes A, C, W_{135}, and Y.

Thus, the benefit-risk ratio is expected to be suitable.

1.5. Description and justification of route of administration, doses, and dosing regimen

1.5.1 Description and justification of the study design

The BCD-148-3 trial is a double-blind, randomized clinical study to compare the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of single intravenous doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in healthy subjects. The study is planned to involve two parallel arms: the BCD-148 arm and the Soliris® arm.

The suggested double-blind randomized parallel-group design that utilizes a drug with demonstrated efficacy (reference drug) as an active control is aimed at proving pharmacokinetic equivalence of a biosimilar BCD-148 (test drug) and Soliris® (reference drug) in terms of the key PK parameters. This is a common approach in the development of biosimilars, which complies with the Russian [40] and international[41] regulations.

The EMA[42,43] The EMA, guidelines state that for long half-life products (such as eculizumab) a parallel-group study design is preferred to crossover *("A parallel group design may be necessary due to the long half-life of MAbs and the potential influence of immunogenicity").*

The study population was selected according to recommendations laid out in the EMA's *Guideline on Similar biological medicinal products containing monoclonal antibodies – non-*

[40] A.N. Mironov, V.G. Kukes, V.I. Petrov, A.L. Kuznetsov, D.V. Goryachev, R.R. Niyazov, A.B. Prokofyeva, S.V. Nedogoda, M.Yu.Frolov, A.Shnayder. Bioequvalence evaluation for generic medicinal products // Guidance on evaluation of medicinal products Vol. I – M.: Grif and K, 2013.
[41] Rulesfor investigation of biologics (Eurasian Economic Comission) https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78
[42] Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010, 2012.
[43] Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)

Samsung Bioepis Exhibit No. 1002
Page 11873

clinical and clinical issues[44] in the Eurasian Economic Unit's guidelines[45] *("... if feasible, a single dose study in healthy volunteers is recommended, which could provide important information on biosimilarity.").*

Blood sampling points for PK assessment were chosen based on the available information on eculizumab PK. According to the international guidelines, blood sampling in single-dose studies should cover a long-term period including the late-phase elimination. With the knowledge of the Soliris® half-life ($T_{½}$ 11.3±3 days or 272±82 h), this study with multiple blood collections for PK, PD, and safety assessment was planned to last for 59 days. This period is approximately 5 half-lives of eculizumab (56.5 days 1360 h). The sampling time should ensure several collections for each fragment of the PK curve - at least 3 samples in the initial increase phase and at least 5 samples in the decrease phase. With this consideration in mind and with the available data on eculizumab PK, the following blood collection timepoints were chosen for the study of BCD-148/Soliris®: immediately before dosing, then 5 min, 4 h, 8 h, 12 h, 24 h, 48 h, 72 h, 120 h, 192 h, 264 h, 360 h, 528 h, 696 h, 864 h, 1032 h, 1200 h and 1392 h post-dose.

The primary endpoint to test the hypothesis ($AUC_{(0-\infty)}$ - the area under the *Time vs. Concentration* curve from 0 h to infinity) and secondary PK parameters were chosen as suggested in the EMA's guideline on biosimilar monoclonal antibodies[46] *("In a single dose study, the primary parameter should be the $AUC_{(0-inf)}$. Secondary parameters such as C_{max}, T_{max}, volume of distribution, and half-life, should also be estimated").*

This study also includes a thorough assessment and comparison of eculizumab PD marker - hemolytic complement activity. This is to provide the most valid and comprehensive data on the comparability of BCD-148 and the reference drug Soliris® (*"Pharmacokinetic studies should be combined with pharmacodynamic (PD) endpoints, where available. This could add valuable information for the overall comparability exercise. PD markers are especially valuable if they are sensitive enough in order to detect small differences, and if they can be measured with sufficient precision)* [47].

[44] Guideline on Similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May, 2012.
[45]Rules for investigation of biologics (Eurasian Economic Commission) https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78
[46] Guideline on Similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues, May, 2012.
[47]Rules for investigation of biologics (Eurasian Economic Commission) https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78

Samsung Bioepis Exhibit No. 1002
Page 11874

1.5.2. Description and justification of the route of administration, doses, and dosage regimen

In this clinical study, healthy subjects will receive a single infusion of 900 mg BCD-148 or 900 mg Soliris® each.

The test drug BCD-148 is a biosimilar to Soliris®, a drug used to treat PNH and aHUS. Therefore, the dose and route of administration (900 mg given as an IV drip infusion) proposed in this study match the standard single therapeutic dose used in the maintenance treatment phase in PNH patients as described in the approved Soliris® Instruction for Medical Use[48].

A single dose of the test drug puts the subjects at a minimal risk of any health damage. A single dose administration with a subsequent follow-up period allows investigating, as full as possible, the PK and PD of the drug. This regimen avoids any carry-over (cumulative) effects, which are possible upon repeated dose administration of a monoclonal drug with unknown pharmacokinetics. Therefore, such regimen brings to a minimum the risk of data contamination. Since there are certain health risks associated with immunosuppression caused by complement C5 inhibition, assessment of the clinical effects of the repeated-dose regimen in patients is preferred in Phase II clinical studies.

A single drip infusion of eculizumab with subsequent follow-up is to demonstrate whether BCD-148 and Soliris® have equivalent PK as well as to investigate and compare their PD and safety.

Eculizumab is used to treat PNH and aHUS. In both diseases, it is used at a 900 mg dose (maintenance phase in PNH and initial phase in aHUS. Thus, this dose is the most sensitive one to detect the differences (if any) in the PK between BCD-148 and Soliris®. This approach is consistent with the international requirements stated in the above listed guidelines *("In principle, it is not required to test all therapeutic dosage regimens; the most sensitive dose should be selected to detect potential differences in PK between the biosimilar and the reference products").*

Conclusions

The study design, route of administration, dosing regimen, and follow up methodology are feasible, ethically and scientifically justified, and do not bring any excessive risk to study subjects.

1.6. Clinical study compliance with regulatory requirements

The clinical trial will be conducted according to this Protocol developed in full compliance with the current law of the Russian Federation, Federal Law No. 61-FZ of April 12, 2012: *On the Circulation of*

[48] https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=775bf971-249e-427e-9b82-1c5c2a9c2c51&t=

Samsung Bioepis Exhibit No. 1002
Page 11875

Medicines; National Standard of the Russian Federation GOST R 52379-2005 *Good Clinical Practice*; the rules of Good Clinical Practice of the Eurasian Economic Union; the Constitution of the Russian Federation; Federal Law No. 323-FZ of November 21, 2011: *On Public Health Protection in the Russian Federation*; the WMA Declaration of Helsinki (Fortaleza 2013), Order No. 200n of April 01, 2016 *On Approval of the Good Clinical Practice*; the GCP principles, and the current law and regulations of the participating countries.

1.7. Study population

Healthy male subjects aged from 18 to 45 years (inclusive) and meeting the eligibility criteria set by the Protocol.

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Samsung Bioepis Exhibit No. 1002
Page 11876

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11. Hillmen P., Muus P., Dührsen U. et al. Effect of the complement inhibitor eculizumab on thromboembolism in patients. Blood. 2007 Dec 1;110(12):4123-8.

12. Extension of indication variation assessment report EMA/CHMP/204109/2015.

Samsung Bioepis Exhibit No. 1002
Page 11877

2. STUDY PURPOSE AND OBJECTIVES

2.1 Study purpose

To perform a comparative assessment of the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of a single intravenous infusion of BCD-148 and Soliris® in healthy subjects.

2.2 Study objectives

1. To determine and compare the PK parameters of BCD-148 and Soliris®, each given as a single intravenous infusion
2. To determine and compare the PD parameters of BCD-148 and Soliris®, each given as a single intravenous infusion
3. To determine and compare the adverse event profile with a single infusion of BCD-148 and Soliris®
4. To evaluate and compare the proportion of BAb- and NAb-positive subjects in the BCD-148 and Soliris® arms after a single drug infusion.

3. STUDY HYPOTHESIS

The study is to test the hypothesis that the test drug BCD-148 and the reference drug Soliris® have equivalent pharmacokinetics. The equivalence hypothesis will be tested for the primary PK endpoint – $AUC_{(0-\infty)}$ of eculizumab after a single IV infusion of BCD-148/Soliris®. BCD-148 will be proved equivalent to Soliris® if the limits of the two-sided 95% CI for the ratio of the geometric means of eculizumab $AUC_{(0-\infty)}$ values after a single IV infusion of BCD-148 and Soliris® fall within 80.00-125.00%.

4. STUDY DESIGN

4.1. Primary and secondary outcome measures to be assessed in the study

4.1.1 PK endpoints

Pharmacokinetic assessment will be based on the concentration of eculizumab (monoclonal antibodies to complement C5) measured in the serum of healthy volunteers.

The primary endpoint for PK assessment after a single infusion of BCD-148/Soliris®:

- $AUC_{0-\infty}$ of eculizumab (the area under the *Concentration vs. Time* curve from 0 to infinity).

Samsung Bioepis Exhibit No. 1002
Page 11878

The secondary endpoints for PK assessment after a single infusion of BCD-148/Soliris®:

- C_{max} of eculizumab (maximum concentration of eculizumab in the serum)
- T_{max} of eculizumab (time to C_{max})
- AUC_{0-1392} of eculizumab (the area under the *Concentration vs. Time* curve from 0 to 1392 h post-infusion)
- $T_{1/2}$ of eculizumab (half-life)
- Vd of eculizumab (steady-state volume of distribution)
- K_{el} of eculizumab (elimination constant)
- Cl of eculizumab (clearance).

Time points for PK blood collections:

- 5 min before the infusion of BCD-148/Soliris®
- 5 min, 4 h (±5 min), 8 h (±10 min), 12 h (±15 min), and 24±1 h post-infusion
- 2 days (48±1 h), 3 days (72±2 h), 5 days (120±3 h), 8 days (192±4 h), 11 days (264±4 h), 15 days (360±4 h), 22 days (528±4 h), 29 days (696±4 h), 36 days (864±4 h), 43 days (1032±4 h), 50 days (1200±4 h), and 58 days (1392±4 h) post-infusion.

  The PK endpoints will be analyzed when all the subjects complete the main study period.

4.1.2 PD endpoints

Pharmacodynamics will be investigated by measuring the hemolytic complement activity in the serum (CH50), where one unit of hemolytic activity is the reciprocal of the serum dilution which causes a 50% hemolysis.

The secondary endpoints for PK assessment after a single infusion of BCD-148/Soliris®:

- $ABEC_{(0-1392)}$ CH50 (the area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h)
- $AUEC_{(0-1392)}$ CH50 ((area under the *Time vs. Effect* curve from 0 to 1392 h)
- E_{min} CH50 (minimum hemolytic complement activity from 0 to 1392 h)
- T_{min} CH50 (time to minimum hemolytic complement activity within the period from 0 to 1392 h).

Time points for PD blood collections:

- 5 min before the infusion of BCD-148/Soliris®

Samsung Bioepis Exhibit No. 1002
Page 11879

- 5 min, 4 h (±5 min), 8 h (±10 min), 12 h (±15 min), and 24±1 h post-infusion
- 2 days (48±1 h), 3 days (72±2 h), 5 days (120±3 h), 8 days (192±4 h), 11 days (264±4 h), 15 days (360±4 h), 22 days (528±4 h), 29 days (696±4 h), 36 days (864±4 h), 43 days (1032±4 h), 50 days (1200±4 h), and 58 days (1392±4 h) post-infusion.

The PD endpoints will be analyzed when all the subjects complete the main study period.

Samsung Bioepis Exhibit No. 1002
Page 11880

4.1.3. Safety endpoints:

- The proportion of subjects who develop AEs/SAEs that, in the investigator's opinion, are related to eculizumab
- The proportion of subjects who develop CTCAE v. 4.03 grade 3/4 AEs that, in the investigator's opinion, are related to eculizumab, by study arms.

The safety endpoints will be analyzed when all the subjects complete the main study period.

4.1.4. Immunogenicity endpoints

- The proportion of BAb- and NAb-positive subjects

Time points for immunogenicity blood collections:

- 5 min before the infusion of BCD-148/Soliris®
- 29 days after the infusion of BCD-148/Soliris®
- Completion of the main study period (Day 59 of the study).

The immunogenicity endpoints will be analyzed when all the subjects complete the main study period.

4.2. Study Design

This is a double-blind, randomized clinical study to compare the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of single intravenous doses of BCD-148 (JSC BIOCAD, Russia) and Soliris® in healthy volunteers

The suggested double-blind randomized parallel-group design that utilizes a drug with demonstrated efficacy (reference drug) as an active control is aimed at proving pharmacokinetic equivalence of a biosimilar BCD-148 (test drug) and Soliris® (reference drug) in terms of the key PK parameters. This is a common approach in the development of biosimilars, which complies with the Russian [49] and international[50] regulations.

The EMA[51,52] guidelines state that for long half-life products (like eculizumab) a parallel-group study design is preferred to crossover.

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[49] A.N. Mironov, V.G. Kukes, V.I. Petrov, A.L. Kuznetsov, D.V. Goryachev, R.R. Niyazov, A.B. Prokofyeva, S.V. Nedogoda, M.Yu.Frolov, A.Shnayder. Bioequvalence evaluation for generic medicinal products // Guidance on evaluation of medicinal products Vol. I – M.: Grif and K, 2013.

[50] Rulesfor investigation of biologics (Eurasian Economic Comission) https://docs.eaeunion.org/docs/ru-ru/01411969/cncd_21112016_78

[51] Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010, 2012.

[52] Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)

Samsung Bioepis Exhibit No. 1002
Page 11881

It is planned to randomized 78 adult healthy volunteers who then will be assigned at a 1:1 ratio to one of two treatment arms: 39 subjects in the BCD-148 arm and 39 subjects in the Soliris® arm.

During the study, each volunteer will receive a single IV infusion of 900 mg BCD-148 (test drug) or 900 mg Soliris® (reference drug).

Before enrollment, all volunteers will be given all the information about this clinical study, its purpose and the risks associated with study participation. After signing the informed consent form (ICF), each subject will undergo a screening examination (no longer than 20 days), which is to find out whether the subject meets the eligibility criteria.

Study periods

1. Screening period will include 3 visits and 1 phone call:

Screening visit 1/ Day -20 – -18

The subject signs the ICF; the screening ID is assigned and eligibility is assessed (subject interview, medical history, physical examination, vital signs [BP, pulse, body temperature, weight, and height]). Laboratory/instrumental tests. Recording SAEs.

Visit 2/ Day -17

The physician performs an additional assessment of the subjects eligibility based on the laboratory/instrumental results, performs a physical examination, and measures axillary temperature, BP, and wrist pulse. If the test results are within the reference range of this particular laboratory, further screening procedures can be performed.

It has been shown that patients treated with eculizumab may have increased susceptibility to infections caused by encapsulated bacteria, especially to meningococcal infection. Therefore, all subjects who are considered eligible for the study will be preventively vaccinated against *Neisseria meningitidis* to ensure their safety (no vaccination will be given at screening if the subject was vaccinated within 2 years before signing the ICF)[53].

One dose (0.5 mL) of the vaccine is given as an intramuscular injection. According to the Instruction for Medical Use of the vaccine used in this study, syncope or pronounced weakness can occur after the vaccine is injected. Therefore, the study team member who gives the vaccine should make sure that the subject will bot jet injured in the case of a syncope. The subject should be monitored for 30 min post-injection.

[53]The subject should have a documented confirmation and should be vaccinated with an MCV4 conjugate vaccine (serotypes A, C, Y and W-135). If the previous vaccination was performed with a vaccine other that MCV4, the subject has to be re-vaccinated. If the subject has a documented confirmation of proper vaccination, the screening period can be shortened by excluding the Screening Visit 2/Day -17 and the Screening Phone Contact/ Day 15.

Samsung Bioepis Exhibit No. 1002
Page 11882

AEs/SAEs are captured.

Screening Phone Contact / Day -15 (2nd day after vaccination)

Two days after the vaccine is injected, the phone contact is performed to check the subject for potential post-vaccination complications[54].

Screening Visit 3/ Days -3 to -1

This visit occurs at least 14 days post-vaccination. This time is enough for a subject to develop post-vaccination immunity. During this visit, each subject will be re-evaluated for eligibility based on their clinical and laboratory results. Blood is collected for hematology and chemistry testing; the subject is checked for post-vaccination complications; a physical examination is performed to detect any signs of acute and/or aggravated chronic infections and non-infectious diseases that, in the investigator's opinion, can prevent the subject from further study participation. Only those subjects will be assigned the Subject ID, whose lab test results (hemoglobin, RBC, WBC, leukocytes, neutrophils, ESR, bilirubin total, ALT, AST) from the Screening Visit 3 / Day -3 – -1 are within the reference range, and who have no post-injection complications or signs of acute and/or aggravated chronic infections and non-infectious diseases that, in the investigator's opinion, can prevent the subject from further study participation. During this visit, the study team member(s) will also: ask the subject about any concurrent therapy, evaluate subject's vital signs (BP, wrist pulse, body temperature) and document any AEs/SAEs.

2. Main study period

This period is 59 days including the day of BCD-148/Soliris® infusion. The main period includes 12 visits during which multiple blood samples will be collected for PK/PD, safety, and immunogenicity assessment.

Visit 1 / Day 1

Is performed not later than on the 3rd day after the subject was randomized in the study.

At the study site, the subject takes the saliva test for alcohol and the urine test for psychoactive substances/ medications and narcotics. The physician performs physical examination, checks BP, heart rate HR, respiratory rate, and axillary temperature. A venous catheter is inserted to the subject's vein in the arm. A blood sample for PK/PD and immunogenicity is collected 5 min before the start of the BCD-148/Soliris® infusion. Then the study drug is

[54]In subjects from 18 to 55 years old, the most common post-vaccination complications reported in literature are pain in the injection site, headache, and weakness.

Samsung Bioepis Exhibit No. 1002
Page 11883

administered through the same venous catheter. The study drug is given via a 25-45 min IV infusion. When the infusion is completed, 5 mL of normal saline is added to the catheter to rinse it and remove any remaining drug. BP, wrist pulse, and body temperature are checked immediately after the infusion. Five minutes after the infusion, a blood sample is collected for PK/PD assessment. Adverse events are captured.

Subsequent blood samples for PK/PD assessment at Visit 1 / Day 1 are collected 4 h (±5 min), 8 h (±10 min), and 12 h (±15 min) after the end of the infusion (all times are counted from the moment when the infusion was stopped).

The subsequent BP, wrist pulse, and body temperature checks during Visit 1 / Day 1 are performed 1 h, 4 h, 8 h, and 12 h after the end of the infusion (all times are counted from the moment when the infusion was stopped).

The subject will stay at the clinic for two days post-infusion. Adverse events and concomitant therapy are registered, if any. The study site where the infusion is given and the following monitoring is performed must have all the necessary equipment for emergency care.

Visit 1 / Day 2

On Day 2 (24±1 h post-infusion), blood samples are collected for PK/PD assessment and hematology testing. The venous catheter is removed. Adverse events and concomitant therapy are registered, if any.

Visit 1 / Day 3

On Day 3 (48±1 h post-infusion), blood samples are collected for PK/PD assessment. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back next day to give a blood sample for PK/PD assessment.

Visit 2 / Day 4

On Day 4 (72±2 h post-infusion), blood samples are collected for PK/PD assessment. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 3 / Day 6

On Day 6 (120±3 h post-infusion), blood samples are collected for PK/PD assessment. The site team member checks the subject's BP, wrist pulse, and body temperature, and performs the physical examination. The tests done during this visit include hematology, chemistry, coagulation tests, and urinalysis. Adverse events and concomitant therapy are registered, if any. After these

Samsung Bioepis Exhibit No. 1002
Page 11884

procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 4 / Day 9

On Day 9 (192±4 h post-infusion), blood samples are collected for PK/PD assessment and hematology testing. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 5 / Day 12

On Day 12 (264±4 h post-infusion), blood samples are collected for PK/PD assessment. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 6 / Day 16

On Day 16 (360±4 h post-infusion), blood samples are collected for PK/PD assessment. The site team member checks the subject's BP, wrist pulse, and body temperature, and performs the physical examination. The tests done during this visit include hematology, chemistry, coagulation tests, and urinalysis. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 7 / Day 23

On Day 23 (528±4 h post-infusion), blood samples are collected for PK/PD assessment and hematology testing. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 8 / Day 30

On Day 30 (696±4 h post-infusion), blood samples are collected for PK/PD and immunogenicity assessment. The site team member checks the subject's BP, wrist pulse, and body temperature, performs the physical examination and ECG The tests done during this visit include hematology, chemistry, coagulation tests, and urinalysis. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 9 / Day 37

On Day 37 (864±4 h post-infusion), blood samples are collected for PK/PD assessment. Adverse events and concomitant therapy are registered, if any. After these procedures are

Samsung Bioepis Exhibit No. 1002
Page 11885

completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 10 / Day 44

On Day 44 (1032±4 h post-infusion), blood samples are collected for PK/PD assessment and hematology testing. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 11 / Day 51

On Day 51 (1200±4 h post-infusion), blood samples are collected for PK/PD assessment. Adverse events and concomitant therapy are registered, if any. After these procedures are completed, the subject can go home, but he should come back for the next visit to give a blood sample for PK/PD assessment.

Visit 12 / Day 59

On Day 59 (1392±4 h post-infusion), blood samples are collected for PK/PD and immunogenicity assessment. The site team member checks the subject's BP, wrist pulse, and body temperature, and performs the physical examination and ECG. The tests done during this visit include hematology, chemistry, coagulation tests, and urinalysis. Adverse events and concomitant therapy are registered, if any.

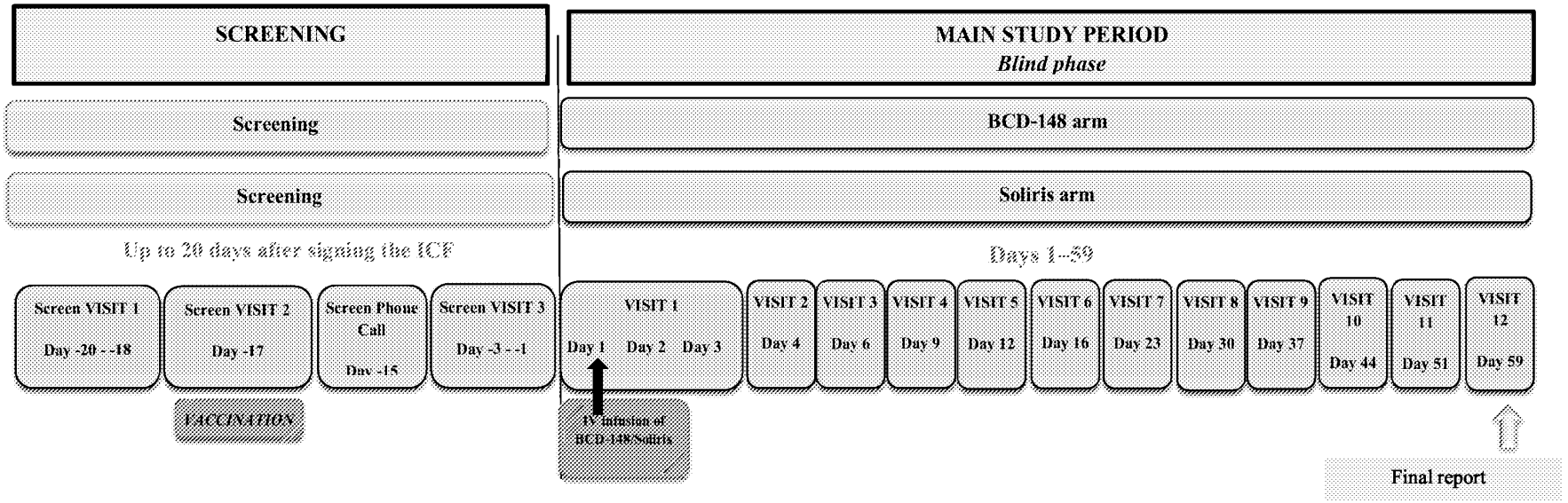
In total, the planned visits are as follows: 3 visits and 1 phone call during the screening period and 12 visits in the main study period.

The expected duration of study participation for each particular subject is 82 days from the moment the subject signs the ICF. This includes the screening period (20 days maximum), maximum of 3 days from randomization to Visit 1/ Day 1, and the main study period (59 days).

The study flow chart is shown in Figure 6.

Samsung Bioepis Exhibit No. 1002
Page 11886

Figure 6. The BCD-148-3 study flow-chart



Samsung Bioepis Exhibit No. 1002
Page 11887

Safety and tolerability assessment

The safety and tolerability of BCD-148/Soliris® will be evaluated through monitoring the vital signs (BP, wrist pulse, and body temperature), regular physical examinations, hematology/chemistry/coagulation tests, urinalysis, and ECG. These values will be evaluated during 59 days after the single injection of BCD-148/Soliris®.

In addition, the subjects will be monitored for any post-vaccination complications. If any post-vaccination complications are revealed, they will be captured as AEs not related to the study treatment.

Reports

A study report will be prepared after the data for the last study participant are obtained.

Samsung Bioepis Exhibit No. 1002
Page 11888

4.3. Measures to minimize/eliminate bias

4.3.1. Inclusion of subjects in the study and assigning the screening and study IDs

Subjects will be randomized and assigned study IDs according to internal JSC BIOCAD procedures.

The study site will be assigned a two-digit ID (e.g. 01, etc.).

After the subject signs the ICF, he is assigned a 5-digit screening number consisting of a 2-digit site number and a 3-digit subject number (continuing numbering in sequence, as subjects are enrolled at this site). This information is recorded in the source documents and screening log. *For example, at the study site 02, the first subject who has signed the ICF will receive the screening number 02-01.*

When all screening procedures are completed, and the investigator decides that the subject meets all eligibility criteria, the investigator enters all the required information into the eCRF (Screening Visit). The Sponsor gets an automatic notification that the investigator filled out these pages. If JSC BIOCAD approves the subject, he is then randomized and assigned a Subject ID and a drug lot number. The investigator must document the Subject ID and lot number in the source documents and eCRF.

Only those subjects will be assigned the Subject ID, whose lab test results (hemoglobin, RBC, WBC, leukocytes, neutrophils, ESR, bilirubin total, ALT, AST) from the Screening Visit 3 / Day -3 – -1 are within the reference range, and who have no post-injection complications or signs of acute and/or aggravated chronic infections and non-infectious diseases that, in the investigator's opinion, can prevent the subject from further study participation.

The Subject ID consists of 5 digits with 2 digits for the study site and 3 digits for the subject's number in the study.

For example, the Subject ID is "01-030", where "01" is the site number and "030" is the order number as the subject was included in the study.

4.3.2. Stratification procedure

As this study involves only healthy male subjects all from the same age group, no stratification will be performed.

Samsung Bioepis Exhibit No. 1002
Page 11889

4.3.3. Randomization procedure

Randomization in the study will be centralized. The subjects will be randomized in 1:1 ratio to the BCD-148 and Soliris® arms.

During randomization, JSC BIOCAD will monitor the total number of enrolled participants.

4.3.4. Blinding

Neither subjects nor investigators will be aware of what drug was administered to which subject during Visit 1 / Day 1. The study/reference drug will be delivered to the study site in identical secondary packaging (cartons) differing only by lot numbers and expiry dates. The lot numbers will be subject-specific.

4.4. Description of the study treatment, dose and dosing regimen for the investigational product(s). Pharmaceutical form, packaging, and labeling of investigational products

4.1.4. Description of the study treatment, dose, and dosing regimen for the investigational product(s)

In this clinical study, each healthy volunteer will get one infusion of either the test drug BCD-148 or the reference drug Soliris®, depending on the study arm to which the subject is randomized. Both eculizumab products (BCD-148/Soliris®) will be administered as a single 900 mg drip infusion given over 25-45 min. The infusion will be given at the study site.

See section 1.2.4. *Description and justification of route of administration, doses, and dosing regimen.*

4.4.2. Pharmaceutical form, packaging, and labeling of investigational products

4.4.2.1. Test drug

See Section 1.2.1. *Test Drug* and 1.2.3. *Labeling of the Study and Reference Products in this Study.*

4.4.2.2. Reference drug

See section 1.2.2. *Reference Drug* and 1.2.3. *Labeling of the Study and Reference Products in This Study.*

Samsung Bioepis Exhibit No. 1002
Page 11890

4.4.2.3. Meningococcal vaccine

Invented name: Menactra® (meningococcal (serotypes A, C, Y and W-135 polysaccharide diphtheria toxoid conjugate vaccine).

Generic Name: Vaccine to prevent meningococcal infection.

Therapeutic category: Medical immunobiologic vaccine

Dosage form: Solution for intramuscular injection.

Composition:

1 dose (0.5 mL) of the vaccine contains:

Active substances:

Meningococcal polysaccharides conjugated with a protein carrier:

Meningococcal A polysaccharide* – 4 μg

Meningococcal C polysaccharide* – 4 μg

Meningococcal Y polysaccharide* – 4 μg

Meningococcal W-135 polysaccharide* – 4 μg

* Each polysaccharide in conjugated to diphtheria toxoid protein. One vaccine dose contains approximately 48 μg of diphtheria toxoid protein.

Excipients:

Sodium chloride 4.35 mg, sodium hydrogen phosphate 0.348 mg, sodium dihydrogen phosphate monohydrate

0.352 mg, water for injection ad 0.5 mL.

Description:

Colorless clear or slightly opalescent solution.

Marketing authorization holder Sanofi Pasteur Inc.[55].

Shelf life: 2 years.

Storage and transportation conditions: At a temperature from 2 to 8 °C. Do not freeze. Keep out of the sight and reach of children. Do not use if the vaccine had been frozen.

Packaging:

This is a marketed drug. The package is in accordance with the approved specification.

Posology and route of administration:

Menactra® is administered as a 0.5 mL dose.

[55] If the product is not available or difficult to purchase in the Russian Federation, it will be purchased in other countries.

Samsung Bioepis Exhibit No. 1002
Page 11891

The preferred injection site is the deltoid muscle. Subjects 2 years to 55 years of age should receive one dose (0.5) of Menactra®.

4.5. Expected duration of the study and subjects' participation in the study

The study is expected to last for 2 years, which includes subject recruitment, the treatment and follow-up period, and statistical processing of results.

The expected duration of study participation for each particular subject is 82 days from the moment the subject signs the ICF. This includes the screening period (20 days maximum), maximum of 3 days from randomization to Visit 1/ Day 1, and the main study period (59 days).

4.6. Study periods

4.6.1 Study visits and procedures

The visit schedule and procedures are the same for both study arms. The study includes the screening period and 12 visits in the main study period.

The visits in the main study period cannot be re-scheduled because each of these visits involves blood collection for PK/PD assessment.

Samsung Bioepis Exhibit No. 1002
Page 11892

Table 6. Schedule of study visits and assessments

Visit	Screening - Visit 1	Screening - Visit 2	Screening Phone Call	Screening - Visit 3	1			2	3	4	5	6	7	8	9	10	11	12
Visit	**-20 – -18**	**-17**	**-15**	**-3 – -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 9**	**Day 12**	**Day 16**	**Day 23**	**Day 30**	**Day 37**	**Day 44**	**Day 51**	**Day 59**
Signing the ICF	+																	
Life and disease history	+																	
Information about concomitant therapies	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vital signs[56]	+	+		+	+[57]				+			+		+				+
Physical examination	+	+		+	+				+			+		+				+
Chest x-ray and fluorography[58]	+																	
ECG	+													+				+
Venous catheter inserted into the vein					+													
Venous catheter removed						+												
Hematology	+			+		+			+	+		+	+	+		+		+
Chemistry	+			+					+			+		+				+
Coagulation pattern	+								+			+		+				+
Urinalysis	+								+			+		+				+
Blood for PK/PD assessment[59]					+[60]	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood for immunogenicity testing					+[61]									+				+

[56]BP, wrist pulse, body temperature, body weight, and height (body weight and height are measured on Screening Visit 1).
[57]BP, wrist pulse, and body temperature are checked on Day 1 before the infusion, immediately after the infusion, and 1 h, 4 h, 8 h, and 12 h post-infusion.
[58] Results obtained within 2 months before signing the ICF can be used at screening.
[59] Details of timepoints for blood sampling are described in Table 9.
[60]Blood samples for PK/PD study on Day 1 are collected 5 min before the infusion and then 5 min, 4 h (±5 min), 8 h (±10 min), and 12 h (±15 min) post-infusion.
[61]Blood is collected before the infusion of BCD-148/Soliris.

Samsung Bioepis Exhibit No. 1002
Page 11893

Visit	Screening - Visit 1	Screening - Visit 2	Screening Phone Call	Screening - Visit 3	1			2	3	4	5	6	7	8	9	10	11	12
Visit	**-20 – -18**	**-17**	**-15**	**-3 – -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 9**	**Day 12**	**Day 16**	**Day 23**	**Day 30**	**Day 37**	**Day 44**	**Day 51**	**Day 59**
Blood tests for HIV, hepatitis and syphilis[62, 63]	+																	
Alcohol test	+				+[64]													
Urine test for psychotropic and recreational drugs, psychoactive medications	+				+[65]													
Vaccination		+[66]																
Infusion of BCD-148/Soliris®					+													
Documenting SAEs/AEs	+	+[67]	+	+	+[68]	+	+	+	+	+	+	+	+	+	+	+	+	+
Assess conformance to inclusion/exclusion criteria	+			+[69]														
Phone interview			+															

[62]Results of not earlier than 2 months ago before signing the ICF can be used at screening.
[63] Antibodies to HIV, HBsAg, HCV, syphilis.
[64]Alcohol testing on Visit 1 is performed before the first pre-infusion blood sampling.
[65]Performed before the first pre-infusion blood sampling.
[66]The subject is vaccinated only if he meets all eligibility criteria according to the interview, medical history, physical examination from Screening Visit 1, and laboratory/instrumental test results.
[67]During the period from vaccination (Screening Visit 2) and until the end of the screening, all AEs (including SAEs) considered by the investigator as post-vaccination complications must be captured.
[68]Starting from Visit 1 / Day 1 post-infusion, all AEs/SAEs must be captured (regardless of how the investigator assesses the casual relationship to the study drug).
[69]On Screening Visit 3, to re-confirm the subject-s eligibility blood will be collected for hematology and chemistry tests and subjects will be evaluated for any post-vaccination complications and any signs of acute and/or aggravated chronic infections or non-infectious diseases that may, in the investigator's opinion, prevent the subject from further participation in the study. Only those subjects will be assigned the Subject ID, whose lab test results (hemoglobin, RBC, WBC, leukocytes, neutrophils, ESR, bilirubin total, ALT, AST) from the Screening Visit 3 / Day -3 – -1 are within the reference range, and who have no post-injection complications or signs of acute and/or aggravated chronic infections and non-infectious diseases that, in the investigator's opinion, can prevent the subject from further study participation.

Samsung Bioepis Exhibit No. 1002
Page 11894

4.6.2. Procedures by visits

Procedures of the screening period

The screening period starts when the subject signs the ICF and lasts up to 20 days. The screening period includes 3 visit and one phone call.

Screening Visit 1/ Days -20 to -18

- The subject signs the ICF
- The site team member takes life and disease history
- The site team member documents information about concomitant therapies
- Vital signs (BP, wrist pulse, body temperature, body weight and height)
- Physical exam
- X-ray / Fluorography
- ECG
- Hematology and chemistry
- Coagulation pattern
- Urinalysis
- Alcohol test
- Urine test for psychoactive and recreational drugs
- Tests for HIV, HCV, HBV, syphilis
- Eligibility assessment
- Documenting SAEs

Screening Visit 2/ Day -17

- The site team member documents information about concomitant therapies
- Vital signs (BP, wrist pulse, body temperature)
- Physical exam
- Meningococcal vaccine
- Documenting AEs/SAEs (post-vaccination complications)

Screening phone call (Day -15)

- The site team member documents information about concomitant therapies
- Documenting AEs/SAEs (post-vaccination complications)

Samsung Bioepis Exhibit No. 1002
Page 11895

Screening Visit 3/ Days -3 to -1

- The site team member documents information about concomitant therapies
- Vital signs (BP, wrist pulse, body temperature)
- Physical exam
- Hematology and chemistry
- Eligibility assessment[70].
- Documenting AEs/SAEs (post-vaccination complications)

Visit 1 / Day 1

- The site team member documents information about concomitant therapies
- Pre-infusion vital signs (BP, wrist pulse, body temperature)
- Pre-infusion physical exam
- Alcohol testing, before the first pre-infusion blood sampling
- Urine test for psychoactive and recreational drugs, before the first pre-infusion blood sampling
- Venous catheter inserted (15 min before the infusion)
- Blood collection for PK/PD/immunogenicity, performed 5 min before the infusion
- Infusion of BCD-148/Soliris®
- Vital signs (BP, wrist pulse, body temperature) immediately after the infusion, then 1 h, 4 h, 8 h, and 12 h post-infusion.
- Blood collection for PK/PD 5 min, 4 h (±5 min), 8 h (±10 min), and 12 h (±15 min) post-infusion.
- Documenting AEs/SAEs

Visit 1 / Day 2

- The site team member documents information about concomitant therapies
- Blood collection for PK/PD 24±1 h post-infusion

[70]On Screening Visit 3, to re-confirm the subject-s eligibility blood will be collected for hematology and chemistry tests and subjects will be evaluated for any post-vaccination complications and any signs of acute and/or aggravated chronic infections or non-infectious diseases that may, in the investigator's opinion, prevent the subject from further participation in the study. Only those subjects will be assigned the Subject ID, whose lab test results (hemoglobin, RBC, WBC, leukocytes, neutrophils, ESR, bilirubin total, ALT, AST) from the Screening Visit 3 / Day -3 – -1 are within the reference range, and who have no post-injection complications or signs of acute and/or aggravated chronic infections and non-infectious diseases that, in the investigator's opinion, can prevent the subject from further study participation.

Samsung Bioepis Exhibit No. 1002
Page 11896

- Hematology
- Venous catheter removed
- Documenting AEs/SAEs

Visit 1 / Day 3

- The site team member documents information about concomitant therapies
- Blood collection for PK/PD 48±1 h post-infusion
- Documenting AEs/SAEs

Visit 2 / Day 4

- The site team member documents information about concomitant therapies
- Blood collection for PK/PD 3 days (72±2 h) post-infusion
- Documenting AEs/SAEs

Visit 3 / Day 6

- The site team member documents information about concomitant therapies
- Vital signs (BP, wrist pulse, body temperature)
- Physical exam
- Hematology and chemistry
- Coagulation pattern
- Urinalysis
- Blood collection for PK/PD 5 days (120±3 h) post-infusion
- Documenting SAEs/AEs

Visit 4 / Day 9

- The site team member documents information about concomitant therapies
- Blood collection for PK/PD 8 days (192±4 h) post-infusion
- Hematology
- Documenting AEs/SAEs

Visit 5 / Day 12

- The site team member documents information about concomitant therapies

Samsung Bioepis Exhibit No. 1002
Page 11897

- Blood collection for PK/PD 11 days (264±4 h) post-infusion
- Documenting AEs/SAEs

Visit 6 / Day 16

- The site team member documents information about concomitant therapies
- Vital signs (BP, wrist pulse, body temperature)
- Physical exam
- Hematology and chemistry
- Coagulation pattern
- Urinalysis
- Blood collection for PK/PD 15 days (360±4 h) post-infusion
- Documenting SAEs/AEs

Visit 7 / Day 23

- The site team member documents information about concomitant therapies
- Blood collection for PK/PD 22 days (528±4 h) post-infusion
- Hematology
- Documenting AEs/SAEs

Visit 8 / Day 30

- The site team member documents information about concomitant therapies
- Vital signs (BP, wrist pulse, body temperature)
- Physical exam
- ECG
- Hematology and chemistry
- Coagulation pattern
- Urinalysis
- Blood collection for PK/PD 29 days (696±4 h) post-infusion
- Blood collection for immunogenicity testing
- Documenting SAEs/AEs

Visit 9 / Day 37

Samsung Bioepis Exhibit No. 1002
Page 11898

- The site team member documents information about concomitant therapies
- Blood collection for PK/PD 36 days (864±4 h) post-infusion
- Documenting AEs/SAEs

Visit 10 / Day 44

- The site team member documents information about concomitant therapies
- Blood collection for PK/PD 43 days (1032±4 h) post-infusion
- Hematology
- Documenting AEs/SAEs

Visit 11 / Day 51

- The site team member documents information about concomitant therapies
- Blood collection for PK/PD 50 days (1200±4 h) post-infusion
- Documenting AEs/SAEs

Visit 12 / Day 59

- The site team member documents information about concomitant therapies
- Vital signs (BP, wrist pulse, body temperature)
- Physical exam
- ECG
- Hematology and chemistry
- Coagulation pattern
- Urinalysis
- Blood collection for PK/PD 58 days (1392±4 h) post-infusion
- Blood collection for immunogenicity testing
- Documenting SAEs/AEs

Procedures of Early Withdrawal Visit

- The site team member documents information about concomitant therapies
- Physical examination
- Vital signs (BP, wrist pulse, body temperature)

Samsung Bioepis Exhibit No. 1002
Page 11899

- Hematology, chemistry, and urinalysis
- Documenting AEs/SAEs

Procedures of an unscheduled visit (if an AE occurs)

- The site team member documents any subject's complaints
- The site team member documents information about concomitant therapies
- Physical exam
- Vital signs (BP, wrist pulse, body temperature)
- Hematology, chemistry, and urinalysis

4.6.3. Description of individual clinical, laboratory, and instrumental tests

Table 7. Clinical and laboratory examinations in the study

Test	Tested variable	Frequency	Where the test is done
Life and disease history	Life history Medical history Allergy history	1x: - Screening Visit 1	Study site
Concomitant therapies	Ask the subject if he takes any medications other than the study drugs	18x: - Screening Visit 1, Screening Visit 2, Screening Phone Call, Screening Visit 3, Day 1, Day 2, Day 3, Day 4, Day 6, Day 9, Day 12, Day 16, Day 23, Day 30, Day 37, Day 44, Day 51, Day 59.	Study site
Physical examination	Standard medical examination by organs and systems	8x: - Screening Visit 1, Screening Visit 2, Screening Visit 3, Day 1, Day 6, Day 16, Day 30, and Day 59.	Study site
Vital signs[71]	BP Wrist pulse Body temperature Body weight	13x: - Screening Visit 1, Screening Visit 2, Screening Visit 3, Day	Study site

[71]Body weight and height are measured at Screening Visit 1 only.

Samsung Bioepis Exhibit No. 1002
Page 11900

Test	Tested variable	Frequency	Where the test is done
	Height	1[72], Day 6, Day 16, Day 30, and Day 59.	
Instrumental examinations	12-lead ECG	3x: - Screening Visit 1, Day 30, Day 59	Study site / external clinic
	Fluorography / X-ray exam[73]	1x: - Screening Visit 1	Study site / external clinic
Alcohol test	• Ethanol • Methanol • Propanol	2x: Visit 1/ Day 1	Study site
Urine test for psychotropic and recreational drugs, psychoactive medications	Amphetamine, methamphetamine, marijuana, morphine, cocaine (and metabolites	2x: Visit 1/ Day 1	Study site / external clinic
Blood tests for serologic infection markers (HIV, HBV, HCV, and syphilis)	HIV: Anti-HIV antibodies 1,2 Hepatitis B: HbsAg Hepatitis C: Hepatitis C antibody test (anti-HCV) Test for syphilis (RW, anticardiolipin antibody test, etc.)	1x - Screening Visit 1	Central laboratory / Study site
Hematology	Hemoglobin (g/L) RBC ($\times 10^{12}$/L) Platelets ($\times 10^{9}$/L) WBC ($\times 10^{9}$/L)	10x - Screening Visit 1, Screening Visit 3, Day 2, Day 6, Day 9,	Central laboratory / Study site

[72]BP, wrist pulse, and body temperature are checked on Day 1 before the infusion, immediately after the infusion, and 1 h, 4 h, 8 h, and 12 h post-infusion
[73] Results obtained within 2 months before signing the ICF can be used at screening.

Samsung Bioepis Exhibit No. 1002
Page 11901

Test	Tested variable	Frequency	Where the test is done
	Neutrophils ($\times 10^9$/L) Lymphocytes ($\times 10^9$/L) ESR (mm/h)	Day 16, Day 23, Day 30, Day 44, Day 59.	
Chemistry	Total protein (g/L) Glucose (mmol/L) ALT (U/L) AST (U/L) GGT (U/L) Bilirubin total (µmol/L) Creatinine (µmol/L)	6x - Screening Visit 1, Screening Visit 3, Day 6, Day 16, Day 30, and Day 59.	Central laboratory / Study site
Coagulation tests	INR PTV	5x: - Screening Visit 1, Day 6, Day 16, Day 30, Day 59.	Central laboratory / Study site
Urinalysis	General properties Sediment microscopy	5x - Screening Visit 1, Day 6, Day 16, Day 30, Day 59.	Central laboratory / Study site
Blood drawing for PK assessment	Eculizumab assay in the serum	18x: - 5 collections on Day 1, Day 2, Day 3, Day 4, Day 6, Day 9, Day 12, Day 16, Day 23, Day 30, Day 37, Day 44, Day 51, Day 59.	Bioanalytical Laboratory, Analytical Development Department, JSC BIOCAD
Blood collection for PD assessment	Complement CH50 assay in the serum	18x: - 5 collections on Day 1, Day 2, Day 3, Day 4, Day 6, Day 9, Day 12, Day 16, Day 23, Day 30, Day 37, Day 44, Day 51, Day 59.	Bioanalytical Laboratory, Analytical Development Department, JSC BIOCAD

Samsung Bioepis Exhibit No. 1002
Page 11902

Test	Tested variable	Frequency	Where the test is done
Blood collection for immunogenicity testing	Titer of anti-eculizumab BAbs Titer if anti-eculizumab NAbs	3x: - Day 1, Day 30, Day 59	Bioanalytical Laboratory, Analytical Development Department, JSC BIOCAD

Table 8. Blood volumes to be collected from each subject

Visit	Laboratory test (frequency/blood collected per 1 sample)	Total blood volume
Screening	• Hematology (2 × 3 mL) • Chemistry (2 × 4 mL) • Blood coagulation (1 × 4 mL) • Serology (1 × 4 mL)	22 mL
Day 1 Visit 1	• PK/PD (5 × 18 mL) • Immunogenicity (1 × 9 mL)	99 mL
Day 2 Visit 1	• PK/PD (1 × 18 mL) • Hematology (1 × 3 mL)	21 mL
Day 3 Visit 1	• PK/PD (1 × 18 mL)	18 mL
Day 4 Visit 2	• PK/PD (1 × 18 mL)	18 mL
Day 6 Visit 3	• PK/PD (1 × 18 mL) • Hematology (1 × 3 mL) • Chemistry (1 × 4 mL) • Blood coagulation (1 × 4 mL)	29 mL
Day 9 Visit 4	• PK/PD (1 × 18 mL) • Hematology (1 × 3 mL)	21 mL
Day 12 Visit 5	• PK/PD (1 × 18 mL)	18 mL
Day 16 Visit 6	• PK/PD (1 × 18 mL) • Hematology (1 × 3 mL) • Chemistry (1 × 4 mL) • Blood coagulation (1 × 4 mL)	29 mL
Day 23 Visit 7	• PK/PD (1 × 18 mL) • Hematology (1 × 3 mL)	21 mL
Day 30 Visit 8	• PK/PD (1 × 18 mL) • Immunogenicity (1 × 9 mL) • Hematology (1 × 3 mL) • Chemistry (1 × 4 mL) • Blood coagulation (1 × 4 mL)	38 mL
Day 37 Visit 9	• PK/PD (1 × 18 mL)	18 mL
Day 44 Visit 10	• PK/PD (1 × 18 mL)	21 mL

Samsung Bioepis Exhibit No. 1002
Page 11903

Visit	Laboratory test (frequency/blood collected per 1 sample)	Total blood volume
	• Hematology (1 × 3 mL)	
Day 51 Visit 11	• PK/PD (1 × 18 mL)	18 mL
Day 59 Visit 12	• PK/PD (1 × 18 mL) • Immunogenicity (1 × 9 mL) • Hematology (1 × 3 mL) • Chemistry (1 × 4 mL) • Blood coagulation (1 × 4 mL)	38 mL
Total blood volume taken from one subject over the entire study [74]		**429 mL**

4.6.3.1. Physical examination

The physical exam must include assessments of the following systems/organs:

- Overall health
- Skin and mucosa
- Peripheral lymph nodes
- Auscultation of the heart and lungs
- Gastrointestinal tract
- Renal and urinary system
- Liver palpation

4.6.3.2. Clinical data, demographics, and medication history

The following subject information should be recorded during the screening examination:

- Date of birth
- Sex
- Age
- Reproductive function (contraception or information about sterilization if applicable); information about the pregnant partner (if applicable)
- Medical history (infections, including meningococcal infection, performance status, surgeries, etc.)
- Medication history: any medications that the study subject has been taking within 30 days before screening. The dose, dosing regimen, treatment duration, and reason for discontinuation (if applicable) should be specified.

[74] The overall volume of blood collected during the study may increase if any technical errors/issues occur during collection or if the physician deems necessary to run additional tests in the case of an AE

Samsung Bioepis Exhibit No. 1002
Page 11904

4.6.3.3. Vital signs

The vital signs assessment includes periodic measurements of axillary body temperature (° C), blood pressure (mm Hg, one hand), and wrist pulse (bpm). Subject's body weight (kg) and height (cm) are measured only at Screening Visit 1.

The subject should be warned not to smoke for 1 h before the BP is measured.

4.6.3.4. Hematology, chemistry, coagulation test, and urinalysis

Hematology test is to be performed according to the standard procedure in fasting subjects (8 hours after the last meal). Study material: venous blood; the volume of blood taken: at least 3 mL. In this study, the following hematology parameters will be tested:

- Hemoglobin (g/L)
- RBC ($\times 10^{12}$/L)
- Platelets ($\times 10^{9}$/L)
- WBC ($\times 10^{9}$/L)
- Neutrophils ($\times 10^{9}$/L)
- Lymphocytes ($\times 10^{9}$/L)
- ESR (mm/h)

Chemistry test is performed according to the standard procedure in fasting subjects (8 hours without food, including sweat and alcohol drinks). Study material: venous blood; the volume of blood taken: at least 4 mL. The following variables are to be evaluated:

- Total protein (g/L)
- Glucose (mmol/L)
- ALT (U/L)
- AST (U/L)
- GGT (U/L)
- Bilirubin total (µmol/L)
- Creatinine (µmol/L)

Coagulation test is performed according to the standard procedure, at fasting (8 hours after the last meal, including sweat and alcohol drinks). Study material: venous blood; the volume of blood taken: at least 4 mL. The following variables are to be evaluated:

- International Normalized Ratio (INR)

Samsung Bioepis Exhibit No. 1002
Page 11905

- Prothrombin time (PT) (sec)

Urinalysis is performed according to the standard procedure and includes the assessment of physical and chemical properties and sediment microscopy.

4.6.3.5. Blood tests for infection markers

HIV testing includes detection of anti-HIV1 and anti-HIV2 antibodies in the serum or plasma.

The RPR or RW will be used as a screening test for syphilis. The test will be performed with serum. Other tests can be used as well.

HBV testing includes detection of HBsAg in the serum or plasma. The presence or absence of hepatitis C is assessed based on the anti-HCV antibody test results (total IgM + IgG)

All these tests are performed using routine procedures of the study site or central laboratory. The subject is required to fast for 8 hours before blood collection. Blood volume for the test: 4 mL.

4.6.3.6. Eculizumab assay, hemolytic complement activity assay, and immunogenicity assessment

All study subjects will be requested to provide blood samples for PK, PD, and immunogenicity studies.

Pharmacokinetics will be assessed based on the concentration of eculizumab (monoclonal antibodies to complement C5) measured in the serum of healthy subjects.

Pharmacodynamics will be investigated by measuring the hemolytic complement activity in the serum (CH50), where one unit of hemolytic activity is the reciprocal of the serum dilution which causes a 50% hemolysis.

Immunogenicity will be evaluated as part of the mandatory drug safety monitoring. Assessments will be performed before the drug infusion, on Day 30 (29 days post-infusion) and at the completion of the main study period on Day 59 (58 days post-infusion). Immunogenicity will be assessed by detecting binding and neutralizing anti-eculizumab antibodies (BAbs and NAbs) in the serum of the study subjects.

Tested material: venous blood serum.

Eculizumab assay

Concentrations of anti-C5 MAbs will be measured with the test-system developed by JSC BIOCAD. This test-system measures both C5-conjugated and free eculizumab. Serum levels of

Samsung Bioepis Exhibit No. 1002
Page 11906

anti-C5 MAb (conjugated and free) will be measured by ELISA with horseradish peroxidase as an indicator enzyme.

In the free eculizumab assay, sensitize the wells of a 96-well plate with the natural C5 in carbonate buffer and then incubate the plate for 16 to 18 h at 4°C. Remove unbound immunoglobulins from the wells. Add 300 µL of the blocking buffer to each well and incubate the plate for 30 min at 37°C to block all non-specific binding sites. Remove the blocking buffer and add 100 µL of the test serum in appropriate dilution. In parallel, add 100 µL of the coating buffer containing different concentrations of the anti-C5 MAb to each well (all anti-C5 concentrations fall in the calibration range). Incubate the plates for 30 min at 37°C. Remove the well contents and rinse the wells in triplicate with the wash buffer; then add the polyclonal anti-Fc antibodies conjugated to horseradish peroxidase and incubate the plates for 30 min at 37°C. Remove the well contents and wash the wells 4 times with the wash buffer. Add 100 µL of 0.1 M Na-acetate buffer pH 5.0 with 0.1 mg/mL tetramethylbenzidine and 0.003% of H_2O_2. You will see the blue color. Stop the reaction by adding 100 µL of 1N H_2SO_4 to each well. Read the absorbance in the wells at 450 ng with a Tecan reader.

To find the concentrations of anti-C5 MAb in the test samples, plot a calibration curve for absorbance vs. anti-C5 MAb concentration in standard samples. Use the absorbance of a test sample to find the anti-C5 MAb concentration in this sample. The range of this analytical procedure is from 3.13 ng/mL to 100 ng/mL.

In the conjugated eculizumab assay, sensitize the wells of a 96-well plate with the anti-C5 antibodies in carbonate buffer and then incubate the plate for 16 to 18 h at 4°C. Remove unbound immunoglobulins from the wells. Add 300 µL of the blocking buffer to each well and incubate the plate for 30 min at 37°C to block all non-specific binding sites. Remove the blocking buffer and add 100 µL of the test serum in appropriate dilution. In parallel, add 100 µL of the coating buffer containing different concentrations of the anti-C5 MAb to each well (all anti-C5 concentrations fall in the calibration range). Incubate the plates for 30 min at 37°C. Remove the well contents and rinse the wells in triplicate with the wash buffer; then add the polyclonal anti-Fc antibodies conjugated to horseradish peroxidase and incubate the plates for 30 min at 37°C. Remove the well contents and wash the wells 4 times with the wash buffer. Add 100 µL of 0.1 M Na-acetate buffer pH 5.0 with 0.1 mg/mL tetramethylbenzidine and 0.003% of H_2O_2. You will see the blue color. Stop the reaction by adding 100 µL of 1N H_2SO_4 to each well. Read the absorbance in the wells at 450 ng with a Tecan reader.

To find the concentrations of anti-C5 MAb in the test samples, plot a calibration curve for absorbance vs. anti-C5 MAb concentration in standard samples. Use the absorbance of a test

Samsung Bioepis Exhibit No. 1002
Page 11907

sample to find the anti-C5 MAb concentration in this sample. The range of this analytical procedure is from 6.25 ng/mL to 200 ng/mL.

Complement CH50 assay in the serum

The serum complement activity test is performed with sheep erythrocytes and rabbit anti-sheep serum (hemolytic serum). The complement activity will be measured in CH50 units. One unit of the hemolytic complement (CH50) is the amount of complement that results in 50% hemolysis of 0.5 mL standard suspended sensitized erythrocytes after a 45-min incubation at 37 °C[75].

Test-system to detect binding antibodies against anti-C5 MAb

The binding antibodies to anti-C5 MAb include both human antibodies targeting murine sequences in the anti-C5 MAb and human antibodies targeting human Ig (human anti-human antibody, HAHA). ELISA with horseradish peroxidase as an indicator enzyme will be used to detect BAbs in the serum and measure their titer. The linear range of this analytical procedure is from 78 ng/mL to 5000 ng/mL.

The test-system uses streptavidin-coated plates (JSC BIOCAD) with the anti-C5 MAb conjugated to biotin (JSC BIOCAD) added to the wells. Calibration solutions will be added to certain plate wells. Calibration solutions contain polyclonal rabbit anti-eculizumab antibodies at known concentrations with pooled serum after the acid dissociation step being used as a diluent. To maintain the pH and ensure bridge formation by BAbs present in the sample, 1M Tris will be added to each well prior to all other reagents.

After plate incubation and washing, add anti-C5 MAb conjugated to digoxigenin (JSC BIOCAD). Incubate and then wash the plate. Add anti-digoxigenin murine MAb conjugated to horseradish peroxidase.

Incubate and wash the plate. Detect the bound conjugate in a reaction with murine anti-digoxigenin MAbs labeled with horseradish peroxidase in the presence of hydrogen peroxide and TMB. Stop the reaction by adding 1N H_2SO_4 and measure the absorbance in the wells at 450 nm. The yellow color intensity is proportional to the amount of binding antibodies against the anti-C5 MAb in the sample.

During the screening analysis, this ELISA method detects serum samples with an absorbance greater than the cut point (CP). It is assumed that these serum samples may contain anti-drug BAbs.

[75]Measuring the 50% Haemolytic Complement (CH50) Activity of Serum. Maurizio Costabile. J. of Vis. Exper. 37. 2010.

Samsung Bioepis Exhibit No. 1002
Page 11908

The samples with signal lower than the CP are considered negative, i.e. containing no BAbs. The samples considered positive during screening are re-tested in the confirmatory analysis. The serum samples are incubated with an excess of the investigational product to detect signal changes. If the signal of the sample incubated with an excess of the investigational product is < CP, this shows the specificity of the signal and the presence of BAbs in the sample. In this case, the sample is considered true positive. If the signal in the confirmatory analysis does not decrease or decreases insignificantly, the sample is considered negative for BAbs.

Test-system to detect neutralizing antibodies against anti-C5 MAb

Neutralizing antibodies (neutralizing activity of binding antibodies) against anti-C5 MAb in subject' serum samples were detected by the validated ELISA with horseradish peroxidase as an indicator enzyme. The test-system uses the plates coated with BCD-148 (the method validation will include testing of both BCD-148 and Soliris® as an anti-BAb antibody) and Costar 3590 binding plates. Calibration solutions will be added to certain plate wells. Calibration solutions contain polyclonal rabbit anti-eculizumab neutralizing antibodies (JSC BIOCAD) at known concentrations.

To each Corning Costar 3590 well, add 100 µL of 5 µg/mL solution of BCD-148 in carbonate buffer and incubate for 16-18 h at 4°C. Then add 25 µL of the calibration standard, 25 µL of the QC standard, or 25 µL of the test solution and 225 µL of 100 mM glycine buffer (pH 2.5) to the wells of the polypropylene plate. Allow dissociation for 30 min at 25°C. Add 5 µL of 1M Tris (pH 11.2) to the wells of the plate with BCD-148 and transfer 100 µL portions of each sample after acid dissociation in glycine buffer. Incubate for 1 h at 25°C under 450 rpm. Wash the plate in triplicate and add 100 µL of Gly-HCl pH 2.5, incubate for 5 min at 25° C (to allow elution of anti-drug antibodies bound to BCD-148). Transfer 90 µL aliquots to a clean Corning Costar 3590 plate containing 5 µL/well of 1M Tris (pH 11.2). Incubate for 1 h at 25°C and 450 rpm. Wash the plate in triplicate and add 300 µL/well of 1% milk solution (30 min, 37°C). Wash the plate in triplicate and add 100 µL/well of 2 µg/mL biotinylated BCD-148 in 0.5% milk solution to the rows containing calibration standards, test samples, and QC standards. Add the premix of 2 µg/mL biotinylated BCD-148 and 20 µg/mLC5 complement in 0.5% milk solution to the rows containing test samples and QC standards. Incubate the plate for 30 min at 25° C and 450 rpm. Wash the plate in triplicate and add 100 µL/well of streptavidin-HRP conjugate 1/10000 in 0.5% milk solution. Incubate for 30 min at 25° C and 450 rpm. Wash the plate and perform a color reaction with hydrogen peroxide and TMB. Stop the reaction by adding 1N H_2SO_4 and measure the absorbance

Samsung Bioepis Exhibit No. 1002
Page 11909

in the wells at 450 nm. The % of signal inhibition for the wells containing biotinylated anti-C5 MAb vs. the wells containing biotinylated anti-C5 MAb and the ligand C5 is proportional to the amount of neutralizing antibodies to BCD-148/Soliris®.

This method allows detecting subjects' serum samples that contain anti-BCD-148/Soliris® antibodies possessing neutralizing activity. The samples with the signal above or equal to the CP are considered positive (i.e. containing neutralizing anti-drug antibodies). The samples with the signal below the CP are considered negative (i.e. not containing neutralizing anti-drug antibodies).

Blood preparation for PK/PD and immunogenicity testing

Draw a venous blood sample (at least 9 mL) to a labeled clot activator tubes (without anticoagulants). Rotate the tube with a sample so the blood contacts the clot activator. Let it stand for 20-30 min at room temperature in an upright position. For complete clotting, allow the test tube to stand vertically at 2°C to 8°C for another 20 to 30 min. Spin the tube at 2000 rpm (approx. 700 G) for 20 min. If needed, it is allowed to spin the tube for 10 min at 1500G. After spinning, take the sample from the centrifuge. The precipitate contains debris of blood cells and cell elements. The serum is above the clot. Do not shake and invert the tube.

For PK/PD study, divide the resulting serum into two equal aliquots (A and B, at least 1.0 mL each). Transfer the aliquots to pre-labeled dry plastic tubes (cylindrical cryovials).

For immunogenicity (BAb/NAb) testing, use at least 9 mL of venous blood. Process the collected blood as described above. Divide the serum sample into 3 aliquots (A, B, and C, at least 1.0 mL each).

Immediately place the cryotubes for storage at -70 °C (storage at -80 °C is also acceptable). The serum samples can be stored at the study site until they are requested by a Sponsor's representative or the study site close-out (but for not longer than one year). The samples can be stored at –20°C for up to 30 days.

Each tube should be clearly labeled so that the information could not be erased. Each tube label should show the Protocol ID, Subject's ID, and Sample ID. The unique Sample ID consists of letters and digits. Letters refer to the sample type (PK - sample for eculizumab concentration assay; PD - sample for the CH50 test; IG - sample for BAb/NAb test), A and B (for PK and PD), or A, B, and C (for IG) refer to the sample aliquot. Digits in the Sample ID show the sample number as it was collected. For example, IG-1-B.

To ensure the correct labeling, the Sponsor will provide labels with all necessary information pre-printed. The site staff has to attach these labels to the corresponding cryovials.

Samsung Bioepis Exhibit No. 1002
Page 11910

The study staff may also use individual sets of test tubes for IG/PK/PD studies. The tubes must be labeled with the Protocol ID, subject-specific tube set number, and a time point.

Samsung Bioepis Exhibit No. 1002
Page 11911

Table 9. Details of blood collections for the PK, PD, and IG studies

Visit	Time point	PK (Pharmacokinetics)	PD (Pharmacodynamics)	IG (Immunogenicity)	Acceptable deviation in the sampling time	Blood volume for each test
Visit 1 / Day 1	5 min before the infusion of BCD-148/Soliris®	PK1-A, PK1-B	PD1-A, PD1-B	IG1-A, IG1-B, IG-1-C	Not acceptable	9 mL
	5 min after the end of the BCD-148/Soliris® infusion (i.e. immediately after the infusion)	PK2-A, PK2-B	PD2-A, PD2-B		Not acceptable	9 mL
	4 h after the infusion of BCD-148/Soliris®	PK3-A, PK3-B	PD3-A, PD3-B		± 5 min	9 mL
	8 h after the infusion of BCD-148/Soliris®	PK4-A, PK4-B	PD4-A, PD4-B		± 10 min	9 mL
	12 h after the infusion of BCD-148/Soliris®	PK5-A, PK5-B	PD5-A, PD5-B		± 15 min	9 mL
Visit 1 / Day 2	24 h after the infusion of BCD-148/Soliris®	PK6-A, PK6-B	PD6-A, PD 6-B		± 60 min	9 mL
Visit 1 / Day 3	2 days (48 h) after the infusion of BCD-148/Soliris®	PK7-A, PK7-B	PD7-A, PD7-B		± 60 min	9 mL
Visit 2 / Day 4	3 days (72 h) after the infusion of BCD-148/Soliris®	PK8-A, PK8-B	PD8-A, PD8-B		± 2 h (120 min)	9 mL
Visit 3 / Day 6	5 days (120 h) after the infusion of BCD-148/Soliris®	PK9-A, PK9-B	PD9-A, PD9-B		± 3 h (180 min)	9 mL
Visit 4 / Day 9	8 days (192 h) after the infusion of BCD-148/Soliris®	PK10-A, PK10-B	PD10-A, PD10-B		± 4 h (240 min)	9 mL
Visit 5 / Day 12	11 days (264 h) after the infusion of BCD-148/Soliris®	PK11-A, PK11-B	PD11-A, PD11-B		± 4 h (240 min)	9 mL

Samsung Bioepis Exhibit No. 1002
Page 11912

Visit	Time point	PK (Pharmacokinetics)	PD (Pharmacodynamics)	IG (Immunogenicity)	Acceptable deviation in the sampling time	Blood volume for each test
Visit 6 / Day 16	15 days (360 h) after the infusion of BCD-148/Soliris®	PK12-A, PK12-B	PD12-A, PD12-B		± 4 h (240 min)	9 mL
Visit 7 / Day 23	22 days (528 h) after the infusion of BCD-148/Soliris®	PK13-A, PK13-B	PD13-A, PD13-B		± 4 h (240 min)	9 mL
Visit 8 / Day 30	29 days (696 h) after the infusion of BCD-148/Soliris®	PK14-A, PK14-B	PD14-A, PD14-B	IG2-A, IG2-B, IG2-C	± 4 h (240 min)	9 mL
Visit 9 / Day 37	36 days (864 h) after the infusion of BCD-148/Soliris®	PK15-A, PK15-B	PD15-A, PD15-B		± 4 h (240 min)	9 mL
Visit 10 / Day 44	43 days (1032 h) after the infusion of BCD-148/Soliris®	PK16-A, PK16-B	PD16-A, PD16-B		± 4 h (240 min)	9 mL
Visit 11 / Day 51	50 days (1200 h) after the infusion of BCD-148/Soliris®	PK17-A, PK17-B	PD17-A, PD17-B		± 4 h (240 min)	9 mL
Visit 12 / Day 59	58 days (1392 h) after the infusion of BCD-148/Soliris®	PK18-A, PK18-B	PD18-A, PD18-B	IG3-A, IG3-B, IG3-C	± 4 h (240 min)	9 mL

Samsung Bioepis Exhibit No. 1002
Page 11913

4.6.3.6.1. Eculizumab assay in the serum

Serum levels of anti-C5 MAb were determined by ELISA with horseradish peroxidase as an indicator enzyme[1],[2].

The hemolytic complement activity in the serum will be analyzed in the test with sheep erythrocytes and rabbit anti-sheep serum (hemolytic serum)[3].

The presence and titer of binding antibodies (BAbs) to anti-C5 MAb in the serum will be determined by ELISA with horseradish peroxidase as an indicator enzyme[4].

Neutralizing antibodies against anti-C5 MAb in subject' serum samples are detected by the validated ELISA with horseradish peroxidase as an indicator enzyme.

4.6.3.7. Chest X-ray and fluorography

Chest X-ray/fluorography to exclude lung diseases will be performed according to a standard procedure of the study site. If necessary, the Sponsor's representative may request the images (e.g. if the subject develops active TB while in the study).

4.6.3.8. ECG

A 12-lead ECG is performed according to the standard procedure.

4.6.3.9. Urine test for psychotropic and recreational drugs, psychoactive medications

This test is performed at Screening Visit 1 and Visit 1 / Day 1 before the infusion. The samples are tested by an immunochromatographic assay (test strips) to trace amphetamines, marihuana, morphine, cocaine (and its metabolites), and methamphetamine. If the test shows uncertain results for any of these substances, a re-test may be arranged.

4.6.3.10. Saliva alcohol test

The saliva alcohol test uses an indicator test strip for qualitative and semi-quantitative alcohol detection in the saliva. The test is performed at Screening Visit 1 and Visit 1 / Day 1 before the drug infusion. If the test shows a positive or uncertain result, a re-test may be arranged.

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[1] Report: Validation of Analytical Procedure "Assay of Free Anti-C5 Monoclonal Antibody in Human Serum by ELISA".
[2] Report: Validation of Analytical Procedure "Assay of Conjugated Anti-C5 Monoclonal Antibody in Human Serum by ELISA".
[3] Report: Validation of Analytical Procedure "Assay of Hemolytic Complement Activity in Human Serum"/
[4] Report: Validation of Bioanalytical Procedure "Detection of Binding Antibodies Against Anti-C5 Monoclonal Antibody in Human Serum by ELISA".

Samsung Bioepis Exhibit No. 1002
Page 11914

The test strip allows a one-step qualitative and semi-quantitative *in vitro* enzyme-based testing for alcohol in the human saliva. This test can be used for screening, emergency blood alcohol content assessment, and for self-control. The testing procedure does not require any specific equipment or skills.

Principle of the method: The test is based on the high specificity of alcohol oxidase for primary alcohols in the presence of peroxidase and an enzyme chromogenic substrate. The color on the test strip is compared to a color scale. The color and intensity of coloration indicate the alcohol concentration in the sample

Characteristics: The reactive pad is sensitive to methyl, ethyl, and propyl alcohols but does not react to other alcohols or acetone.

Precautions: The test strip is for *in vitro* diagnostics only. All components of the sensor pad are non-toxic. Do not touch the sensor pad to keep the test strip in a working state. Protect the sensor pad from direct sun light during the test. Wear disposable gloves when working with the test strips. Human saliva is a potentially infectious material; it can preserve and spread viral agents over a long time. Ensure that there are no alcohol vapors in the air of the testing facility to avoid false-positive results.

Testing procedure:

1. Open the package and remove the test strip.
2. Apply a saliva sample to the circle marked on the package or to any clean vessel or surface.
3. Dip the reaction pad into the saliva specimen for 5 to 10 seconds.
4. Shake off the excess saliva or dry the strip with clean filter paper.
5. At 2 minutes, compare the reactive pad with the provided colored chart.
6. Use the test strip within 20 min after opening.
7. Perform the test at +15 to +25°C.

4.6.3.11. Unscheduled visits

If a study subject develops an adverse event, he may need an unscheduled visit for additional safety assessment. Additional safety assessments must include assessment of subject complaints and concomitant therapy, physical examination, body temperature, BP, and wrist pulse check, hematology and chemistry, urinalysis and/or other tests deemed necessary by the investigator.

Samsung Bioepis Exhibit No. 1002
Page 11915

4.7. Stop rules and criteria for premature withdrawal for study subjects, study periods, and study as a whole

Study subjects will be withdrawn from the study in the following cases:

1. A violation of inclusion/exclusion criteria is revealed after the subject has been enrolled in the study (by the decision of JSC BIOCAD)
2. The subject recalls his consent to participate in the study
3. Adverse events or serious adverse events, laboratory abnormalities or concomitant conditions, which in the investigator's opinion, make further participation in the study impossible, dangerous or non-beneficial regarding subject's well-being/safety
4. Post-vaccination reactions (post-vaccination complications, acute and/or aggravated chronic infections or non-infectious diseases, or laboratory abnormalities (Hb, RBC, WBC, neutrophils, ESR, bilirubin total, ALT, AST) at assessment)
5. Poor treatment compliance (see section 6.6)
6. The subject misses 2 or more PK/PD blood collections in the study
7. The study is terminated by JSC BIOCAD, local ethics committee, or regulatory authorities.
8. The subject dies. The investigator must fill out the SEA Report Form and inform JSC BIOCAD about the SAE within 24 h of learning of the subject's death.

The investigator must inform JSC BIOCAD about the subject's premature withdrawal and specify the reason.

If the subject discontinues the study, an Early Withdrawal Form should be filled in in the CRF. The follow up procedures for discontinued subjects are described in section 5.4.

4.8. Drug accountability

The investigator is responsible for the investigational product accountability at the trial site. Throughout the study, the investigator must ensure proper accountability of the investigational product as required by regulatory authorities. The investigator must maintain accurate records regarding the receipt of the investigational product from JSC BIOCAD.

When the investigator or the pharmacist receives the investigational product, he/she should check the delivery, sign and date a receipt form and documentation provided by JSC BIOCAD, and return it to JSC BIOCAD. A copy of this documentation should be stored in the investigator's File.

Samsung Bioepis Exhibit No. 1002
Page 11916

The amount of investigational product delivered to the study site must be recorded in the receipt form provided by JSC BIOCAD. This form will be used as an investigational product accountability record.

Accurate accountability records should be available to the CRA during each monitoring visit. Drug accountability records should include:

- Delivery confirmation
- Inventory at the study site
- Use of investigational product by each study subject
- Return of unused drug product to JSC BIOCAD.

Records should include dates, amounts, batch numbers, and expiry dates of the investigational product (if applicable). Investigators must maintain accountability records to ensure that:

- The total amount of the investigational product provided by JSC BIOCAD is accurately checked and delivered undamaged.

Unused investigational product must not be used for any other purpose except for this study.

The CRA from JSC BIOCAD will regularly inspect drug accountability records.

4.1.8. Handling of investigational products

The investigational products are stored at the trial site at a temperature from 2°C to 8°C in a room accessible only to the Principal Investigator, co-investigators, and an authorized representative of the study site administration (who is authorized to enter the storage area by study site's rules).

The investigational products must be stored only in the official study center. The investigator must ensure safe storage of the investigational drug to prevent loss, theft, or improper environmental conditions (temperature) specified by the Sponsor and described in the Investigator Brochure. The investigator must maintain a temperature log.

4.9. Procedure for code keeping and unblinding

As the study is double-blind, the test product and the reference product will be identified only by Lot IDs and shelf life printed on the pack. JSC BIOCAD will prepare a certain number of envelop kits with treatment group codes (i.e. with lot numbers corresponding to the test drug and the reference drug). These envelopes will be distributed to the principal investigators and will be stored in the Investigator's File.

Samsung Bioepis Exhibit No. 1002
Page 11917

The investigator is allowed to unblind the treatment only in case of an emergency. The investigator must exercise his/her best efforts to prevent the loss or unblinding of study codes when unnecessary.

The treatment can be unblinded only in case of an emergency when this is necessary to give an appropriate treatment to the subject and ensure his well-being. If a medical situation occurs that requires unblinding, the principal investigator must contact a representative from JSC BIOCAD (Medical expert, trial manager, or CRA) and explain the reason for unblinding. The investigator must document the fact of unblinding in the source documents.

When all the subjects complete this clinical study, the Sponsor will retrieve the envelopes with treatment group codes from the sites.

All volunteers participating in the study will be given **Study ID Cards**. A Study ID Card has the subject's full name, protocol code, information about the study site, and contacts of the principal investigator.

Study team members should clearly explain to the subjects that they should carry their Subject ID cards all the time and notify medical staff at any other medical facility that they participate in this clinical study. If necessary (for example, to administer another medicinal product), a physician at another medical facility (other than the study center) can contact the investigator to discuss benefits and potential risks related to concomitant therapy.

4.10. Data entered directly into the CRF (i.e. no prior written or electronic record of data) and considered as source data

All data entered to the eCRF must be recorded in the source documentation.

In this study, no data will be entered directly to the eCRFs without being recorded in the source documents.

5. ELIGIBILITY AND EXCLUSION OF STUDY SUBJECTS

5.1. Inclusion criteria

1. Signed ICF for participation in the study
2. Men from 18 to 45 years old (inclusive) at the time of signing the ICF
3. BMI within the normal limits (18.0 to 30 kg/m^2)
4. The subject is able to follow the Protocol procedures (in the investigator's opinion)
5. The subject is verified as "Healthy" according to results of standard clinical, laboratory and instrumental tests

Samsung Bioepis Exhibit No. 1002
Page 11918

6. Normal hemodynamic parameters: systolic BP from 90 mmHg to 130 mmHg; diastolic BP from 60 mmHg to 90 mmHg; HR from 60 bpm to 90 bpm
7. The subject and his sex partner of childbearing potential consent to implement reliable contraceptive methods from the moment the subject signs the ICF and until the subject completes the study. This requirement does not apply to those subjects who had undergone surgical sterilization. Reliable contraception methods mean one barrier method in combination with one of the following: spermicides, intrauterine device and/or oral contraceptives used by the subject's partner.
8. The subject agrees not to drink alcohol for 24 h prior to the infusion of the test/reference drug and for the entire period while the subject is in the study.

5.2 Exclusion criteria

1. Psychiatric disorders or other conditions that can affect the ability of the subject to follow the study protocol
2. Acute infections within 4 weeks before signing the ICF
3. Results of laboratory and/or instrumental tests are outside the site's normal range
4. Any surgery done within 30 days before the screening or planned within 30 days after the subject completes the study
5. Impossibility to insert an intravenous catheter for blood collection (e.g., because of a skin condition at the venipuncture site)
6. A history of allergies
7. Known hypersensitivity to any component of BCD-148 or Soliris®, murine proteins or other drug components; hypersensitivity to any component of the meningococcal vaccine
8. The subject had used any medications that significantly affect hemodynamics, liver function, etc. (barbiturates, omeprazole, cimetidine, etc.) within 30 days before signing the ICF and/or the subject needs any medications (other than the study drugs) to be taken during the entire study period
9. The subject had previously used eculizumab and/or other therapeutic monoclonal antibodies against complement C5
10. Regular use (oral or parenteral) of any drugs, including OTC products, vitamins or biologically active supplements within 14 calendar days before signing the ICF
11. A history of recurrent/chronic hemorrhages or any hemorrhage within 30 days prior to signing the ICF
12. Acute or chronic infections or other diseases that, in the investigator's opinion, may affect

Samsung Bioepis Exhibit No. 1002
Page 11919

the PK, PD or safety of the study products

13. HIV, HCV, HBV infection, syphilis.
14. Meningococcal infection in the past (documented or mentioned verbally by the subject)
15. Vaccination within 4 weeks before the planned infusion date, except for vaccination against *Neisseria meningitidis* given to all subjects in the screening period
16. The subject refuses to get a vaccination against *Neisseria meningitidis* during the screening period[76].
17. The subject smokes more than 10 cigarettes per day
18. The subject consumes more than 10 units of alcohol per week (1 unit equals to 0.5 L of beer, 200 mL of wine or 50 mL of a strong alcohol beverage) or has a history of alcohol, recreational drug or medication abuse, or tests positive for alcohol and/or psychoactive substances during the screening examination
19. Donation of ≥ 450 mL of blood or plasma within 60 calendar days before signing the ICF.
20. Participation in any drug clinical studies within 30 calendar days prior to signing the informed consent form and through the entire period of study participation.

5.3. Withdrawal criteria

Refer to section 4.7. *Stop rules and criteria for premature withdrawal for study subjects, study periods, and study as a whole.*

The investigator must inform JSC BIOCAD about the subject's premature withdrawal within 24 h and specify the reason.

5.3.1. Replacing drop-outs

Those subjects who dropped out after randomization will not be replaced. The sample size was calculated with an account for potential dropouts.

[76] Except for cases when the subject has a documented evidence that he received a tetravalent meningococcal vaccine (serogroups A, C, Y, and W-135) within 2 years before signing the informed consent form If the previous vaccination was performed with a vaccine other that MCV4, the subject has to be re-vaccinated.

Samsung Bioepis Exhibit No. 1002
Page 11920

5.4 Follow-up of subjects withdrawn from the study or subjects who discontinued the study treatment but remain in the study for follow-up

5.4.1. Follow-up of subjects who received at least one dose of BCD-148/Soliris®

If the subject discontinues the study after receiving the test/reference drug, an Early Withdrawal Visit is performed and the Early Withdrawal Form is filled out.

Procedures of the Early Withdrawal Visit:

1. Information about concomitant therapies
2. Physical examination
3. Vital signs (BP, wrist pulse, body temperature)
4. Hematology, chemistry, and urinalysis
5. Documenting AEs/SAEs

If the subject discontinues the study due to an AE/SAE, the investigator should conduct further treatment and follow-up after the Early Withdrawal Visit in accordance with the study site standards for the treatment of a certain AE or SAE. The subject should be followed up until the AE or SAE resolves completely.

6. ADMINISTRATION OF THE INVESTIGATIONAL PRODUCT

6.1 Route of administration used in the study

In this clinical study, each subject will get one infusion of either the test drug BCD-148 or the reference drug Soliris®, depending on the study arm to which the subject is randomized. Both eculizumab products (BCD-148/Soliris®) will be administered as a single 900 mg drip infusion given over 25-45 min. The infusion will be given at the study site.

See section 1.2.4. *Posology and route of administration*.

6.2. Dose modification for the study drug

Not applicable.

6.3. Overdose

Any dose higher than the dose specified by the Protocol is considered an overdose. Repeated administration of the study drug is also considered an overdose, regardless of the dose and time of infusion.

Samsung Bioepis Exhibit No. 1002
Page 11921

In the case of an overdose, the subject should be monitored for any toxicity signs. If any toxicity signs are observed, standard symptomatic therapy should be given.

In the case of an overdose, either associated or not with an adverse event (serious or non-serious), the investigator must fill out the Overdose Report Form. An Overdose Report has to be **immediately (within 24 h)** submitted to the Sponsor at safety@biocad.ru (please put "ATTN Responsible Pharmacovigilance Officer" in the subject field).

6.4. Concomitant therapy, medications allowed and prohibited by the Protocol

The Protocol does not include any medications other than the test/reference drug.

Symptomatic treatment can be used if the investigator believes it will not affect the assessment of eculizumab PK/PD. Instruction on the use of symptomatic treatments are provided in the relevant Instructions for Medical Use.

If during the study, the subject develops an intercurrent illness/condition, a concurrent therapy can be prescribed in accordance with the site standard of care. Such therapy can include antipyretic drugs, pain-relief drugs, antihistamine, and mucolytic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), etc. For example, the symptomatic treatment of an acute upper respiratory tract infection may include (based on the indication): Ascorbic acid, mucolytic agents, expectorants, antipyretics (paracetamol, ibuprofen, etc.), oral/throat antiseptic solutions, nasal vasoconstriction sprays, inhaled vasoconstrictors (if the subject has signs of respiratory obstruction or has any other indications for inhaled vasoconstrictor therapy), and detoxification therapy. If the subject develops a bacterial infection which requires antibiotics actively secreted by the renal tubule (e.g. cephalosporins) should be the treatment of choice.

In the case of any life-threatening complications or conditions that require additional medication and/or in the case of severe adverse reactions, the investigator may use any medications (including antibacterial and hormonal) needed to stabilize and improve the subject's health. All medications used to treat the complication/condition should be listed in the respective section of the eCRF.

6.5. Compliance with study procedures

In this study, the information will be documented about each administration of the investigational product, doses, and intervals between the study visits.

The CRA will review accountability records during the monitoring visits and at the end of the study.

Samsung Bioepis Exhibit No. 1002
Page 11922

6.6. Compliance

In this study, a subject will be considered non-compliant if:

- He did not attend 2 or more visits
- Time deviations were reported for 2 or more visits[77,78].

7. PK AND PD ASSESSMENT

7.1. List of pharmacokinetic parameters

Pharmacokinetic assessment will be based on the concentration of eculizumab (monoclonal antibodies to complement C5) in the serum of healthy subjects.

The primary PK endpoint for PK after a single infusion of BCD-148/Soliris®:

- AUC0-∞ of eculizumab (the area under the *Concentration vs. Time* curve from 0 to infinity).

The secondary PK endpoints after a single infusion of BCD-148/Soliris®:

- C_{max} of eculizumab (maximum drug concentration in the serum).
- T_{max} of eculizumab (time to C_{max})
- $AUC_{0\text{-}1392}$ of eculizumab (area under the *Concentration vs. Time* curve from 0 to 1392 h post-infusion)
- $T_{1/2}$ of eculizumab (half-life).
- Vd of eculizumab (steady-state volume of distribution)
- K_{el} of eculizumab (elimination constant)
- Cl of eculizumab (clearance).

The PK endpoints will be analyzed when all the subjects complete the main study period.

[77]If the study visit is performed on the scheduled date but outside the acceptable time window, all the visit procedures should be performed including blood collections for immunogenicity testing, but no blood should be collected for PK and PD assessment.
If the visit is performed not on a scheduled date (deviation in the visit date), the procedures scheduled for this visits are not performed. This visit is considered a missed visit. The subject should attend the next scheduled visit. All other situations should be discussed with the Sponsor.
[78]If the subject did not attend Visit 1/ Day 1 due to force majeure, this visit can be re-scheduled but has to be performed within 5 days from the original visit date. In this case, dates of all subsequent visits will be counted from the actual date of Visit 1.

Samsung Bioepis Exhibit No. 1002
Page 11923

7.2. List of pharmacodynamics parameters

Pharmacodynamics will be investigated by measuring the hemolytic complement activity in the serum (CH50), where one unit of hemolytic activity is the reciprocal of the serum dilution which causes a 50% hemolysis.

The secondary endpoints for PD assessment after a single infusion of BCD-148/Soliris®:

- $ABEC_{(0\text{-}1392)}$ CH50 (the area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h).
- $AUEC_{(0\text{-}1392)}$ CH50 ((area under the *Time vs. Effect* curve from 0 to 1392 h)
- E_{min} CH50 (minimum hemolytic complement activity from 0 to 1392 h)
- T_{min} CH50 (time to minimum hemolytic complement activity within the period from 0 to 1392 h).

The PD endpoints will be analyzed when all the subjects complete the main study period.

8. SAFETY ASSESSMENT

8.1 List of safety endpoints

- The proportion of subjects who develop AEs/SAEs that, in the investigator's opinion, are related to eculizumab
- The proportion of subjects who develop CTCAE v. 4.03 grade 3/4 AEs that, in the investigator's opinion, are related to eculizumab, by study arms.

Immunogenicity assessment:

- The proportion of BAb- and NAb-positive subjects

8.2 Definitions

8.2.1 Adverse events

Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product: Adverse events are to be reported from eculizumab infusion and through the entire period of subject's participation in the

Samsung Bioepis Exhibit No. 1002
Page 11924

study (66 days). If the subject discontinues the study due to an AE/SAE, the investigator should conduct further treatment and follow-up after the Early Withdrawal Visit in accordance with the study site standards for the treatment of a certain AE or SAE.

The subject will be followed up until the AE/SAE resolves (or stabilizes, if it is a chronic condition).

In this study, the investigator is required to document all AEs from grade 1 and higher (CTCAE 5.0), regardless of their clinical significance.

8.2.2 Serious adverse events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacitation or disability
- Is a congenital anomaly or birth defect.
- Requires medical intervention to prevent any of the above listed conditions.

In case of any uncertainty whether the event meets the seriousness criteria or not, it should be treated as a serious adverse event.

An immediate risk of death from a reported event is considered **life-threatening**. A life-threatening event does not include an adverse event that, had it occurred in a more severe form, might have caused death, but is not associated with an immediate risk of death in the form it occurred. For example, hepatitis resolved without signs of hepatic insufficiency will not be considered life-threatening in spite of the fact that more severe hepatitis can lead to a fatal outcome. Similarly, an allergic reaction resulting in face angioedema will not be considered life-threatening despite the fact that larynx angioedema, allergic bronchospasm or anaphylaxis may lead to a fatal outcome.

Hospitalization is an official admission to the hospital. Hospitalization or its prolongation is a criterion of AE seriousness; however, hospitalization itself is not a serious adverse event. Hospitalization or its prolongation not associated with an AE should not be reported by the investigator as a serious adverse event. This is applicable (including but not limited) to the following cases:

- Hospitalization or prolongation of existing hospitalization is necessary to perform procedures required by the Protocol.

Samsung Bioepis Exhibit No. 1002
Page 11925

- Hospitalization or prolongation of existing hospitalization is a part of routine procedures in this study site (for example, stent removal after a surgery). An appropriate confirmation should be kept in a study file.
- Hospitalization due to a pre-existing condition which did not aggravate.

Disability can be described as a substantial, persistent or permanent disruption of a person's ability to conduct normal life functions as a result of an illness, injury or its consequences, etc.

The "Requires medical intervention to prevent any of the above listed conditions' criterion can be applied when the investigator believes an emergency medical intervention is necessary to treat an acute condition that, left untreated, is likely to result in death, become life-threatening, result in hospitalization or prolongation of existing hospitalization, disability or incapacitation, or a congenital anomaly or birth defect.

Other reportable information. Certain information not considered an SAE must be recorded, presented in the report, and followed up as an SAE. This includes:

- An overdose with the study drug as defined in the Protocol, whether or not it was associated with an AE. An overdose in breast-feeding women without AEs is an exception.
- Unintentional or accidental use of the investigational product, whether or not considered related to an AE.
- Drug misuse regardless of the development of AE (including the intended or incidental use of investigational products, a confusion in using investigational products, improper route of administration, etc.).

8.2.3. Unexpected adverse drug reaction

An unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (Investigator's Brochure).

8.3 Methods and time of assessment, recording, and analysis of safety parameters

8.3.1 Time windows for analysis of safety parameters

Information about serious adverse events will include information about the SAEs that occurred from the moment the subject has signed an ICF and until he has completed the study (as planned or prematurely).

SAEs that occurred in the screening period will be evaluated separately. These events are technically not adverse events, as they occurred before the infusion of the study drug. However,

Samsung Bioepis Exhibit No. 1002
Page 11926

they can characterize the safety of the screening procedures or become the reason for removing the subject from the study at screening, therefore these SAEs must also be captured.

Information about AEs that do not meet seriousness criteria will be recorded from the time when the subject has received an infusion of BCD-148/Soliris® until the time he has completed the study (as planned or prematurely).

The Drug Safety Division of JSC BIOCAD will analyze information about every SAE immediately after receiving an SAE report, provided that the investigator has sent the report within the due time window. The cumulative analysis of SAEs will be performed during the preparation of the final study report.

AEs not meeting the seriousness criteria will be analyzed routinely during the preparation of the final study report.

8.3.2 Methods and timeframes for assessment and recording of safety parameters

The safety analysis will include all subjects who received an infusion of BCD-148/Soliris®. The safety will be analyzed based on the following information:

- AEs/SAEs
- Physical examination findings and vital signs
- Hematology and chemistry results, urinalysis results
- ECG results

The frequency of these procedures is specified in section 4.6.1 S*tudy visits and procedures.* AEs/SAEs will be documented and reported in accordance with the Sponsor's Manual.

The investigator is responsible for recording adverse events in the clinical study.

AEs are to be documented from the time when the subject has received an infusion of BCD-148/Soliris® and through the moment he has completed the study (as planned or prematurely). SAEs are to be documented from the time when the subject has signed the ICF and through the moment he has completed the study (as planned or prematurely). SAEs registered during the screening period are not included in the safety analysis. The investigator can also capture SAEs that occurred after the time specified by the Protocol if he/she believes that this SAE is associated with the study drug or study procedures.

The study investigator must document non-serious AEs in the source documents and in the CRF, and show them to the CRA at the next monitoring visit. All serious adverse events (SAEs) must be reported to the Sponsor immediately **(within 24 hours)** through the SAE Report Form. An SAE Report Form must be immediately (within 24 h) submitted to the Sponsor

Samsung Bioepis Exhibit No. 1002
Page 11927

atsafety@biocad.ru (please put "ATTN Responsible Pharmacovigilance Officer" in the subject field). The investigator should receive a receipt/delivery confirmation.

During Screening Visit 2, subjects will be given a meningococcal vaccine. Therefore, all AEs that occur starting from Visit 2 and considered by the investigator as post-vaccination complications will also be captured. AEs considered by the investigator as post-vaccination complications may meet a seriousness criterion specified by this protocol. These AEs will not be included in the safety analysis. After the subject gets an infusion of the test/reference drug on Visit 1/Day 1, all AEs (both related and unrelated in the investigator's opinion to the study drugs) must be captured during the entire main study period (59 days). All abnormal physical findings, abnormal vital signs, and abnormal laboratory/instrumental results, either clinically significant or non-significant, must be captured in the source documentation and eCRF.

8.4 Requirements for reports. Documenting and reporting AEs and completing AE Report Forms

8.4.1 Documenting AEs/SAEs

At every visit, make a record about whether or not any AEs occurred during the period from the previous visit Any SAE reported for the study subject must be recorded in source documents and a special adverse event form in the eCRF.

AEs should be registered and numbered consecutively as they occur. Each AE is reported in an *AE Report Form*. Rules for reporting AE/SAE are described in details in the Sponsor's Manual.

Adverse events must be recorded regardless of their seriousness and causal relationship with the study therapy. **In this study, all AEs (including those of CTCAE v.5.0 grade 1) are to be recorded.** All abnormal physical findings, abnormal vital signs, and abnormal laboratory/instrumental results, either clinically significant or non-significant, must be captured in the source documentation and eCRF. If the same adverse event reoccurs after resolution, it is recorded as a new one and assigned a new number.

8.4.2 AE/SAE reporting

The AE Report Form must be filled out during the study visit (or the investigator can do it later the same day), except for data not available/not known at that moment. All sections of the form must be filled out. If no data are available, put: "Data not available" or "N/A". However, all actions should be taken to receive all necessary data on emerging adverse events.

Samsung Bioepis Exhibit No. 1002
Page 11928

The following information must be recorded in source documents and in the AE Report Form in the CRF

- AE No. as it occurred
- Visit No.
- A brief description of the AE
- Seriousness (yes/no)
- Seriousness criteria
- Severity grade, CTCAE 5.0
- Onset date
- End date
- Outcome
- Actions taken due to the AE
- Causality.
- Comments specifying any clinically meaningful (in the investigator's opinion) information related to AE development or its therapy.

If any medication therapy was prescribed, all drugs should be listed in the Concomitant Therapy section of the eCRF (with the note that they were used to manage the AE).

Columns *Grade*, *Outcome*, *Measures*, and *Causal Relationship* should be filled using digital codes explained in the *Notes* section. If the investigator considers an AE to be an SAE, he/she must fill out an SAE Report Form in the eCRF in addition to the AE Report From (printed copies).

One SAE Report Form is filled out for one SAE. If the SAE remains unresolved at the next visit, the check box in the *Adverse Events* section of the eCRF should be ticked for this visit and marked as "unresolved". In this case, a new SAE Report Form should be filled out marked as "Follow-up".

The SAE Report Form must contain the following information:

1) Clinical study:

- Protocol ID

2) SAE information:

- SAE name
- Initial or Follow-up
- Internal SAE code assigned by the Sponsor (this field is filled out by the Sponsor)

3) Information on the investigator who reported the SAE, and information on the study site:

- Full Name of the investigator

Samsung Bioepis Exhibit No. 1002
Page 11929

- Contact information (tel. and e-mail)
- Site name and code
- Principal investigator's name

4) Study subject:

- Subject ID
- Sex
- Body weight
- Height
- Date of birth
- Renal/hepatic impairment
- Allergies

5) Information on the test drug:

- Product code
- Indication
- Date when the drug was first administered
- Batch number (associated with the SAE)
- Dose (associated with the SAE)
- Treatment start date and time (associated with the SAE)
- Treatment stop date and time (associated with the SAE)
- Route of administration
- Dosage and dosing frequency

6) Information about recent (within 3 months) concomitant therapy or concomitant therapy used at the time of SAE onset:

- INNs and brand names of concomitant medications
- Indication
- Treatment start date
- Treatment stop date
- Dosages, frequency and route of administration
- Any suspected causal relationship between the SAE and concomitant medications

7) SAE narrative:

- SAE description including all relevant symptoms, laboratory and other test results, onset date, and end date
- Time after the last dose of the study drug

Samsung Bioepis Exhibit No. 1002
Page 11930

- Autopsy data if the subject died (specifying the cause of death according to postmortem conclusion). If no autopsy findings are available, the cause of death is designated according to the clinical report.

- Time of hospitalization (if applicable)

8) Severity (CTCAE 5.0)

9) Seriousness

10) Medical history (with dates)

11) Investigations of particular interest at the onset of the SAE

- Investigation

- Normal limits

- Date of the analysis

- Result

12) Actions taken to resolve the SAE

- Medication / non-medication

For medication therapy, the following should be specified: INNs and brand names of drugs, treatment start and stop dates, dosages, frequencies, and routes of administration.

13) Actions taken regarding the suspected drug

- Drug discontinued/dose reduced/dose maintained, etc.

- Dechallenge/rechallenge test results (if applicable)

14) Outcome

15) Signatures

The investigator must sign (put a signature and full name) each page of the SAE Report Form to verify his/her responsibility for the reported information. Signed SAE Report Form is then submitted to the Sponsor.

8.5 Information concerning the method and duration of follow-up for study subjects after the onset of AE/SAE

In case of the subject's withdrawal from the study due to an AE/SAE, further subject's treatment and follow-up is performed by the investigator as per standard institutional practices for the treatment of the developed AE or SAE. The subject should be followed up until the AE or SAE resolves completely. See section 5.4 for further details.

Samsung Bioepis Exhibit No. 1002
Page 11931

9. STATISTICAL METHODOLOGY

9.1 Calculation of PK and PD parameters

9.1.1. PK parameters

Eculizumab (anti-C5 MAb) concentrations in the serum of each study subject will be measured at timepoints specified by the Protocol, and the following PK parameters will be calculated:

$AUC_{0-\infty}$ of eculizumab (the area under the *Concentration vs. Time* curve from 0 to infinity).

$$AUC_{0-\infty} = AUC_{0-1392} + \frac{C_{1392}}{k_{el}}, \text{ where}$$

C_{1392} refers to eculizumab concentration in the serum over 1392 h post-infusion, where k_{el} is the elimination constant.

AUC_{0-1392} (the area under the *Concentration vs. Time* curve from 0 to 392 h). AUC_{0-1392} will be determined with the trapezoidal rule and the formula where Cp is the concentration of eculizumab in the serum at t_p (h:)

$$AUC_{(0-1392)} = \sum_{p=2}^{18} \frac{(C_p + C_{p-1}) * (t_p - t_{p-1})}{2}$$

t_p

$\in \{0; 0{,}083; 4;\ 8; 12; 24; 48; 72; 120; 192; 264; 360; 528; 696; 864; 1032; 1200;\ 1392\}_{p=1,\ldots,18}$

C_{max} is the maximum eculizumab serum concentration achieved during the observation period.

$Tmax_{max}$ is the time to maximum concentration (C_{max}).

$AUMC_{0-1392}$ is the total area under the first moment curve from 0 to 1392 h. $AUMC_{0-1392}$ is calculated using the following formula:

$$AUMC_{0-1392} = \sum_{p=2}^{18} \frac{(C_p * t_p + C_{p-1} * t_{p-1}) * (t_p - t_{p-1})}{2},$$

где C_p – концентрация экулизумаба

в сыворотке крови в момент времени t_p

t_p

$\in \{0; 0{,}083; 4;\ 8; 12; 24; 48; 72; 120; 192; 264; 360; 528; 696; 864; 1032; 1200;\ 1392\}_{p=1,\ldots,18}$

Total clearance (Cl) is the volume of a test tissue from which a drug is completely removed per unit time. It is calculated as a drug dose (*DOSE*) divided by AUC_{0-1392}:

Samsung Bioepis Exhibit No. 1002
Page 11932

$$CL = \frac{DOSE}{AUC_{0-1392}}$$

Mean residence time (MRT) is calculated as a $AUMC_{0\text{-}1392}$ to $AUC_{0\text{-}1392}$ ratio:

$$\mathrm{MRT} = \frac{\mathrm{AUMC}_{0-1392}}{\mathrm{AUC}_{0-1392}}$$

Elimination rate constant (k_{el}) will be calculated as follows:

$$k_{el} = \frac{1}{MRT}$$

Elimination half-life ($T_{1/2}$) will be calculated as follows:

$$T_{1/2} = \frac{\ln(2)}{k_{el}} = \ln(2) * MRT$$

Volume of distribution (V_d) is a proportionality factor that relates the drug concentration in a test tissue to the amount of drug in the body. It shows the intensity of drug distribution between a test tissue and other tissues:

$$V_d = CL * MRT$$

9.1.2. PD parameters

The hemolytic complement activity (CH50) (where one unit of hemolytic activity is the reciprocal of the serum dilution which causes a 50% hemolysis) at protocol-specified endpoints will be used to calculate the following PD measures:

$AUEC_{(0\text{-}1392)}$ - the area under the *Time vs. Effect* curve from 0 to 1392 h) The $AUEC_{0\text{-}1392}$ will be calculated using the trapezoidal rule and the following formula:

$$AUEC_{0-1392} = \sum_{p=2}^{18} \frac{(C_p + C_{p-1}) * (t_p - t_{p-1})}{2},$$

Where Cp is the hemolytic complement activity in the serum at t_p (h)
$\in \{0; 0{,}083; 4; 8; 12; 24; 48; 72; 120; 192; 264; 360; 528; 696; 864; 1032; 1200; 1392\}_{p=1,\ldots,18}$

ABEC - the area between the baseline and effect curves for hemolytic activity of serum complement from 0 to 1392 h. To account for baseline variations, the baseline (pre-infusion) values will be subtracted from all subsequent measurements.

$$ABEC = AUEC_{0-1392} - c_0 * 1392\,,$$

Where c_0 is the pre-infusion hemolytic complement activity.

E_{min} CH50 - the minimum hemolytic complement activity from 0 to 1392 h.

Samsung Bioepis Exhibit No. 1002
Page 11933

T_{min} CH50 - the time to minimum hemolytic complement activity within the period from 0 to 1392 h.

9.2. Statistical methods

The statistical analysis will be performed using two-tailed hypothesis tests. The statistical significance level is 0.05.

The normally distributed quantitative data will be compared using the following tests: the two-tailed Student's *t*-test, Welch's *t*-test, and ANOVA.

The non-normally distributed quantitative data will be compared by using the Mann-Whitney test, Wilcoxon test, Kruskal-Wallis test, and Friedman's test.

The quantitative data:

- **Safety:**
  - ✓ Hematology results
  - ✓ Chemistry results
  - ✓ Coagulation pattern.
- **Assessment of PK and PD**
- **Demographics**

Demographic data will be tested for normality using the Shapiro-Wilk test.

Normally-distributed quantitative variables will be described with the following characteristics: Mean values, geometric means (PK/PD), SD, CV, medians, quartiles, Min, and Max. In addition, the 90% CIs for the ratio of the geometric means will be calculated for $AUC_{(0-1392)}$ and C_{max}.

The categorical data:

Safety and tolerability:

- ECG findings
- Urinalysis results
- The proportion of subjects with AEs/SAEs
- The proportion of subjects with a grade 3/4 AE/SAE.

Immunogenicity:

- The proportion of BAb- and NAb-positive subjects

The categorical data will be processed using the frequency tables, exact Fisher's test, χ^2 test, and Cochran-Mantel-Haenszel test. The categorical data will be described using percentages or proportions.

Samsung Bioepis Exhibit No. 1002
Page 11934

Statistical methods will be chosen based on the type and distribution of raw data. Applicability of certain statistical tests will be evaluated after all the data are collected because it is impossible to predict the distribution pattern, data homogeneity and other data characteristics in advance.

9.3. Justification of sample size, including reasoning or calculations to justify statistical power and clinical justification of the study

The study is to test the hypothesis that the test drug BCD-148 and the reference drug Soliris® have equivalent pharmacokinetics. The equivalence hypothesis will be tested for the primary PK endpoint – $AUC_{(0-\infty)}$ of eculizumab after a single IV infusion of BCD-148/Soliris®. BCD-148 will be proved equivalent to Soliris® if the limits of the two-sided 95% CI for the ratio of the geometric means of eculizumab $AUC_{(0-\infty)}$ values after a single IV infusion of BCD-148 and Soliris® fall within 80.00-125.00%.

The sample size sufficient for testing the equivalence of eculizumab $AUC_{(0-\infty)}$ was calculated. The estimation was based on single-dose eculizumab $AUC_{(0-\infty)}$ and C_{max} data available from literature. Single-doses of the original eculizumab have not been tested in healthy subjects or PNH and aHUS patients, therefore the calculations for this protocol were based on AUC and C_{max} of single-dose 8 mg/kg eculizumab in rheumatoid arthritis patients (C97-001-01) and SLE patients (C97-002-01) [79,80]. The 8 mg/kg dose was selected as the one closest to the therapeutic dose of eculizumab used in this clinical trial.

Type I error was set as 5% (α=0.05); type II error was set as 20% (β=0.2); test power was 80%.

The "sampleN.TOST" function (PowerTOST R package).[http://cran.r-project.org/web/packages/PowerTOST/PowerTOST.pdf] was used to compute the sample size for the parallel-group design from the CV and the $AUC_{(0-\infty)}$ and C_{max} ratios.

Group coefficients of variation were calculated with the following formula:

$$CV = \frac{\sigma}{\mu},$$

Where: σ is the standard deviation of $AUC_{(0-\infty)}$ or C_{max}; μ is the mean $AUC_{(0-\infty)}$ or C_{max}.

[79] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000791/WC500054212.pdf
[80] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_ClinPharmR.pdf (table 1, page 10)

Samsung Bioepis Exhibit No. 1002
Page 11935

Table 10. Estimated CV values for $AUC_{(0-\infty)}$

Clinical study	Mean and standard deviation[81]	CV
C97-001-01	μ = 37.8 mg*h/mL σ = 5.9 mg*h/mL	$CV = \frac{5,9}{37,8} = 0,1561$
C97-002-01	μ = 31.6 mg*h/mL σ = 9.1 mg*h/mL	$CV = \frac{9,1}{31,6} = 0,288$

The group CV was also estimated for the C_{max}.

Table 11. Estimated CV values for C_{max}

Clinical study	Mean and standard deviation[82]	CV
C97-001-01	M = 182 μg/mL σ = 19 μg/mL	$CV = \frac{19}{182} = 0,1044$
C97-002-01	μ = 160 μg/mL σ = 10 μg/mL	$CV = \frac{10}{162} = 0,0625$

The table below summarizes the statistical data for the sample size based on the CVs for $AUC_{(0-\infty)}$ and C_{max}.

Table 12. Power and sample size ("sampleN.TOST")

Variable	Ratio of mean values	CV	Sample size (N)	Power
C97-001-01 clinical study				
$AUC_{(0-\infty)}$	$\frac{\mu_T}{\mu_C} = 0.95$	0.1561.	$N_{AUC\ 0-\infty} = 24$ subjects (12 subjects/arm)	83.18%

[81] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_ClinPharmR.pdf
[82] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_ClinPharmR.pdf

Samsung Bioepis Exhibit No. 1002
Page 11936

Variable	Ratio of mean values	CV	Sample size (N)	Power
C_{max}	$\frac{\mu_T}{\mu_C} = 0.95$	0.1044.	N_{Cmax} = 12 subjects (6 subjects/arm)	83.96%
C97-001-01 clinical study				
$AUC_{(0-\infty)}$	$\frac{\mu_T}{\mu_C} = 0.95$	0,288	$N_{AUC\ 0-\infty}$ = 70 subjects (35 subjects/arm)	80.01%
C_{max}	$\frac{\mu_T}{\mu_C} = 0.95$	0,0625	N_{Cmax} = 6 subjects (3 subjects/arm)	86.11%

Thus, statistical estimate based on the C97-001-01 study shows that this protocol should include N= max{$N_{AUC\ 0-\infty}$, N_{Cmax}} =

= max{24.12}=24 subjects (12 subjects per study arm).

Statistical estimate based on the C97-002-01 study shows that this protocol should include N= max{$N_{AUC\ 0-\infty}$, N_{Cmax}} =

= max{70.6}=70 subjects (35 subjects per study arm).

It was shown that to get the full and valid data for testing the hypothesis of PK equivalence (the primary PK endpoint of $AUC_{(0-\infty)}$) 70 subjects have to be enrolled in total (35 subjects in each arm). This sample size will be sufficient to demonstrate with the 80% power that the two-sided CI for the $AUC_{(0-\infty)}$ ratio between BCD-148 and Soliris® falls within the range from 80.00% to 125.00%. The expected dropout rate due to reasons not related to the study drugs is approximately 10%. Therefore, 8 more volunteers will be enrolled to compensate for the premature withdrawal of randomized subjects. Thus, the overall number of study participants will be 78 subjects (39 in each study arm).

9.4. Statistical analysis steps and timelines for reports

Clinical study results will be analyzed after all protocol-specified data of the last study subject have been received (i.e. after all subjects have completed the trial).

Samsung Bioepis Exhibit No. 1002
Page 11937

9.5. Study termination criteria

JSC BIOCAD can suspend or terminate the study due to safety or ethical issues, Protocol compliance issues, or due to other reasons. If JSC BIOCAD suspends or terminates the study, the study site will be notified in advance. In case of suspension or termination, JSC BIOCAD and the investigator have to inform Ethics Committees and regulatory authorities in due time. If the study is suspended or terminated, all study information must be transferred to and all unused investigational product must be returned to JSC BIOCAD.

9.6. Handling of missing, unevaluable or uncertain data

All information specified in the eCRF has to be confirmed by appropriate data in the source documents. To collect missing data or correct wrong data, the BIOCAD's CRA or clinical trial specialist generates queries, which are study- and site-specific, i.e. generated for each subject individually.

The investigator must respond within 5 working days from the date when the query was received.

None of the missing, non-evaluable, or uncertain data will be replaced with available data or projected.

9.7. Reporting any deviations from the initial statistical plan

If the initial study plan requires modifications, all changes will be described and explained in a protocol amendment or final clinical study report.

9.8 Selection of subjects for analysis

Demographics and baseline clinical and laboratory characteristics will be evaluated in all subjects included in the study.

PK/PD analysis:

The PK/PD analysis will include data from all subjects who received the test drug/ reference drug. However, subjects who had two or more PK/PD blood samples missed/lost/spoiled will be removed from the analysis.

To obtain valid results, individual concentration values will be excluded from analysis if a technical issue occurs during the concentration analysis due a human error (e.g., a whole biospecimen is compromised because a wrong reagent or wrong amount of an appropriate reagent was added; a sample was re-frozen after thawing: a sample was contaminated with foreign

Samsung Bioepis Exhibit No. 1002
Page 11938

substances, etc.) or due to an unexpected technical problem, and it is impossible to retest the sample. If, with the inappropriate sample excluded from the analysis, a subject has two or more blood samples missed/lost/spoiled over the entire study period, this volunteer will be completely removed from the PK assessment.

Safety analysis

The safety analysis will include all subjects dosed with BCD-148/Soliris®.

Immunogenicity analysis

The immunogenicity analysis will include data from all subjects who received BCD-148/Soliris® except for those whose pre-infusion sample and at least one post-infusion sample are missed/lost/spoiled.

10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution involved in the study must ensure direct access to source data/documents by the monitor, the auditor, the LEC/IRB or regulatory authorities.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data quality assurance

According to the National Standard "Good Clinical Practice", ICH GCP, and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory authorities, or LEC/IRB may perform audits/inspections to assure the quality of the study. Audits/inspections can be performed at any time during the study or after its completion. The investigator must give the auditor/inspector direct access to all study documents (including source documents) and discuss (personally, or designate someone from the study team) the audit/inspection results and other matters with the auditor/inspector.

11.2. Investigator adherence to the Protocol

Before beginning the study, the investigator must read and accept all provisions of this Protocol. The investigator must conduct the study in accordance with this Protocol, the current law of the Russian Federation, Federal Law #61-FZ of April 12, 2012: *On the Circulation of Medicines*; National Standard of the Russian Federation GOST R 52379-2005 *Good Clinical Practice*; the rules of Good Clinical Practice of the Eurasian Economic Union; the Constitution of the Russian Federation; Federal Law #323-FZ of November 21, 2011: *On Public Health Protection in the Russian Federation*; the WMA Declaration of Helsinki (Fortaleza 2013), Order

Samsung Bioepis Exhibit No. 1002
Page 11939

#200n of April 01, 2016 *On Approval of the Good Clinical Practice*; the GCP principles, and the applicable regulations.

No protocol deviations are allowed during the study without a previous written approval from JSC BIOCAD, the Ministry of Healthcare of the Russian Federation and Local Ethics Committees, except for the cases when the deviation is necessary to protect a subject from an immediate hazard.

The investigator should have enough time to accurately perform and complete the study within the timeframes specified by JSC BIOCAD, enough employees of appropriate qualification, and adequate equipment to conduct the study according to the Protocol.

Each sub-investigator participating in the study must read the Protocol and be aware of his/her responsibilities/functions in the study. If the principal investigator delegates some of his/her functions to sub-investigators, this must be documented in a relevant section of the Investigator's File.

11.3. Investigator responsibility to comply with the Protocol

If the investigator decides to withdraw a subject from the study, he/she must notify the responsible Clinical Trial Manager (CTM) or CRA at JSC BIOCAD via e-mail within 48 h after making this decision. The e-mail should contain the Subject ID, reason and date of withdrawal from the study. The fact of withdrawal must be captured in the eCRF.

If the subject missed the scheduled visit, or if any study drug dose modification was revealed other than those allowed by the Protocol, the investigator must notify the responsible CTM or CRA at JSC BIOCAD via e-mail within 24h of event discovery. The event must be captured in the eCRF.

If the investigator fails to follow these procedures or if multiple Protocol violations occur, JSC BIOCAD may suspend or terminate the study at this particular study site.

11.4. Study monitoring

Before the study start(during the Study Initiation Visit or Investigators' Meeting), a CRA/CTM of JSC BIOCAD or an authorized CRO will explain the Protocol, IB, eCRF, and other study documentation to the investigators and members of the study teams. The CRA will periodically come to the study site during the study to check that the rights and wellbeing of the study subjects are being protected, the data submitted are valid, complete, and supported by appropriate source documents, and that the study is being conducted according to the current

Samsung Bioepis Exhibit No. 1002
Page 11940

approved Protocol version/amendment, GCP, and regulations. During these visits, key members of the study team should be available to assist the CRA and resolve arising issues (if any).

Study monitoring is performed according to appropriate SOPs of JSC BIOCAD.

For each study subject, the investigator should keep source documents containing the subject data and records made during visits (medical records of the study center), including demographics, medical information, laboratory findings, ECG, and all other tests or examinations. Any information contained in the eCRF should be also recorded in the subject's source documents. The investigator must keep the original ICF. A copy of the signed ICF will be given to the subject.

The investigator has to provide the CRA with all relevant subject source documents to confirm that data in the source documents is consistent with the data in the eCRF. The investigator should ensure the timely completeness of the eCRFs before the CRA's visit.

To confirm the conformance of the study to the Declaration of Helsinki, Russian National Standard *Good Clinical Practice*, ICH GCP, regulatory requirements, and the Study Protocol, as well as the authenticity, accuracy, and completeness of data, the CTM will check the eCRFs and other study-related documents by verifying raw data.

Upon the study completion, a BIOCAD representative (CTM/CRA) should visit the study site to perform the study closeout visit. During this visit, the Sponsor's representative will collect all necessary documentation in accordance with the SOP of JSC BIOCAD.

11.5. Data management and quality control

In the trials that involve eCRFs, JSC BIOCAD employees (or employees of an authorized CRO) will check the data entered by the study team members for accuracy and completeness. If there are any inconsistent or missing data points, queries will be generated with a request for clarification. All queries are sent to the study site. A designated member of the study team must immediately answer the request and make all required changes to the database.

At the end of the study, any protocol deviations will be determined. After all these actions have been taken and the completeness and accuracy of study data have been verified, the database is locked.

11.6. Study termination

JSC BIOCAD can suspend or terminate the study due to safety or ethical issues, Protocol compliance issues, or due to other reasons. If JSC BIOCAD suspends or terminates the study, the study site will be notified in advance. In case of suspension or termination, JSC BIOCAD and the investigator have to inform Ethics Committees and regulatory authorities in due time. If the study

Samsung Bioepis Exhibit No. 1002
Page 11941

is suspended or terminated, all study information must be transferred to and all unused investigational product must be returned to JSC BIOCAD.

12. ETHICS

12.1. Ethical aspects of the study

This clinical study will be conducted in accordance with the ethical principles laid out in the WMA Declaration of Helsinki (Fortaleza 2013); Federal Law #61-FZ of April 12, 2012: *On the Circulation of Medicines*; Order #200n of April 01, 2016 *On Approval of the Good Clinical Practice*; National Standard of the Russian Federation GOST R 52379-2005 *Good Clinical Practice*; the rules of Good Clinical Practice of the Eurasian Economic Union; the Constitution of the Russian Federation; Federal Law #323-FZ of November 21, 2011: *On Public Health Protection in the Russian Federation*; the GCP principles, and the applicable regulations.

The final version of the Protocol, including the Subject Information Sheet with the Informed Consent Form, will be submitted to regulatory authorities and local ethics committees for approval before the study start.

All subsequent protocol amendments (other than administrative amendments) must be approved before implementation.

Informed consent must be obtained from the subject before any study procedures are initiated. The Subject Information Sheet contains all the information that a subject may need to make a conscious and independent decision about whether to participate.

During the study, all cases of SAEs will be reported to JSC BIOCAD within 24 hours. JSC BIOCAD will analyze the reports and may suspend the study if considered necessary. Local Ethics Committees will also be notified of all SAEs that are related, in the investigator's opinion, to the investigational product.

All subject personal information is confidential and can be disclosed only if required by law (including court decisions).

All study subjects will be insured. If a subject gets injured directly due to the investigational product, the Sponsor will cover all reasonably justified treatment expenses.

12.2. Confidentiality of study subjects

The investigator should keep confidentiality concerning subjects' identity, the text of this Protocol, and all other study materials and results.

Samsung Bioepis Exhibit No. 1002
Page 11942

The investigator should ensure subjects' confidentiality. Subjects should be identified in the CRFs and other documents provided by JSC BIOCAD using identification numbers and/or initials, but not with their complete names.

The investigator should keep a separate log with volunteers' identification numbers, last names, addresses, telephone and medical record numbers (if applicable). The investigator must keep confidentiality of the data not intended for submission to JSC BIOCAD.

All study materials proprietary to JSC BIOCAD cannot be transferred to a third party unless required by the law of the Russian Federation.

13. DATA HANDLING AND RECORD KEEPING

13.1. Record keeping at the study site

All study documents must be archived at the study site or at the central archive of the institution. A list of all study subject identifiers should be made.

According to the ICH GCP, essential documents include: signed Protocol and amendments; signed ICFs for all subjects; medical records and other source documents; approvals from LECs and regulatory authorities and all correspondence including approved documents; drug accountability records; study correspondence; and the list of subject names and addresses. These are the essential documents that must be kept in the Investigator's File.

The investigator must keep all the essential documents over a period of time specified by applicable regulations.

By the end of this period, the Sponsor will inform the investigator(s) about the date when the documents may be destroyed.

Study subject documentation will be archived in accordance with the site in-house SOPs.

The investigator must inform the Sponsor about the place where essential documents are stored and request an approval from JSC BIOCAD before destroying any of the essential documents. Appropriate measures must be taken to prevent the accidental or premature destruction of these documents.

13.2. Confidentiality of data

All information about study subjects will be kept confidential. The information will be processed in compliance with all applicable laws and regulations. These regulations require informing study subjects and obtaining their written authorization regarding the following: questions:

Samsung Bioepis Exhibit No. 1002
Page 11943

- What protected health information will be collected in this study?
- Who will have access to this information and on what grounds?
- Who will use or disclose this information?
- Do study subjects have the right to recall their consent for using their confidential health information?

According to the current regulations, if the subject recalls his/her authorization to collect or use his/her protected health information, the investigator still can use all information obtained before the authorization was withdrawn. If the subject recalls authorization to collect or use his/her protected health information, the investigator should do as much as possible to get subject's permission for collecting at least the safety information (i.e. onset of new or aggravation of existing adverse events) until the scheduled end of the study period.

To prevent unauthorized access to protected subject information, the data management system uses integrated safety elements encrypting all the data when sending them in both directions. The access to the system will be controlled with a sequence of individually assigned identification codes and user passwords. These codes and passwords will be given only to authorized members of the study team who have received a special training.

13.3. Collection of data

This trial uses an electronic data capture (EDC) system. Designated study team members will enter the data required by the Protocol to eCRFs. The eCRFs have been developed with a validated and safe web-based software. The study team members will get access to the EDC system only after being appropriately trained. An automated validation program inspects the eCRFs for inconsistencies and allows the study team members to change or verify the entered data.

The principal investigator is responsible for completeness and accuracy of all the data entered to the eCRFs and for entering and updating the information in a timely manner.

The study site personnel will collect PK/PD/IG blood samples and send them to the central laboratory for processing.

14. FINANCE AND INSURANCE

Study subjects will receive a monetary compensation for participating in the study.

The compensation for study participation is 65 000 (sixty-five thousand) Russian Rubles. The total amount is paid to the subjects who have completed the entire study. If the subject discontinues the study due to a safety issue but not due to any non-compliance issue or violation

Samsung Bioepis Exhibit No. 1002
Page 11944

of the Protocol, he will be paid the full compensation. In all other cases the compensation amount will be pro-rated according to the number of actual blood collections. Blood samples for PK and blood samples for PD will be collected at the same time over the entire study. Thus, the study includes 18 blood collections for PK and PD assessment, and the compensation for each PK/PD blood collection is 3600 Russian Rubles. No payments are provided for the screening examination and vaccination.

The Sponsor will not provide any special compensation for the subject's travel to the study site or other expenses.

During the study, each study subject will be insured as a study participant according to the applicable law of the Russian Federation. In the Russian Federation, subjects will be insured by the Russian company SPAO Ingosstrakh. The investigator will provide the subject a certificate of compulsory insurance of the life and health of a drug clinical study participant. If the subject needs to make changes to the compulsory insurance certificate, he will need to return the previously issued certificate and receive a new one.

The insurance policy covers only claims regarding life and health harmed as a result of study participation. The insurance object is the subject's property interest related to the harm to the subject's life or health due to his/her participation in the clinical trial if there is a causal relationship between the event and subject's participation in the clinical trial. The Insurer shall pay the following compensations according to the Compulsory Insurance Contract (insurance payment):

a) If the insured person dies: 2 million Russian Rubles. Insurance payment in the specified size is distributed among beneficiary parties in equal parts.
b) If the insured person gets injured, and the injury results in:
Group I disability - 1.5 million Russian Rubles
Group II disability - 1 million Russian Rubles
Group III disability - 500 000 Russian Rubles
c) If the insured person gets injured, and the injury does not result in disability: not more than 300 000 Russian Rubles.

15.0. PUBLICATIONS

After completion of the study, its results will be summarized and prepared for publication. The investigator must not publish any study results, including those obtained at his/her study site,

Samsung Bioepis Exhibit No. 1002
Page 11945

without a permission from JSC BIOCAD. Results from individual study sites must not be published before the publication of the overall study results.

Samsung Bioepis Exhibit No. 1002
Page 11946

APPENDIX P

GALIEN FOUNDATION

Thursday October 24th, 2019

10th Galien Forum

13rd Prix Galien USA Awards Ceremony

THE 10TH GALIEN FORUM EVENT:

The 2019 Galien Forum will take place on the morning of October 24th, 2019, and will feature round table debates focusing on critical global healthcare issues and challenges.

Our annual life science Forum is rapidly becoming a leading event for discussing issues of innovation in the industry. The Galien Forum brings together leading CEOs, biomedical experts from industry, academia and government.

10th GALIEN FORUM
Alexandria Center™ for Life Science -
450 East 29th Street, 2nd Floor
(between 1st Avenue and the East River)
New York City - 7:30 AM - 5:00 PM

THE 13TH GALIEN AWARDS CEREMONY

The Prix Galien Awards, is considered the industry's equivalent of the Nobel Prize, the highest accolade for biomedical research and innovation.

Each year our distinguished Awards Committee, selects among many candidates the best products competing in three categories – Best Pharmaceutical Agent, Best Biotechnology Product and Best Medical Technology approved by the FDA in the past five years.

American Museum of Natural History
Central Park West at 79th Street
New York City - 6:30 PM

Book online

Book online your seat at the prestigious Awards Ceremony and your day pass to attend the Galien Forum.



Please contact us at (212) 685-1592 or by mail contact@galienfoundation.org

APPENDIX Q

FEATURE

Biopharmaceutical benchmarks 2018

Gary Walsh

Monoclonal antibodies (mAbs) continue to reign supreme, although cellular and gene therapies are slowly starting to gather momentum. Burgeoning growth in biosimilars may threaten future brand monopolies for mAbs and other biologics.

Antibodies continue to dominate biopharmaceutical approvals, but new nucleic acid modalities and cellular therapies are also slowly launching on the market. This article provides an update on three previous surveys of biopharmaceutical approvals[1–3]. The current survey period (January 2014 to July 2018) witnessed the approval of 155 biopharmaceutical products (see **Table 1** for definition) in the United States and/or European Union, when counted by product trade name. Some products contain identical active ingredients or are sold under different trade names in the two regions. Taking this into account, 129 distinct biopharmaceutical active ingredients entered the market.

With these new approvals, the number of individual biopharmaceutical products having gained a license in these regions now totals 374, containing 285 distinct active biopharmaceutical ingredients. However, over the years, 58 products have been withdrawn from the market following approval in one or both regions, almost always for commercial reasons. When withdrawals are taken into account, the number of individual biopharmaceutical products with current active licenses stands at 316 (**Table 1**).

Annual approval numbers over the current survey period ranged from a low of 14 in Europe in 2014 to a high of 36, also in Europe, in 2017 (**Fig. 1a**). Products approved over the four and a half years include 68 mAbs, 23 hormones, 16 clotting factors, 9 enzymes, 7 vaccines, 5 nucleic acid–based products and 4 engineered cell–based products. As this study period was coming to a close, the first RNA interference (RNAi) drug was approved in the United States.

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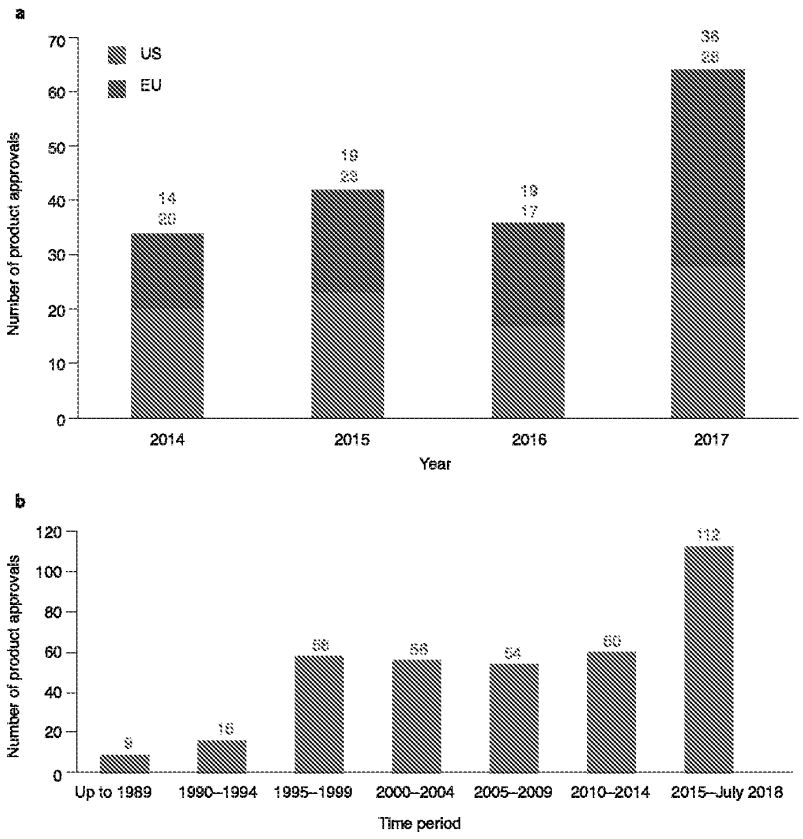


Figure 1 Product approvals profile. (**a**) Annual product approval numbers (by product trade name) by individual region. (**b**) Number of product approvals in one or both regions over the indicated periods.

Here I list all recombinant biologics approved during the past four and a half years (from January 2014 to July 2018), examining the types of biopharmaceutical drugs that have reached the US and EU markets as well as the indications for which they are registered. As in previous articles[1–3], I have not included tissue-engineering products, which the US Food and Drug Administration (FDA) classifies as pure medical devices.

In a snapshot

Overall, new approvals followed relatively predictable lines, with cancer representing the single most common indication (33 products). Other common indications included various

Samsung Bioepis Exhibit No. 1002
Page 11950

inflammation-related conditions (24 products), hemophilia (16 products) and diabetes (15 products). Approvals for other indications, less commonly targeted by biopharmaceuticals, included asthma, migraine, HIV and inhalational anthrax.

Of the 155 individual biopharmaceutical products approved, 81 (52%) were genuinely new to the market, with the remaining products representing biosimilars, me-too products, and products previously approved elsewhere. Those 81 new products (by trade name) contained a total of 71 distinct active biopharmaceutical ingredients (**Table 2**). Looking at each region independently, 97 products were licensed in the United States in the survey timeframe while 109 products gained marketing authorization in the European Union.

In the same period, US regulators approved a grand total of 207 products containing novel molecular (chemical or biological) entities, indicating that 47% of all genuinely new drug approvals in the US were biopharmaceuticals. This represents a substantial increase over values reported in our previous surveys in 2010 and 2014 (21% and 26%, respectively)[1,2], but tallies well with data presented in our 2006 survey[3], which estimated that some 44% of all drugs in the then developmental pipeline were biotech-based. Ambiguity in EU data reporting structures precludes calculation of an analogous figure for Europe.

Table 2 Biopharmaceuticals approved in the US and/or EU January 2014–July 2018 by category

Category	Products (by trade name)
Genuinely new biopharmaceuticals	Adynovi/Adynovate, Vonvendi, Obizur, Elocta/Eloctate, Andexxa, Rebinyn/Refixia, Alprolix, Idelvion, Suliqua/Soliqua, Xultophy, Myalepta/Myalept, Ozempic, Eperzan/Tanzeum, Trulicity, Oxervate, Plegridy, Shingrix, Trumenba, pandemic influenza vaccine H5N1, Mosquirix, Aimovig, Crysvita, Fasenra, Hemlibra, Ilumya, Trogarzo, Bavencio, Besponsa, dinutuximab beta Apeiron/Qarziba, Dupixent, Imfinzi, Kevzara, Kyntheum/Siliq, Rituxan Hycela, Tecentriq, Tremfya, Zinplava, Anthim, Cinqair/Cinqaero, Darzalex, Empliciti, Lartruvo, Taltz, Blincyto, Cosentyx, Keytruda, Nivolumab BMS[a]/Opdivo, Nucala, Praluent, Praxbind, Repatha, Unituxin[a], Cyramza, Entyvio, Sylvant, Palynziq, Lamzede, Brineura, Mepsevii, Kanuma, Strensiq, Vimizim, Tegsedi, Luxturna, Spinraza, Exondys 51, Imlygic, Alofisel, Kymriah, Yescarta, Strimvelis, Zalmoxis
Biosimilars	Semglee, insulin lispro Sanofi, Lusduna, Abasaglar/Basaglar, Bemfola, Movymia/Terrosa, Retacrit[b], Fulphila, Nivestym/Nivestim[b], Zarxio[b], Accofil, Halimatoz/Hefiya/Hyrimoz, Herzuma, Kanjinti, Mvasi, Trazimera, Zessly, Amgevita/Amjevita/Solymbic, Blitzima/Truxima/Ritemvia/Rituzena, Cyltezo, Imraldi, Ixifi, Ogivri, Ontruzant, Renflexis/Flixabi, Rixathon/Riximyo, Inflectra/Remsima[b], Erelzi, Benepali
Reformulated, me-too, different indication, and related	Afstyla, Vihuma/Nuwiq, Iblias/Kovaltry, Ixinity, Admelog, Fiasp, Toujeo, Afrezza, Rekovelle, Natpara, Natpar, Saxenda, Ristempa[a], Heplisav-b, Gardasil 9, Ocrevus, Portrazza, Zinbryta[a], Oncaspar, Lifmior, Spectrila
Previously approved elsewhere	Rixubis, Ruconest, Ryzodeg 70-30/Ryzodeg, Tresiba, Bexsero, Mylotarg, Gazyva/Gazyvaro

[a]Products were both approved and subsequently withdrawn from one or both regions within the survey timeframe.
[b]Biosimilars approved in one region since 2014, but which were approved in the other region before 2014.

Overall trends

Comparing approvals over the current survey period with those in earlier periods, or with cumulative approvals, reveals interesting, if not somewhat predictable, trends. Approval numbers in each five-year period from 1995 until 2014 have remained remarkably constant (54–60 approvals; **Fig. 1b**). However, approvals have accelerated markedly since that time. The past three and a half years alone (January 2015 to July 2018) have seen 112 (**Fig. 1b**) product approvals—essentially double the typical five-yearly historical approval pace. Although a wave of biosimilar approvals contributed to this trend, the number of genuinely novel approved products hasn't lagged far behind: such drugs represented 52% of approvals in the past four and a half years compared with 59% in the period 2010 to 2014 (ref. 1).

The era of the antibody is upon us

The data also show an increasing dominance of mAbs within the universe of biopharmaceutical approvals. Although they represented just over a quarter (27%) of all first-time approvals from 2010 to 2014, they comprise over half (53%) of first time approvals from 2015 to July 2018 (**Fig. 2a**). The relative importance of mAbs in terms of the percentage of overall biopharmaceutical product sales also continues to grow steadily (**Fig. 2b**), although not so dramatically as product approval numbers might imply. However, antibody sales, both in terms of absolute value and as a percentage of overall biopharmaceutical sales, will likely continue to increase, particularly as revenues derived from the recent glut of mAb approvals grow toward maximum market value.

Notably, approvals of gene- and other nucleic acid–based products (antisense oligonucleotides (ASOs) and gene therapies, including gene-engineered cells) increased as well during this period. The number of nucleic acid and cell-based products approved in the period totaled nine, five nucleic acid and four engineered cells (**Table 1**).

The period of this study also witnessed a pickup in approvals of some traditional product classes as compared with previous study periods, notably clotting factors (**Box 1**) and some hormones, although approvals of most traditional product classes continued to drop off. For example, no recombinant thrombolytic agent, anticoagulant, interleukin or human growth hormone has been approved since 2014, and only one interferon and one erythropoietin were approved. This continued trend likely reflects market saturation relative to demand for these products.

Another continuing trend is the increased prominence of mammalian over nonmammalian expression systems used for producing approved products (**Fig. 3**). In fact, the trend toward mammalian cell lines has accelerated dramatically in the past three to four years. Sixty-two of the 71 genuinely new biopharmaceutical active ingredients that have come on the market in the survey period (**Table 2**) are recombinant proteins. Of those, 52 (84%) are expressed in mammalian cell lines, one (Kanuma, sebelipase alfa) is expressed in a mammalian transgenic system, and the remaining nine are produced using *Escherichia coli* (five products) or yeast (four products), all in *S. cerevisiae*. The surge in mammalian-based production is unsurprising, given the many recent mAb and clotting factor product approvals, with both product classes bearing post-translational modifications and thus requiring mammalian expression systems.

Chinese hamster ovary (CHO) cell-based systems remain by far the most common mammalian cell line in use; 84% (57 of the 68 mAb products approved in the current survey period) are produced in CHO systems, with the remaining antibodies approved produced in either NS0 cells (nine products) or Sp2/0 cells (two products). Overall, recent approvals (**Tables 1** and **2**) also confirm that there is little industrial enthusiasm for exploring new expression systems.

The current survey period has also been characterized by a continual rise in the market value of biopharmaceuticals. Data from various La Merie financial reports indicate that cumulative sales over 2014–2017 reached $651 billion, whereas total sales for 2017 alone reached $188 billion (http://www.lamerie.com)[4].

Samsung Bioepis Exhibit No. 1002
Page 11951

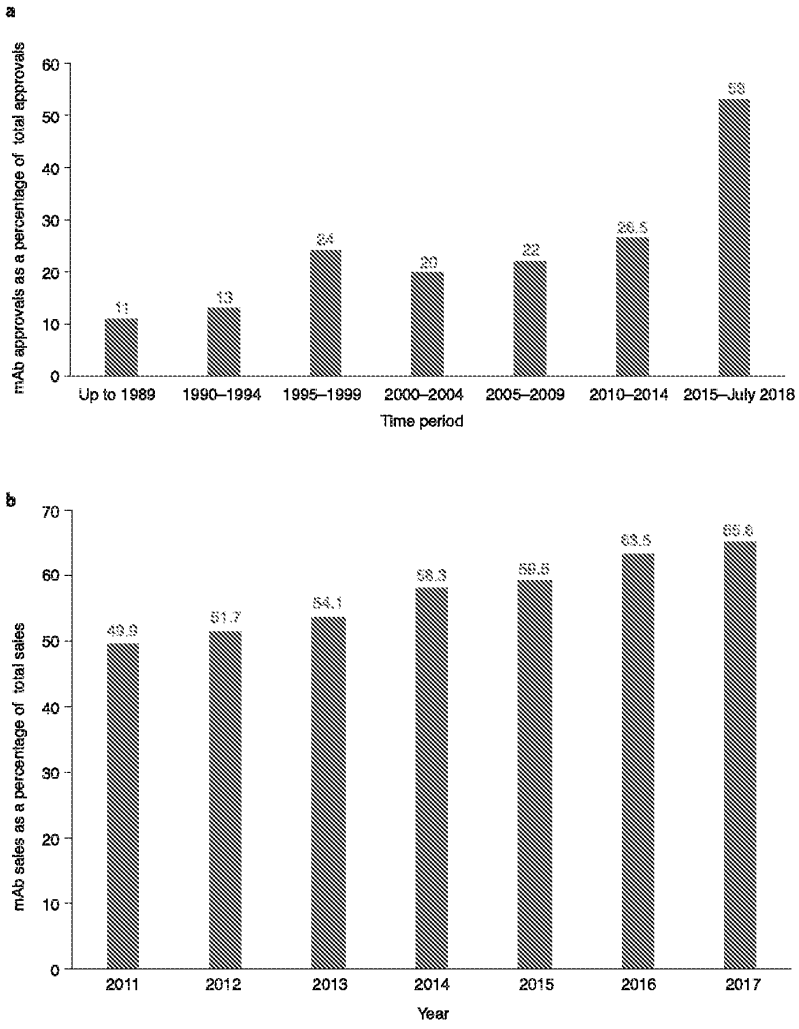


Figure 2 Overview of mAb approvals. (**a**) mAbs approved for the first time in the indicated periods, expressed as a percentage of total biopharmaceuticals approved for the first time in the same time period. (**b**) mAbs global annual sales value expressed as a percentage of total biopharmaceutical global sales for the indicated years. Financial data from La Merie Business Intelligence.

The mAb Humira (adalimumab) has been by far the single most lucrative product each year during the survey period, having generated global sales just short of $19 billion in 2017 and $62.6 billion cumulatively between 2014 and 2017 (**Table 3**). The top ten selling biopharmaceuticals together generated sales of $80.2 billion in 2017, representing almost 44% of total biopharmaceutical product revenues. Forty-five individual biopharmaceutical products recorded 'blockbuster' status sales (>$1 billion) last year.

mAbs continue to represent the most lucrative single product class. Total mAb sales (including Fc fusion protein–based antibody-like traps) reached $123 billion last year ($103.4 billion if fusion products are excluded). Moreover, mAbs represented eight of the top ten products by sales in 2017 (six of the top ten if the fusion traps are excluded). In terms of target indications, the vast majority of antibody or antibody-like trap fusion products target inflammatory, autoimmune conditions (cumulative 2017 sales of $64.6 billion, with products targeting tumor necrosis factor (TNF)-α alone generating $39.8 billion) and cancer (2017 cumulative sales of $43.1 billion). In terms of non-antibody-based products, insulins are the next most lucrative product class, collectively generating sales of $22 billion in 2017.

Biosimilars blossom

The survey period witnessed a surge in biosimilar approvals, signaling that this class of product is maturing. When considered by product trade name, 52 biosimilars have gained approval in the European Union and/or the United States since 2006 (**Table 4**), although 3 were subsequently withdrawn for commercial reasons.

By product category, the majority of biosimilar product approvals were antibody based (27 of 52), with 10 approvals of granulocyte colony stimulating factor (G-CSF) biosimilars and single-digit approvals of all others. The 52 licensed biosimilar products are actually based on 34 distinct active ingredients (**Table 4**). For example, the four rituximab-based biosimilars approved in Europe in 2017 (under the trade names Blitzima, Truxima, Ritemvia and Rituzena) all contain the same active substance: Celltrion's biosimilar rituximab, developed as CT-P10.

By region, 48 biosimilar products have received marketing authorization in the European Union, with 31 of these (65%) having gained authorization in the current survey period. In the United States, far fewer (13) biosimilars gained a license, the first being Zarzio (filgrastim-sndz) in March 2015, with the first biosimilar mAb (Inflectra; infliximab-dyyb) gaining approval in April 2016. This geographical discrepancy is unsurprising, given that the EU biosimilar regulatory framework (including the underpinning legislation and follow-on regulatory guidelines) pre-dates the US regulatory framework by almost a decade.

Of the 52 biosimilars approved thus far, two-thirds (35) are first-time approvals since 2014. This period witnessed few approvals of 'traditional' biosimilars, unlike earlier periods, in which most biosimilars approved were human growth hormone, erythropoietin or G-CSF products. Since 2014, approvals of these biosimilars have invariably been approvals in the United States of products previously approved in the EU. In recent years, the focus of approvals has shifted toward engineered insulins (4 approvals) and mAbs (25 product approvals; **Table 4**). Drivers here are market value, coupled with patent expiry and the availability of analytical methodology capable of demonstrating structural similarity in the context of proteins as large and complex as mAbs (**Box 2**). The survey period has therefore witnessed the approval of a raft of products demonstrating biosimilarity to the top-selling drugs, with biosimilar versions having come on-stream for eight of the top ten global-selling originator products (**Table 3**).

Biosimilars have achieved a widespread degree of acceptance in the European Union, where several such products have been on the market for over a decade. In that time,

Samsung Bioepis Exhibit No. 1002
Page 11952

Box 1 Clotting factors

Genetic defects characterized by lowered expression (or altered amino acid sequence) of any clotting factor can compromise the blood clotting process, leading to congenital hemophilia. Characterized by spontaneous and prolonged hemorrhage, hemophilia is due in over 80% of cases to a deficiency in factor VIII activity (hemophilia A), while in most of the remainder it is due to a deficiency in factor IX (hemophilia B). Global incidence of hemophilia is estimated at between 200,000 and 400,000, with hemophilia A having an average incidence of ~2 people per 10,000. Disease severity is linked to the percentage of residual active factor produced by the patient, and the disease is treated via intravenous administration of the missing clotting factor. Before the introduction of clotting factor concentrates in the 1960s, the life expectancy was of the order of 15–25 years. In the early 1980s, before the advent of screening tests of HIV in donated blood, large numbers of hemophiliacs contracted AIDS from clotting factors purified from human plasma. The introduction of recombinant clotting factors beginning in the early 1990s drastically reduced dependence on plasma-derived products, and the 2017 global market value for such recombinant products stood at $8.5 billion. Treatment costs typically vary from $30,000 to several hundred thousand dollars annually, depending on condition severity and the development of inhibitory antibodies (which 20–30% of hemophilia A patients can develop).

The current survey period witnessed a surge in clotting factor approvals, with ten factor VIII and six factor IX products coming on-stream, although several share the same active ingredient (**Table 1**). In the main, the products approved either are characterized by manufacturing process improvements over earlier-generation products or are engineered to increase serum half-life. For example, Bayer's Kovaltry/Iblias is essentially an updated Kogenate, a recombinant factor VIII. Unlike Kogenate, Kovaltry/Iblias is produced in a baby hamster kidney (BHK) cell line that also expresses heat shock protein 70, with resulting improvement in recombinant productivity. Moreover, all animal- and human-derived additives have been eliminated from the cell culture and purification processes, and a virus filtration step has been introduced for improved nonenveloped viral clearance robustness.

Clotting factor products are usually administered therapeutically (to control active bleeding) or prophylactically (to reduce frequency of future bleeding events). Administration for therapeutic purposes is tailored to individual circumstance while prophylactic administration of unmodified (first-generation) factors typically occurs three times weekly. Engineering to increase serum half-life has relied on PEGylation (Adynovi/Adynovate and Rebinyn/Refixia), Fc fusion (Elocta/Eloctate and Alprolix) or albumin fusion (Idelvion). Engineering had typically reduced prophylactic administration to twice weekly, and such products would be described by some as biobetter clotting factors.

The current survey period also witnessed the approval of a novel mAb-based product indicated for the prophylaxis of hemophilia A in patients who produce anti–factor VIII antibodies, which neutralize any exogenously administered factor VIII). Hemlibra (emicizumab) is a bispecific IgG, one arm of which binds factor IXa while the other binds factor X, effectively triggering factor VIII–independent clot formation. Market analysts predict Hemlibra may attain blockbuster status (sales above $1 billion) by 2019, reaching $4 billion by 2022 (https://clarivate.com/blog/life-sciences-connect/green-light-market-hemlibra-hemophilia-inhibitors-us/).

EU-monitoring systems for safety concerns have not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines, and a decade of clinical experience accrued with these products shows that the approved biosimilars can be used as safely and effectively in all their approved indications as other biological medicines[5]. Acceptance in the United States is not as strong, which is unsurprising given the shorter window of experience with biosimilars.

A 2016 report from consultants IMS Health on the impact of biosimilar competition in the European economic area[6] identifies EU-wide average price reductions from 8% in the case of anti-TNF biosimilar products to 33–34% savings in the context of erythropoietin and G-CSF biosimilars, relative to reference product pricing the year before biosimilar entrance. Moreover, the report found that biosimilar entry affected not only the price of the relevant reference product, but of the whole product class. Globally, 2017 sales generated cumulatively by all biosimilar reference products reached $73.3 billion. An interesting although hypothetical calculation suggests savings of up to $22 billion to global healthcare systems if biosimilar entry drove a 30% savings across the board in relation to all these products.

The development of so-called 'biobetters' represents a potential threat to biosimilar development. A biobetter describes an already approved biopharmaceutical entity altered in some way (e.g., a structural modification or an altered finished product combination or formulation) to improve some aspect of its clinical performance. The current period witnessed the approval of very few such products; mainly, they included novel insulin formulations or combinations (Suliqua/Soliqua and Xultophy; **Table 1**), as well as clotting factors with extended half-lives (**Box 2**). Biobetter development is likely tempered by the fact that such products are treated as a new product from a regulatory perspective.

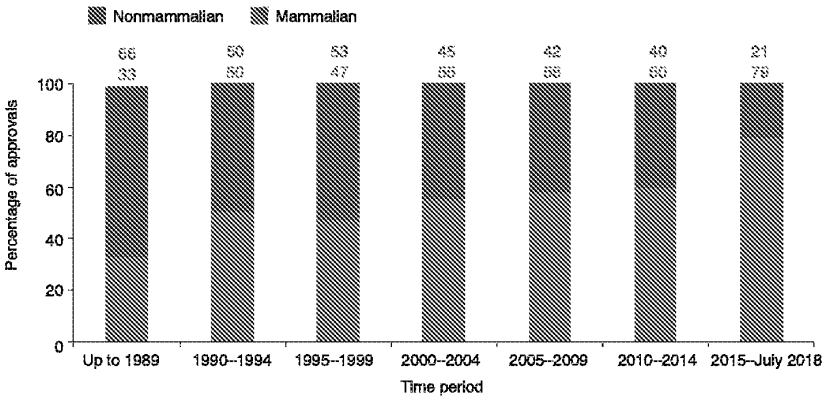


Figure 3 Relative use of mammalian- versus nonmammalian-based production cell lines in the manufacture of biopharmaceuticals approved over the indicated periods. Each dataset is expressed as a percentage of total biopharmaceutical product approvals for the period in question.

Samsung Bioepis Exhibit No. 1002
Page 11953

Table 3 The 20 top-selling biopharmaceutical products in 2017

Rank	Product	Sales, 2017 ($ billions)[a]	Cumulative sales, 2014–2017 ($ billions)	Year first approved	Company	Patent expiry[b]	Biosimilar version(s) approved
1	Humira (adalimumab; anti-TNF)	18.94	62.6	2002	AbbVie, Eisai	2016 (US) 2018 (EU)	Halimatoz/Hefiya/Hyrimoz, Amgevita/Amjevita/Solymbic, Cyltezo, Imraldi
2	Enbrel (etanercept; anti-TNF)	8.34	35.4	1998	Amgen, Pfizer, Takeda Pharmaceuticals	2015 (EU) 2028 (US)	Erelzi, Benepali
3	Rituxan/MabThera (rituximab; anti-CD20)	7.78	29.1	1997	Roche, Biogen Idec	2013 (EU) 2016 (US)	Blitzima/Truxima, Ritemvia, Rituzena, Rixathon/Riximyo
4	Remicade (infliximab; anti-TNF)	7.77	35.6	1998	Johnson & Johnson, Merck, Mitsubishi Tanabe Pharma	2015 (EU) 2018 (US)	Zessly, Ixifi, Renflexis/Flixabi, Inflectra/Remsima
5	Herceptin (trastuzumab; anti-HER2)	7.39	27.1	1998	Roche	2014 (EU) 2019 (US)	Herzuma, Kanjinti, Trazimera, Ogivri, Ontruzant
6	Avastin (bevacizumab; anti-VEGF)	7.04	27.0	2004	Roche	2017 (US) 2019 (EU)	Mvasi
7	Lantus (insulin glargine)	6.72	27.4	2000	Sanofi	2014 (EU & US)	Semglee, Lusduna, Abasaglar/Basaglar
8	Eylea (aflibercept; anti-VEGF)	5.93	18.0	2011	Regeneron, Bayer	2020 (EU) 2021 (US)	
9	Opdivo (nivolumab; anti-PD-1 receptor)	5.79	11.4	2014	Bristol-Myers Squibb, Ono Pharmaceutical	2027 (US) 2026 (EU)	
10	Neulasta (pegfilgrastim)	4.53	20.1	2002	Amgen, Kyowa Hakko Kirin	2014 (US) 2015 (EU)	Fulphila
11	Stelara (ustekinumab; anti-IL-12 & IL-23)	4.01	12.2	2009	Janssen Cilag (Johnson & Johnson)	2023 (US) 2024 (EU)	
12	Keytruda (pembrolizumab, anti-PD-1)	3.81	5.7	2014	Merck	2036 (US) 2028 (EU)	
13	Prolia/Xgeva (denosumab, anti-RANKL)	3.54	11.6	2010	Amgen	2025 (US) 2022 (EU)	
14	Lucentis (ranibizumab; anti-VEGF)	3.38	14.3	2006	Roche, Novartis	2016 (EU & US)	
15	Novolog/Novorapid (insulin aspart)	3.31	11.7	1999	Novo Nordisk	2015 (EU & US)	
16	Soliris (eculizumab; anti–C5 complement protein)	3.14	10.7	2007	Alexion Pharmaceuticals	2021 (US) 2020 (EU)	
17	Simponi (golimumab; anti-TNF)	2.94	9.7	2009	Merck, Janssen, Mitsubishi Tanabe	2024 (EU & US)	
18	Humalog mix 50:50 (insulin lispro)	2.86	11.3	1996	Eli Lilly	2014 (US) 2015 (EU)	Insulin lispro Sanofi
19	Xolair (omalizumab) anti-IgE	2.75	8.7	2003	Roche, Novartis	2017 (EU & US)	
20	Aranesp/Nesp (darbepoetin alfa)	2.62	10	2001	Amgen, Kyowa Hakko Kirin	2016 (EU) 2024 (US)	

[a]Financial data from La Merie Business Intelligence. [b]Patent data from various sources, including http://www.gabionline.net/Biosimilars/General/Biologicals-patent-expiries.
HER2, human epidermal growth factor receptor 2; IgE, immunoglobulin E; IL, interleukin; PD-1, programmed cell death receptor 1; RANKL, receptor activator of nuclear factor-κB ligand; VEGF, vascular endothelial growth factor.

mAb approvals

The data in our survey underscore the current and increasing dominance of mAbs in the biopharma sector, in terms of overall product approvals, biosimilar approvals and market value. Whereas cancer remains the most common target indication, during the period several products aimed at nontraditional mAb target conditions were approved. These include Aimovig (erenumab), indicated for migraine; Fasenra (benralizumab) and Cinqair/Cinqaero (reslizumab) for asthma; Trogarzo (ibalizumab) for HIV infection; and Anthim (obiltoxaximab) for inhalation anthrax. Also notable was the approval of several anti-interleukin mAbs to treat psoriasis, as opposed to the more traditional anti-TNF products for this indication. The new products include Cosentyx (secukinumab), Ilumya (tildrakizumab-asmn), Kyntheum/Siliq (brodalumab), Tremfya (guselkumab) and Taltz (ixekizumab). Taltz is also unusual in that it is a humanized immunoglobulin G4 (IgG4). It was consequently engineered to contain a serine-to-proline substitution (S228P), which reduces the frequency of half-antibody formation or other heterologous antibody combinations sometimes observed with IgG4 antibodies.

It is also notable that all the mAbs approved in the survey period were engineered in some way: virtually all novel antibodies approved are either humanized or fully human. One new antibody–drug conjugate (Besponsa, inotuzumab ozogamicin) made it to market, along with two new bispecific products (Hemlibra, emicizumab/emicizumab-kxwh; Blincyto, blinatumomab; **Boxes 1** and **3**). Tecenetriq (atezolizumab), a mAb against programmed cell death receptor ligand 1 (PD-L1), is unusual in that it contains an amino acid substitution (asparagine to alanine) at position 298, in the CH2 domain of each heavy chain. This substitution prevents antibody glycosylation and thus blocks glycan-dependent Fc-effector functions, which is in turn important in the context

Samsung Bioepis Exhibit No. 1002
Page 11954

Table 4 Biosimilar products that had gained marketing authorization within the European Union and/or the United States by July 2018

Product type	Biosimilar (trade name)	Year (and region) approved	Reference product	Drug (active ingredient) manufacturer
Somatropin-based				
Human growth hormone–based	Omnitrope	2006 (EU)	Genotropin	Sandoz (Kundl, Austria)
	Valtropin	2006 (EU) Withdrawn 2012	Humatrope	LG Life Sciences (Jeonbuk-do, Republic of Korea)
Epoetin-based				
Epoetin-based	Binocrit	2007 (EU)	Eprex/Erypo	Rentschler (Laupheim, Germany) & Lek (Menges, Slovenia)
	Epoetin alfa hexal	2007 (EU)	Eprex/Erypo	Rentschler & Lek
	Abseamed	2007 (EU)	Eprex/Erypo	Rentschler & Lek
	Retacrit	2018 (US) 2007 (EU)	Eprex/Erypo (EU) Epogen/Procrit (US)	Norbitec (Uetersen, Germany) Norbitec (Uetersen, Germany)
	Silapo	2007 (EU)	Eprex/Erypo	Norbitec
Filgrastim-based				
G-CSF-based	Ratiograstim	2008 (EU)	Neupogen	Sicor (Vilnius, Lithuania)
	Filgrastim ratiopharm	2008 (EU) Withdrawn 2011	Neupogen	Sicor
	Biograstim	2008 (EU) Withdrawn 2015	Neupogen	Sicor
	Tevagrastim	2008 (EU)	Neupogen	Sicor
	Zarxio (US) Zarzio (EU)	2015 (US) 2009 (EU)	Neupogen	Sandoz (Kundl, Austria)
	Filgrastim hexal	2009 (EU)	Neupogen	Sandoz (Kundl, Austria)
	Nivestym (US) Nivestim (EU)	2018 (US) 2010 (EU)	Neupogen	Hospira (Pfizer) (Zagreb, Croatia)
	Grastofil	2013 (EU)	Neupogen	Intas Biopharmaceuticals (Gujarat, India)
	Accofil	2014 (EU)	Neupogen	Intas Biopharmaceuticals
Pegfilgrastim-based	Fulphila	2018 (US)	Neulasta	Mylan (Zurich)
Follicle-stimulating hormone–based				
Follicle-stimulating hormone–based	Ovaleap	2013 (EU)	Gonal F	Merckle Biotec (Ulm, Germany)
	Bemfola	2014 (EU)	Gonal F	Polymun Scientific Immunbiologische Forschung (Klosterneuburg, Austria)
Insulin-based				
Insulin glargine–based	Abasaglar	2014 (EU)	Lantus	Lilly del Caribe (Carolina, Puerto Rico, USA) Eli Lilly (Indianapolis)
	Lusduna	2017 (EU) 2017 (US), tentative	Lantus	Merck Sharp & Dohme (Elkton, VA, USA)
	Semglee	2018 (EU)	Lantus	Biocon Nusajaya (Johor, Malaysia)
Insulin lispro–based	Insulin lispro Sanofi	2017 (EU)	Humalog	Sanofi-Aventis (Frankfurt)
mAb-based and related				
Infliximab-based	Inflectra	2016 (US) 2013 (EU)	Remicade	Celltrion (Incheon, Republic of Korea)
	Remsima	2013 (EU)	Remicade	Celltrion
	Flixabi	2016 (EU)	Remicade	Biogen (Hillerod, Denmark) Samsung Bioepis (Incheon, Republic of Korea)
	Renflexis	2017 (US)	Remicade	Biogen (Hillerod, Denmark) Samsung Bioepis
	Ixifi	2017 (US)	Remicade	Pfizer
	Zessly	2018 (EU)	Remicade	Boehringer Ingelheim (Biberach an der Riss, Germany)
Adalimumab-based	Amgevita (EU) Amjevita (US)	2017 (EU) 2016 (US)	Humira	Amgen (Thousand Oaks, CA, USA)
	Solymbic	2017 (EU)	Humira	Amgen
	Cyltezo	2017 (EU & US)	Humira	Boehringer Ingelheim (Fremont, CA, USA)
	Halimatoz	2018 (EU)	Humira	Cook Pharmica (Bloomington IN, USA) Sandoz (Langkampfen, Austria)
	Hefiya	2018 (EU)	Humira	Cook Pharmica (Bloomington IN, USA) Sandoz (Langkampfen, Austria)
	Hyrimoz	2018 (EU)	Humira	Cook Pharmica (Bloomington IN, USA) Sandoz (Langkampfen, Austria)
	Imraldi	2017 (EU)	Humira	Biogen (Research Triangle Park, NC, USA) Biogen (Hillerød, Denmark)

Samsung Bioepis Exhibit No. 1002
Page 11955

Table 4 Continued

Product type	Biosimilar (trade name)	Year (and region) approved	Reference product	Drug (active ingredient) manufacturer
Rituximab-based	Blitzima	2017 (EU)	MabThera	Celltrion
	Truxima	2017 (EU)	MabThera	Celltrion
	Ritemvia	2017 (EU)	MabThera	Celltrion
	Rituzena	2017 (EU)	MabThera	Celltrion
	Rixathon	2017 (EU)	MabThera	Sandoz (Langkampfen, Austria)
	Riximyo	2017 (EU)	MabThera	Sandoz (Langkampfen, Austria)
Trastuzumab-based	Ontruzant	2017 (EU)	Herceptin	Biogen (Hillerød, Denmark)
	Ogivri	2017 (US)	Herceptin	Mylan
	Herzuma	2018 (EU)	Herceptin	Celltrion
	Kanjinti	2018 (EU)	Herceptin	Patheon Biologics (Groningen, the Netherlands)
	Trazimera	2018 (EU)	Herceptin	Boehringer Ingelheim (Biberach an der Riss, Germany)
Bevacizumab-based	Mvasi	2018 (EU) 2017 (US)	Avastin	Amgen
Etanercept-based	Benepali	2016 (EU)	Enbrel	Biogen (Hillerød, Denmark)
	Erelzi	2017 (EU) 2016 (US)	Enbrel	Sandoz (Novartis) (Langkampfen, Austria) (EU) Novartis Pharma (Stein, Switzerland) (US)
Teriparatide-based				
Teriparatide-based	Movymia	2017 (EU)	Forsteo	Richter-Helm BioLogics (Bovenau, Germany)
	Terrosa	2017 (EU)	Forsteo	Richter-Helm BioLogics

of the product's mode of action and safety profile. Fasenra, by contrast, is engineered such that its glycocomponent is afucosylated (like that of Gazyva/Gazyvaro (obinutuzumab), approved initially in 2013), which increases the antibody-dependent cell-mediated cytotoxicity activity important for its mode of action. The period also witnessed the approval of one Fab antibody fragment (Praxbind; idarucizumab), designed to bind and thus neutralize the anticoagulant drug dabigatran.

Although technically outside the timeframe of this survey, the approval of Cablivi (caplacizumab) in Europe at the end of August represents a major milestone in mAb therapeutics, as it is the first nanobody to gain regulatory approval. It is indicated to treat acquired thrombotic thrombocytopenic purpura, which is a rare, life-threatening, autoimmune blood clotting disorder. Cablivi is a humanized, 259 amino acid, 2.78 kDa bivalent nanobody produced in *E. coli* that binds to von Willebrand factor, a key protein in hemostasis. This in turn inhibits the interaction of von Willebrand factor with blood platelets, preventing platelet adhesion and hence the clotting characteristic of the condition.

Although often considered the poster child of biopharma, antibody-based products are just as susceptible to commercial influence and pharmacovigilance as any other therapeutic product. Three mAbs approved in the current survey period have been withdrawn within this period. European marketing authorizations for Unituxin (dinutuximab, approved for neuroblastoma) from United Therapeutics and nivolumab BMS (nivolumab, approved for non-small-cell lung cancer) from Bristol-Myers Squibb were withdrawn, due to drug supply difficulties in the case of Unituxin and for commercial reasons in the case of nivolumab BMS. Biogen and AbbVie's Zinbryta (daclizumab), which was approved in 2016 for multiple sclerosis, was withdrawn globally in 2018 after serious adverse events, such as liver damage and immune reactions, became apparent.

Recombinant enzymes and transgenic production

The survey period also witnessed the approval of nine recombinant enzymes for the treatment of various genetic conditions. From a technological perspective, Alexion Pharmaceuticals' Kanuma (sebelipase alfa; recombinant human lysosomal acid lipase) is interesting in that it is produced in the eggs of transgenic chickens, with enzyme purification directly from transgenic egg white. The transgenic chicken line was developed via injection of a retroviral vector carrying the human coding sequence into chick embryos.

However, transgenic-based platforms for biopharmaceutical production have failed to gain widespread use in the biopharmaceutical sector. Technical challenges arising from random integration of transgenes into host chromosomes and the difficulty of controlling transgene copy number in production animals has limited the appetite for commercial investment in transgenic animal platforms capable of generating economically viable levels of recombinant proteins. It will be interesting to follow whether recent developments in CRISPR-based gene editing, which overcome some of these technical difficulties[7], change the industry outlook. Ovalbumin, for example, is expressed at two grams per hen egg, with one hen capable of laying more than 300 eggs a year. CRISPR-targeted insertion of a therapeutic-protein-encoding sequence into the ovalbumin gene could therefore afford high-level protein production[8].

Nucleic acid–based approvals

Nucleic acid–based products (gene therapies, DNA or RNA vaccines, ASOs, small interfering RNAs (siRNA), aptamers and modified RNA molecules) have yet to exert a profound influence on the biopharma product landscape, although the period witnessed the approval of five such products (three ASOs and two gene therapies). This brings the total tally of approvals in this category to nine, although the gene therapy Glybera (alipogene tiparvovec) was withdrawn from the market last year.

Glybera was approved as a single-administration gene therapy for adults suffering from familial lipoprotein lipase deficiency with a treatment price tag on the order of $1 million. The developer and manufacturer opted not to renew its European marketing authorization in 2017 due to lack of demand for the product. Luxturna (voretigene neparvovec-rzyl), approved last year in the United States, appears set to be almost as costly; the one-time treatment will cost $850,000. Luxturna contains a live, nonreplicating adeno-associated virus serotype 2 genetically modified to express the human retinal pigment epithelium-specific 65-kDa (*RPE65*) gene. Delivered directly via

Samsung Bioepis Exhibit No. 1002
Page 11956

subretinal injection, it is indicated for patients with inherited retinal disease due to mutations in both copies of this gene. The headline costs of either of these products likely reflect the rarity of the target conditions and thus potential market size, as opposed to a fundamental cost basis for gene therapy products *per se*. The third gene therapy approval, Imlygic (talimogene laherparepvec), for example, is projected to cost an average of $65,000 per patient. Indicated for the treatment of melanoma recurrent after initial surgery, Imlygic is a live, attenuated herpes simplex virus type 1 carrying the human GM-CSF coding sequence. Viral replication subsequent to injection directly into the tumor is believed to trigger cell lysis, and it is believed that the release of tumor-derived antigens along with the GM-CSF may also promote an antitumor effect.

Three approved ASO products hold orphan status for the treatment of rare conditions with limited therapeutic options. It is notable that one of these ASO products, Ionis Pharmaceuticals' Spinraza (nusinersen) for spinal muscular atrophy, was the main source of sales growth for Biogen in 2017, generating $188 million in sales in the first quarter of 2018. Spinraza targets splicing defects that lead to this disorder, and rare conditions arising due to mRNA mis-splicing are likely to be an increasing area of focus for this modality.

In terms of downregulation of misregulated mRNA expression, ASOs now have to compete with siRNAs. Although technically outside the timeframe of this current survey, the recent approval of Alnylam's Onpattro (patisiran) represents the most notable recent approval of an oligonucleotide-based therapeutic. Approved in both US and EU in August 2018, Onpattro is the first RNAi-based gene expression silencing product to gain approval in either region.

Traditional biotech product approvals

The current survey period also witnessed the approval of 46 traditional biotech products classified as new by regulatory authorities in terms of active substance—just one more than recorded in our previous survey. Traditional products refer to those produced naturally or via nonrecombinant means in or by a biological source.

The profile of approvals (**Supplementary Table 1**) by and large mirrors product types approved in previous surveys and include a range of blood-derived products (for example, plasma-purified human albumin, clotting factors and immunoglobulins), as well as traditional (nonrecombinant) vaccines and nonengineered cells.

Box 2 Analytical approaches to validating biosimilar mAb quality

Biosimilar guidelines require the generation of comparative data between a proposed new biosimilar product and the reference product to which it claims similarity, at the levels of both the active substance and finished product. The marketing application, relative to a standard product application, must contain a full quality module, incorporating comparative quality analysis, as well as reduced comparative clinical and nonclinical data modules. Comparative quality studies largely rely on analytical techniques and instrumentation, now capable of fully characterizing biopharmaceuticals as large and complex as mAbs, with mass spectrometry (MS)-based techniques coming to the fore. Any comparative differences identified (for example, differences in glycocomposition) are then considered in terms of effect on biosimilarity, with further investigation via biological assay or preclinical or clinical evaluation, as appropriate.

An analysis of the comparative quality information presented in the European public assessment reports of approved biosimilar mAbs provide insight into the broad range of state-of-the-art analytical techniques used in practice (similar techniques are used as appropriate in the context of other protein-based biosimilars). The commonly applied analytical approaches discernible in these documents include the following:

- Determination of intact molecular mass by electrospray MS. Other size analysis modalities cited included size exclusion high performance liquid chromatography (SE-HPLC) and capillary electrophoresis in the presence of sodium dodecyl sulfate.
- Primary structural analysis by methods including classic C- and N-terminal sequencing (partial sequence determination), with full sequence determination invariably relying on initial protein fragmentation, peptide mapping and MS techniques such as matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS or liquid chromatography/tandem MS (LC-MS/MS). This includes the detection of C-terminal lysine variability (common in IgGs, but without anticipated clinical impact as C-terminal lysines are rapidly removed in serum).
- Sulfhydryl analysis via ultraviolet (UV)/visible light spectrophotometry and SE-HPLC, with disulfide linkage assignment via LC-MS-based peptide mapping under reducing and nonreducing conditions.
- Higher order structural analysis: secondary structural analysis via far-UV circular dichroism spectroscopy and/or Fourier transform infrared spectroscopy; tertiary analysis via near-UV circular dichroism spectroscopy or intrinsic fluorescence spectroscopy; thermal stability of higher order structure via differential scanning calorimetry; X-ray crystallography of the Fc domain.
- Glycosylation analysis: composition or structural determination, including levels of fucosylation and terminal galactosylation (which can influence antibody effector functions), by exoglucanase digestion and hydrophobic interaction chromatography analysis, high-performance anion-exchange chromatography with pulsed amperometric detection (HPAE-PAD).
- Analysis of additional modifications (for example, site specific deamidation, oxidation) by MS-based methods, peptide mapping with LC-MS).
- Charge heterogeneity profile by ion exchange-based HPLC, isoelectric focusing.
- Purity analysis: HPLC-based separation modalities based on size, charge and hydrophobicity, capillary gel electrophoresis, western blot analysis.

Engineered cell–based approvals

Traditional cell-based therapeutics containing cells extracted from human tissue or blood continue to come on the market. Examples include hematopoietic progenitor cells derived from cord blood, as well as autologous cultured chondrocytes used to treat cartilage defects (**Supplementary Table 1**).

A notable recent milestone in cell-based therapeutics is the approval of genetically engineered cell–based therapies, four of which have been approved since 2016: Kymriah (tisagenlecleucel), Yescarta (axicabtagene ciloleucel), Zalmoxis and Strimvelis. These products may be viewed as both cell and gene therapies, given that the cells carry a therapeutic gene into the patient's body. All four products have orphan status or target niche conditions and either are under additional monitoring or require further postauthorization safety studies. Three of the four (Kymriah, Yescarta and Strimvelis) use autologous cells, whereas the fourth (Zalmoxis) uses allogeneic cells as a starting point. One is a hematopoietic stem cell therapy (Strimvelis) and the other

Samsung Bioepis Exhibit No. 1002
Page 11957

Box 3 BiTE technology

Pioneered by Micromet, a biotechnology company acquired by Amgen, the first bispecific T-cell engager (BiTE) product, Blincyto (blinatumomab), gained approval in the United States and European Union for the treatment of B-cell precursor acute lymphoblastic leukemia during the current survey period. The BiTE platform consists of a bispecific antigen-binding antibody fragment, one arm of which is designed to bind the CD3 cell surface receptor complex, invariably found on cytotoxic T cells, while the other arm is designed to bind a surface tumor antigen associated with a target cancer cell type[17,18]. The BiTE construct therefore acts as a bridge, bringing cytotoxic T cells into close proximity to the target cancer cells and triggering lysis of the latter by the former.

The Blincyto construct consists of two single-chain variable fragments (scFv domains) joined by a short, flexible linker sequence consisting of glycine and serine residues. The 55 kDa, 504 amino acid construct includes a C-terminal hexahistidine sequence, which facilitates purification using zinc-immobilized metal affinity chromatography. One scFv domain targets the T-cell CD3 receptor, while the other binds the pan-B-cell antigen CD19, facilitating T-cell-mediated lysis of B cells. Because of its relatively low molecular mass, the construct has a short serum half-life (2–3 h). This requires continuous infusion over a four-week period, representing a limitation in terms of patient convenience. Approaches to the development of next-generation constructs with extended serum half-lives include fusion to human albumin and Fc-based constructs, with an aim of facilitating a once-weekly dosage schedule.

The Amgen pipeline contains several more BiTE constructs undergoing phase 1 clinical trials for the treatment of various cancers, including multiple myeloma and acute myeloid leukemia. BiTE constructs targeting solid tumors have thus far yielded limited success. Limitations may include the degree of tumor penetration (by the construct and T cells), as well as the relatively broad expression of target antigen, which may limit dose escalation.

three are T-cell therapies. In all cases, genetic modification is undertaken *ex vivo* using a viral vector to achieve transduction, followed by infusion of the genetically modified cells into the patient.

Two of the products (Kymriah and Yescarta) fall into the new wave of cellular immunotherapies for oncology. They are notable in that they are the first chimeric antigen receptor (CAR)-T cell-based products[9,10] to gain regulatory approval, effectively validating this technology from a regulatory standpoint. In addition to US approval in 2017, both gained marketing authorization in Europe in August 2018. In the case of both approved products, the CAR-T cells target the CD19 antigen, found on the surface of B lymphocytes, facilitating efficient T-cell-mediated destruction of B cells—thus their indication for the treatment of B-cell-based cancers, against which they have shown striking clinical results.

Future directions

Although published estimates vary somewhat, some 40% of the 6,000 or more products currently in clinical development globally are biopharmaceuticals. This suggests that the substantial increase in the proportion of approved pharmaceutical products that are biopharmaceuticals seen in this survey period is not a blip, but will be sustained into the future.

The profile of products in advanced-stage clinical trials suggests that biopharmaceutical approvals over the next few years will continue to be predominantly protein-based (rather than nucleic acid- or cell-based), that they will be produced largely using conventional mammalian cell expression systems, that mAb-based products will continue to dominate the approvals, that a steady stream of biosimilars will continue to gain approval (particularly in indications with large, lucrative markets), and that cancer will remain the primary target indication.

Fifty-four genuinely new mAbs in late-stage clinical trials are under regulatory review in the United States and European Union[11], framing nearer-term putative approvals in these regions. Of these, 28 (52%) target cancer, 7 for liquid malignancies and 21 for solid tumors. Most are fully human or humanized IgGs, along with a smaller number (5) of antibody fragment (Fab or single-chain variable fragment (scFv)) products. Of the 28 anticancer products, 9 are conjugated to an effector molecule (radiolabel, chemical or toxin).

The antibody market, although highly successful, is also becoming very crowded. In some cases, multiple mAbs target the same therapeutic target (for example, CD20, TNF and vascular endothelial growth factor) and have overlapping indications. The mainstreaming of biosimilar mAbs and, potentially, the development of competing product types, such as CAR-T cell immunotherapies, further increases the competitive pressure and incentive to innovate. Not surprisingly, a greater diversity of modalities and targets is seen further back in the developmental pipeline, reflected in various antibody formats engineered to enhance functionality in some way, the pursuit of novel disease targets and the assessment of mAbs in combination with a second therapeutic agent.

Indeed, such competitive pressures have driven, and continue to drive, innovation among categories other than mAbs. For example, incentive to innovate is illustrated by the recent approval of several clotting factors engineered to increase serum half-life and an increasing number of trials assessing both previously approved and experimental biopharmaceuticals in combination with other drugs to treat various cancers.

Biosimilars will continue to feature with increasing prominence in the global biopharmaceutical landscape, but their greatest impact will continue to be in regions outside the more developed markets, such as the United States and European Union. Thus far, an estimated 260 biosimilar products have been approved in at least one global market—of which only a relatively small minority (52) have been approved in the European Union and/or the US. That being said, many of the additional products approved would likely find it challenging to meet EU and US regulatory expectations in the context of biosimilarity.

Globally, some 188 biosimilars are in development, 61 of which are in phase 3 trials[12]. Specifically within Europe and the United States there are an estimated 50 biosimilars in development (https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-biosimilars-whitepaper-final.pdf). Despite recent headline approvals, penetration in the US market in particular is likely to occur relatively slowly, underscored by regulatory and legal uncertainties, complex pricing and contracting mechanisms and, of course, patient and clinician acceptance. Overall, however, biosimilar market growth is anticipated to be strong, with market reports (e.g., https://www.marketsandmarkets.com/Market-Reports/biosimilars-40.html) typically forecasting a $23 billion global market value within the next five to six years, up substantially from an estimated 2017 value of the order of $4.5 billion.

The predominance of protein-based approved biopharmaceuticals is likely to remain an industry reality for the foreseeable future. Nucleic acid–based products have yet

Samsung Bioepis Exhibit No. 1002
Page 11958

to make a substantial and sustained impact on the list of biopharmaceutical products that are registered in Europe and the United States. A study[13] from the *Journal of Gene Medicine* estimates that 2,597 gene therapy–based clinical trials have been approved globally since 1989. Despite this large body of data, gene-therapy-based approvals in Europe and the United States remain in the single digits. Advances in adeno-associated virus (AAV) and lentiviral gene therapy modalities (particularly in *ex vivo* cellular therapy contexts)—together with increasing interest in CRISPR endonuclease-based gene editing, with several companies now poised to take such approaches into human testing—are likely to provide further impetus to the development of nucleic acid–based treatments.

The rapid advances and clinical adoption of T-cell-based adoptive therapies (including CAR-T cells) is a particularly notable development in the period of this study. The success of this cellular gene therapy is built on the exceptional responses obtained in some trials for some cancers, particularly liquid malignancies. However, scientific, technological and manufacturing hurdles may all complicate its more widespread adoption, certainly in the nearer term[14–16].

Overall, the past four and a half years have witnessed continued and accelerated growth in the biopharma sector. Antibodies continue to reign supreme and look to dominate for several years to come. Elsewhere, two developments in biopharmaceutical products have been particularly notable over the past five years. First, the massive proliferative capacity of cellular therapy has been effectively harnessed in the form of immunotherapy for late-stage cancers. It is this ability to identify, expand, attack and destroy malignant cells that has made CAR-T cell therapies so successful and overshadowed the longer term goal of cellular therapy: regeneration. Regenerative cell therapy was for many years seen as the main opportunity for modalities based on living cells and, in particular, stem cells; that is no longer the case. Second, increasing evidence of safety and growing familiarity of physicians and insurers with biosimilars means the economic advantages of these products are no longer being ignored. It seems likely that the rapid growth of biosimilar products will continue over the years to come.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper (doi:10.1038/nbt.4305).

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Samsung Bioepis Exhibit No. 1002
Page 11959

BIOPHARMACEUTICAL
Benchmarks

APPENDIX R

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case IPR2019-00740
U.S. Patent No. 9,718,880

DECLARATION OF DANIEL BAZARKO

Mail Stop **PATENT BOARD**
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Samsung Bioepis Exhibit No. 1002
Page 11963

I, Daniel Bazarko, hereby declare and say as follows:

1. I am over the age of twenty-one (21) years and otherwise competent to make this declaration, and if called to testify, I could and would testify about the information in this declaration.

2. This declaration is made in support of Alexion Pharmaceuticals, Inc. ("Alexion") in this proceeding before the United States Patent and Trademark Office. The information set forth in this declaration is based upon my personal knowledge, including my review of Alexion's public filings with the U.S. Securities and Exchange Commission ("SEC") reflecting U.S. sales of Soliris® (eculizumab), which were created at or near the time of the events they reflect, were created by Alexion persons and/or its advisors and consultants with knowledge, and were kept by Alexion in the course of its regularly conducted business activities and pursuant to Alexion's regular record-keeping practices.

3. I am Senior Vice President, Chief Accounting Officer at Alexion. I have been employed by Alexion since May 2013. I work at the Alexion site located at 100 College Street, New Haven, CT 06510. In my current role I am responsible for leading the global accounting, finance operations, shared services and manufacturing finance functions of Alexion. My specific job duties include accounting, internal auditing, SEC filings, financial reporting, and financial analysis.

4. I understand that Alexion markets Soliris® in the United States, as well as outside the United States. I understand that the conditions for which Soliris® currently has FDA approval include (1) "Paroxysmal Nocturnal Hemoglobinuria" ("PNH"), (2) "Atypical Hemolytic Uremic Syndrome ("aHUS"), (3) "Generalized Myasthenia Gravis" ("gMG"), and (4) "Neuromyelitis Optica Spectrum Disorder" ("NMOSD"). (*See* ALXN2054 at 1, 3-4.)

5. I understand that Soliris® was approved by the FDA on March 16, 2007, for "the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis" ("the PNH indication"). (*See* AMG2005 at 1.) I further understand that Soliris® was launched in the United States for the PNH indication in April 2007.

6. As of September 30, 2019, Soliris® sales worldwide account for 78.4% of Alexion's total revenue. (ALXN2114 at 25.)

7. Net product sales of Soliris® in the U.S. are usually reported in Alexion's quarterly and yearly SEC filings. Net product sales here means the sum of Alexion's gross sales of Soliris® minus its net revenue adjustments (which include returns & allowances, discounts/rebates, distribution fees, and volume based arrangements). I have reviewed Alexion's annual U.S. net product sales for Soliris® reported in Alexion's yearly SEC filings from launch in FY2007 through FY 2018, and Alexion's quarterly sales reported for Q1 through Q3 in FY 2019.

8. Appendix A attached to this Declaration lists Alexion's U.S. net product sales for Soliris® for (1) all approved indications, and (2) the PNH indication, including Alexion's annual sales from FY2007 through FY2018, and Alexion's quarterly sales for Q1 through Q3 in FY 2019.

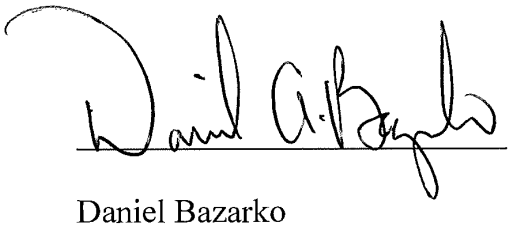
9. The documents I considered with respect to the information provided in Appendix A include: ALXN2100 (excerpts from Alexion Form 10-K for FY 2007 at Note 14, page F-34); ALXN2101 (excerpts from Alexion Form 10-K for FY 2008 at Note 17, page F-41); ALXN2102 (excerpts from Alexion Form 10-K for FY 2009 at Note 16, page F-38); ALXN2103 (excerpts from Alexion Form 10-K for FY 2010 at Note 16, page F-32); ALXN2104 (excerpts from Alexion Form 10-K for FY 2011 at Note 17, page F-35); ALXN2105 (excerpts from Alexion Form 10-K for FY 2012 at Note 15, page F-36); ALXN2106 (excerpts from Alexion Form 10-K for FY 2013 at Note 17, page F-41); ALXN2107 (excerpts from Alexion Form 10-K for FY 2014 at Note 17, page F-42); ALXN2108 (excerpts from Alexion Form 10-K for FY 2015 at F-45); ALXN2109 (excerpts from Alexion Form 10-K for FY 2016 at 58); ALXN2110 (excerpts from Alexion Form 10-K for FY 2017 at Note 18, page F-50); ALXN2111 (excerpts from Alexion Form 10-K for FY 2018 at Note 19, page F-53); ALXN2112 (excerpts from Alexion Form 10-Q for Q1 of FY 2019 at Note 14, page 23); ALXN2113 (excerpts from Alexion Form 10-Q for Q2 of FY 2019 at Note 14, page 25); and

Samsung Bioepis Exhibit No. 1002
Page 11966

ALXN1 (excerpts from Alexion Form 10-Q for Q3 of FY 2019 at Note 14, page 25).

Samsung Bioepis Exhibit No. 1002
Page 11967

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. Executed this 22nd day of November 2019 in New Haven, Connecticut.



Daniel Bazarko

Samsung Bioepis Exhibit No. 1002
Page 11968

Appendix A

Year/Quarter	U.S. net product sales for Soliris® (total) ($M)	U.S. net product sales for Soliris® (PNH only) ($M)[1]
FY 2007	> 45[2]	> 45
FY 2008	**113.2**	**113.2**
FY 2009	**159.8**	**159.8**
FY 2010	**205.8**	**> 200**
FY 2011	**263.4**	**> 200**
FY 2012	**400.5**	**> 200**
FY2013	**561.4**	**> 250**
FY2014	**730.1**	**> 350**
FY2015	**> 800**[3]	**> 400**
FY2016	**> 1,000**	**> 450**
FY2017	**1,235.0**	**> 500**
FY2018	**1,588.4**	**> 500**

---

[1] Although Alexion has not typically disclosed U.S. net product sales for Soliris® ***in PNH only***, based on my role at Alexion, my knowledge of when other indications for Soliris® received FDA approval, and my knowledge of when other products for treating PNH later became available in the U.S., I am able to provide the estimates of U.S. net product sales for Soliris® in PNH shown in the last column of Appendix A.

[2] Alexion did not precisely report U.S. net product sales for Soliris® in its 10-K filing with the Securities and Exchange Commission in 2007. Based on my role at Alexion and my knowledge of the initial sales figures for Soliris® in the U.S., I estimate that the U.S. net product sales for Soliris® were at least greater than $45 million for 2007.

[3] Although Alexion did not expressly break down Soliris® net product sales by region (U.S., EU, etc.) for 2015 and 2016, based on my role at Alexion and my familiarity with the sales figures in addition to the publicly available sales data, I am able to estimate that U.S. net product sales for Soliris® in these years were at least greater than about $800 million and $1 billion for 2015 and 2016, respectively.

Year/Quarter	U.S. net product sales for Soliris® (total) ($M)	U.S. net product sales for Soliris® (PNH only) ($M)[1]
Q1 2019	**463.7**	**> 100**
Q2 2019	**496.3**	**> 100**
Q3 2019	**496.8**	**> 75**

APPENDIX S

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

FOR ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(D)
OF
THE SECURITIES AND EXCHANGE ACT OF 1934

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2007

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. Please see definition of "accelerated and large accelerated filer" in Rule 12b-2 of the Exchange Act. Check One:

Large Accelerated Filer: ☒ Accelerated Filer: ☐ Non-Accelerated Filer: ☐

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2007, was approximately $1,658,668,873.68.

The number of shares of Common Stock outstanding as of February 25, 2008 was 38,106,662.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 9, 2008, are incorporated by reference into Part III of this report.

PART I

Unless the context requires otherwise, references in this report to "we," "our," "us," "Company" and "Alexion" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab), timing and effect of sales of Soliris in various European markets, status of reimbursement, price approval and funding processes in Europe, progress in developing commercial infrastructure and interest and sense of urgency about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies in other countries, prospects for regulatory approval in other countries, the need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, potential costs resulting from product liability or other third party claims, including pending litigation, the sufficiency of our existing capital resources and projected cash needs, results of pending litigation, assessment of impact of recent accounting pronouncements as well as assumptions relating to the foregoing. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors." Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. ***BUSINESS.***

Overview

We are a biopharmaceutical company engaged in the discovery, development and delivery of biologic therapeutic products aimed at treating patients with severe and life-threatening disease states, including hematologic and neurologic diseases, cancer and autoimmune disorders. We have one marketed product, Soliris® (eculizumab), which is the first therapy approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria, or PNH.

Since our incorporation in January 1992 until April 2007, we have devoted most of our resources to drug discovery, research, and product and clinical development. In March 2007, the Food and Drug Administration, or

Samsung Bioepis Exhibit No. 1002
Page 11973

Alexion Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements—(Continued)
For the Years Ended December 31, 2007 and 2006, Five Month Period Ended December 31, 2005, and Year Ended July 31, 2005
(amounts in thousands, except share and per share amounts)

In the event that we are acquired in a merger, other business combination transaction, or 50 percent or more of our assets, cash flow, or earning power are sold, proper provision shall be made so that each holder of a right shall have the right to receive, upon exercise thereof at the then current exercise price, that number of shares of Common Stock of the surviving company which at the time of such transaction would have a market value of two times the exercise price of the right.

13. 401(k) Plan

We have a qualified 401(k) plan covering all eligible employees. Under the plan, employees may contribute up to the statutory allowable amount for any calendar year. We make matching contributions at a rate of $1.00 for each dollar contributed up to the first 3 percent and $0.50 for each dollar contributed of the next 2 percent of compensation. For the years ended December 31, 2007 and 2006, five month period ended December 31, 2005 and the year ended July 31, 2005, we made matching contributions of approximately $1,535, $406, $202 and $390, respectively.

14. Segment Information

In accordance with SFAS 131, "Disclosures about Segments of an Enterprise and Related Information," we present segment information in a manner consistent with the method we use to report this information to our management. We have determined we operate in a single segment.

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		Five Month Period Ended December 31,	Year Ended July 31,
Revenues:	2007	2006	2005	2005
United States	$ 51,856	$ 1,558	$ 664	$ 1,064
Europe	20,185	—	—	—
	$ 72,041	$ 1,558	$ 664	$ 1,064

	December 31, 2007	
Long-lived assets:	2007	2006
United States	$ 126,457	$ 62,534
Europe	545	—
	$ 127,002	$ 62,534

Samsung Bioepis Exhibit No. 1002
Page 11974

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

FOR ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(D) OF THE SECURITIES AND EXCHANGE ACT OF 1934

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2008

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)

203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒
Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐
Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒
Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. Please see definition of "accelerated and large accelerated filer" in Rule 12b-2 of the Exchange Act. Check One:
Large Accelerated Filer: ☒ Accelerated Filer: ☐ Non-Accelerated Filer: ☐
The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2008, was approximately $2,795,465,875.
The number of shares of Common Stock outstanding as of February 17, 2009 was 81,695,309.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 13, 2009, are incorporated by reference into Part III of this report.

PART I

Unless the context requires otherwise, references in this report to "we," "our," "us," "Company" and "Alexion" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries. Amounts, except per share amounts, are denominated in thousands.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab), for its approved indications and any future indications, timing and effect of sales of Soliris in various markets worldwide, level of future Soliris sales and collections, costs, expenses and capital requirements, cash outflows, cash from operations, status of reimbursement, price approval and funding processes in various countries worldwide, progress in developing commercial infrastructure and interest about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies in other countries, prospects for regulatory approval in other countries, the need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, potential costs resulting from product liability or other third party claims, the sufficiency of our existing capital resources and projected cash needs, assessment of impact of recent accounting pronouncements, and the effect of shifting currency exchange rates. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors." Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. ***BUSINESS.***

Overview

Alexion Pharmaceuticals, Inc., Alexion or the Company, is a biopharmaceutical company engaged in the discovery, development and delivery of biologic therapeutic products aimed at treating patients with severe and life-threatening disease states, including hematologic and neurologic diseases, transplant rejection, cancer and autoimmune disorders. Our marketed product Soliris® (eculizumab) is the first therapy approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria, or PNH.

Samsung Bioepis Exhibit No. 1002
Page 11976

Customers

In the United States, our customers are primarily specialty distributors and specialty pharmacies who supply physician office clinics, hospital outpatient clinics, infusion clinics or home health care providers. In some cases, we also sell Soliris to government agencies. Outside the United States, our customers are primarily hospitals, hospital buying groups, pharmacies, other health care providers and distributors.

During 2008, sales to our single largest customer, AmerisourceBergen, accounted for 21% of our Soliris net product sales, and no other customer individually accounted for more than 10% of total net product sales.

During 2007, sales to our three largest customers accounted for the following portions of our Soliris net product sales, and no other customer individually accounted for more than 10% of net sales:

Customer	December 31, 2007
Amerisource Bergen Corporation	40.4%
IDIS Limited	24.7%
McKesson Corporation	11.1%
	76.2%

We generally do not focus our promotional activities on distributors, and they do not set or determine demand for Soliris. Because of the pricing of Soliris, the limited number of patients, the short period from sale of product to patient infusion and the lack of contractual return rights, Soliris customers generally carry limited inventory.

Please also see Management's Discussion and Analysis – Revenues, and Note 17 on Page F-41, for financial information about geographic areas.

Patents and Proprietary Rights

Patents and other proprietary rights are important to our business. Our policy is to file patent applications to protect technology, inventions and improvements to our technologies that are considered important to the development of our business. We also rely upon our trade secrets, know-how, and continuing technological innovations, as well as patents that we have licensed or may license from other parties, to develop and maintain our competitive position.

We have filed several U.S. patent applications and international counterparts of certain of these applications. In addition, we have in-licensed several additional U.S. and international patents and patent applications. As of December 31, 2008, we own or in-license over 78 U.S. patents and 42 U.S. patent applications. These patents and patent applications relate to technologies or products in the C5 Inhibitor program, high throughput screening, vectors, cancer, recombinant antibodies, and other technologies. We own or in-license 61 foreign patents and 140 pending foreign patent applications. We owe royalties to a third party and other fees to owners of one or more patents in connection with the manufacture and sale of Soliris for PNH, and we may owe royalties and fees to other third parties with respect to any future commercial manufacture and sale of Soliris and our product candidates.

Samsung Bioepis Exhibit No. 1002
Page 11977

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2009

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)

203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating
Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☐ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)

Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2009, was approximately $3,615,450,070.

The number of shares of Common Stock outstanding as of February 16, 2010 was 89,137,398.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 12, 2010, are incorporated by reference into Part III of this report.

PART I

Unless the context requires otherwise, references in this report to "we," "our," "us," "Company" and "Alexion" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab) for its approved indications and any future indications, timing and effect of sales of Soliris in various markets worldwide, level of future Soliris sales and collections, costs, expenses and capital requirements, cash outflows, cash from operations, status of reimbursement, price approval and funding processes in various countries worldwide, progress in developing commercial infrastructure and interest about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies in other countries, prospects for regulatory approval in other countries, the need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, the timing for regulatory approval of our manufacturing facility in Rhode Island, potential costs resulting from product liability or other third party claims, the sufficiency of our existing capital resources and projected cash needs, assessment of impact of recent accounting pronouncements, and the effect of shifting currency exchange rates. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors." Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. *BUSINESS.*

Overview

Alexion Pharmaceuticals, Inc. was incorporated in Delaware in 1992. We are a biopharmaceutical company engaged in the discovery, development and commercialization of biologic therapeutic products aimed at treating patients with severe and life-threatening disease states, including hematologic, kidney and neurologic diseases, transplant rejection, cancer and autoimmune disorders. Our marketed product Soliris® (eculizumab) is the first and only therapy approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria, or PNH.

Samsung Bioepis Exhibit No. 1002
Page 11979

We estimate that we will pay employer contributions of approximately $645 in 2010. The expected future cash flows to be paid in respect of the pension plans as of December 31 were as follows:

Estimated future benefit payments	
2010	$ 233
2011	236
2012	228
2013	226
2014	251
2015 to 2019	1,179

16. Revenue and assets by geography

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	2009	2008	2007
United States	$ 159,829	$ 113,299	$ 51,856
Europe	215,763	143,645	20,185
Other	11,208	2,155	—
	$ 386,800	$ 259,099	$ 72,041

	December 31,		
Long-lived assets (1):	2009	2008	2007
United States	$ 158,621	$ 138,200	$ 103,735
Europe	5,637	1,478	545
Other	433	207	—
	$ 164,691	$ 139,885	$ 104,280

(1) Long-lived assets consist of property, plant and equipment.

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2010

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)

203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2010, was approximately $4,611,459,750.

The number of shares of Common Stock outstanding as of February 11, 2011 was 91,308,703.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 10, 2011, are incorporated by reference into Part III of this report.

PART I

Unless the context requires otherwise, references in this report to "we," "our," "us," "Company" and "Alexion" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs, and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab) for its approved indication and any expanded uses, timing and effect of sales of Soliris in various markets worldwide, level of coverage and reimbursement for Soliris, pricing, level of future Soliris sales and collections, plans for acquired companies and programs, timing regarding development and regulatory approvals for additional product candidates and the medical and commercial potential of those product candidates, costs, expenses and capital requirements, cash outflows, cash from operations, status of reimbursement, price approval and funding processes in various countries worldwide, progress in developing commercial infrastructure and interest about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies, prospects for regulatory approval, need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, the outcome of challenges and opposition proceedings to our intellectual property, and assertion or potential assertion by third parties that the manufacture, use or sale of Soliris infringes their intellectual property estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, potential costs resulting from product liability or other third party claims, the sufficiency of our existing capital resources and projected cash needs, assessment of impact of recent accounting pronouncements, declines in sovereign credit ratings or sovereign defaults in countries where we commercialize our products, delay of collection or reduction in reimbursement due to adverse economic conditions, the short and long term effects of government healthcare measures, and the effect of shifting foreign exchange rates. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors". Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. ***BUSINESS.***

Overview

Alexion Pharmaceuticals, Inc. is a biopharmaceutical company engaged in the discovery, development and commercialization of innovative therapeutic products aimed at treating patients with severe and life-threatening disease states, including those in the therapeutic areas of hematology, nephrology including transplant rejection, neurology, ophthalmology and cancer. Our marketed product Soliris® (eculizumab) is the first and only therapy approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), an ultra-rare and life-threatening blood disorder. We were incorporated in 1992 and began commercial sale of Soliris in 2007.

Samsung Bioepis Exhibit No. 1002
Page 11982

Alexion Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements
For the Years Ended December 31, 2010, 2009 and 2008
(amounts in thousands, except per share amounts)

16. Revenue and assets by geography

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	**2010**	**2009**	**2008**
United States	$205,792	$159,829	$113,299
Europe	274,919	215,763	143,645
Other	60,246	11,208	2,155
	$540,957	$386,800	$259,099

	December 31,	
Long-lived assets (1):	**2010**	**2009**
United States	$154,227	$158,621
Europe	6,557	5,637
Other	1,456	433
	$162,240	$164,691

(1) Long-lived assets consist of property, plant and equipment.

17. Subsequent Events

On January 28, 2011, Alexion acquired Taligen Therapeutics, Inc. (Taligen), a privately held development-stage biotechnology company based in Cambridge, Massachusetts, in a transaction accounted for as a business combination. The acquisition was intended to broaden Alexion's portfolio of pre-clinical compounds and to expand Alexion's capabilities in translational medicine. Taligen's pre-clinical compounds include product candidates for the potential treatment of patients with ophthalmic diseases such as age-related macular degeneration (AMD), as well as other novel antibody and protein regulators of the complement inflammatory pathways. Alexion made an upfront cash payment of $111,000 for 100 percent of Taligen's equity interests. Additional contingent payments would be earned upon reaching various clinical efficacy and product approval milestones in both the U.S. and European Union for up to six product candidates. If all such clinical efficacy and product approval milestones were achieved in both the U.S. and European Union for six product candidates, the total payments would be $367,000.

On February 10, 2011, Alexion acquired patents and assets from Germany-based Orphatec Pharmaceuticals GmbH (Orphatec) related to an investigational therapy for patients with Type A molybdenum cofactor deficiency (MoCD), an ultra-rare disorder characterized by severe brain damage and rapid death in newborn infants. The acquisition will be accounted for as a business combination. Orphatec is a privately held development-stage biotechnology company with headquarters in Cologne, Germany. Alexion made an upfront cash payment of approximately $3,000. Additional contingent payments of up to $42,000 would be earned upon reaching various development, regulatory and commercial milestones. Alexion also established a research collaboration with key MoCD researchers from Orphatec to accelerate development of the investigational therapy.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2011

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2011, was $8,659,265,185.

The number of shares of Common Stock outstanding as of February 11, 2012 was 185,993,409.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 07, 2012, are incorporated by reference into Part III of this report.

ALXN2063
IPR2019-00739
Samsung Bioepis Exhibit No. 1002
Page 11984

PART I

Unless the context requires otherwise, references in this report to "Alexion", the "Company", "we", "our" or "us" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs, and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab) for its approved indications and any expanded uses, timing and effect of sales of Soliris in various markets worldwide, level of coverage and reimbursement for Soliris, pricing, level of future Soliris sales and collections, plans for acquired companies and programs, timing regarding development and regulatory approvals for additional indications or in additional territories for Soliris, including for the treatment of aHUS and other product candidates, the medical and commercial potential of additional indications for Soliris and other product candidates, costs, expenses and capital requirements, cash outflows, cash from operations, status of reimbursement, price approval and funding processes in various countries worldwide, progress in developing commercial infrastructure and interest about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies, prospects for regulatory approval, need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, the outcome of challenges and opposition proceedings to our intellectual property, and assertion or potential assertion by third parties that the manufacture, use or sale of Soliris infringes their intellectual property, estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, potential costs resulting from product liability or other third party claims, the sufficiency of our existing capital resources and projected cash needs, assessment of impact of recent accounting pronouncements, declines in sovereign credit ratings or sovereign defaults in countries where we sell Soliris, delay of collection or reduction in reimbursement due to adverse economic conditions or changes in government and private insurer regulations and approaches to reimbursement, the short and long term effects of other government healthcare measures, and the effect of shifting foreign exchange rates. Words such as "anticipates", "expects", "intends", "plans", "believes", "seeks", "estimates", variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors". Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. *BUSINESS.*

Overview

Alexion is a biopharmaceutical company focused on serving patients with severe and ultra-rare disorders through the innovation, development and commercialization of life-transforming therapeutic products. Our marketed product Soliris® (eculizumab) is the first and only therapeutic approved for patients with two ultra-rare and severe disorders resulting from chronic uncontrolled activation of the complement component of the immune system: paroxysmal nocturnal hemoglobinuria (PNH), an ultra-rare and life-threatening blood disorder, and atypical hemolytic uremic syndrome (aHUS), an ultra-rare and life-threatening genetic disease. We are also evaluating other potential indications for Soliris in other diseases in which chronic uncontrolled complement activation is the underlying mechanism, and we are progressing with other biotechnology product candidates in ultra-rare and severe disorders which are now in various stages of development. We were incorporated in 1992 and began commercial sale of Soliris in 2007.

Soliris is designed to inhibit a specific aspect of the complement component of the immune system and thereby treat inflammation associated with chronic disorders in the therapeutic areas of hematology, nephrology, transplant rejection, neurology and ophthalmology. Soliris is a humanized monoclonal antibody that blocks terminal complement activity at the doses currently prescribed. The initial indication for which we received approval for Soliris is PNH. PNH is an ultra-rare, debilitating and life-threatening, deficiency blood disorder defined by chronic uncontrolled complement activation leading to

Samsung Bioepis Exhibit No. 1002
Page 11985

17. Segment Information

We operate as one business segment, which is the business of focusing on serving patients with severe and ultra-rare disorders though the innovation, development and commercialization of life-transforming therapeutic products and therefore, our chief operating decision-maker manages the operations of our Company as a single operating segment.

Revenues and tangible long-lived assets by significant geographic region are as follows:

	December 31,		
Revenues:	**2011**	**2010**	**2009**
United States	$ 263,387	$ 205,792	$ 159,829
Europe	340,812	275,608	215,763
Asia Pacific (primarily Japan)	115,377	22,188	—
Other	63,855	37,369	11,208
	$ 783,431	$ 540,957	$ 386,800

	December 31,	
Long-lived assets (1):	**2011**	**2010**
United States	$ 157,473	$ 154,227
Europe	6,288	6,557
Other	2,091	1,456
	$ 165,852	$ 162,240

(1) Long-lived assets consist of property, plant and equipment.

18. Subsequent Events

On February 7, 2012, we acquired Enobia Pharma Corp. (Enobia), a privately held clinical-stage biotechnology company based in Montreal, Canada and Cambridge, Massachusetts, in a transaction expected to be accounted for as a business combination. The acquisition was intended to broaden our objective to develop and deliver therapies for patients with ultra-rare, severe, and life-threatening disorders. Enobia's lead product candidate ENB-0040 (asfotase alfa), is a human recombinant targeted alkaline phosphatase enzyme-replacement therapy for patients suffering with hypophosphatasia (HPP), an ultra-rare, life-threatening, genetic metabolic disease for which there are no approved treatments. We made an upfront cash payment of $610,000, subject to purchase price adjustments, for 100% of Enobia's capital stock. Additional contingent payments would be earned upon reaching various regulatory and sales milestones. If all such regulatory and sales milestones were achieved, the total additional payments would be $470,000. We financed the acquisition through available cash and proceeds from our new credit facility as noted below. As of December 31, 2011, we incurred $2,039 of acquisition-related costs comprised primarily of professional fees.

In conjunction with our acquisition of Enobia, we entered into a five-year, $440,000 credit facility with a syndication of banks. The credit facility consists of a $240,000 term loan payable in equal quarterly installments of $12,000 starting June 30, 2012 and a $200,000 revolving line of credit. The credit facility bears interest at a per annum rate of LIBOR plus 1.25% to 2.00% depending on certain leverage ratios (as calculated in accordance with the agreement). We borrowed $80,000 on the revolving line of credit in connection with the Enobia acquisition.

Samsung Bioepis Exhibit No. 1002
Page 11986

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2012

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2012, was $18,920,399,568.(1)

The number of shares of Common Stock outstanding as of February 11, 2013 was 195,209,249.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 06, 2013, are incorporated by reference into Part III of this report.

ALXN2064
IPR2019-00739
Samsung Bioepis Exhibit No. 1002
Page 11987

(1) Excludes 2,231,014 shares of common stock held by directors and executive officers at June 30, 2012. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Samsung Bioepis Exhibit No. 1002
Page 11988

The amount in accumulated other comprehensive income as of December 31, 2012 that is expected to be recognized as a component of the net periodic pension costs in 2013 is $424.

We estimate that we will pay employer contributions of approximately $4,285 in 2013. The expected future cash flows to be paid in respect of the pension plans as of December 31, 2012 were as follows:

Year	
2013	$ 1,378
2014	1,271
2015	1,340
2016	1,279
2017	1,513
2018 to 2022	6,510

15. Segment Information

We operate as one business segment, which is the business of serving patients with severe and ultra-rare disorders though the innovation, development and commercialization of life-transforming therapeutic products and therefore, our chief operating decision-maker manages our operations as a single operating segment.

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	**2012**	**2011**	**2010**
United States	$ 400,483	$ 263,387	$ 205,792
Europe	418,321	340,812	275,608
Asia Pacific (primarily Japan)	161,480	115,377	22,188
Other	153,830	63,855	37,369
	$ 1,134,114	$ 783,431	$ 540,957

	December 31,	
Long-lived assets (1):	**2012**	**2011**
United States	$ 157,019	$ 157,473
Europe	5,988	6,288
Other	2,622	2,091
	$ 165,629	$ 165,852

(1) Long-lived assets consist of property, plant and equipment.

16. Subsequent Events

In January 2013, we entered into a license agreement providing an exclusive research license and an option for an exclusive commercial license for specific targets and products to be developed from a platform technology. Under the terms of the agreement, we made an upfront payment of $3,000 and are also required to pay annual maintenance fees. In addition, for each product we develop, we could be required to pay up to an additional $70,500 in license fees, development and sales milestones as the specific milestones are met over time.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2013

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The NASDAQ Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The NASDAQ Stock Market LLC on June 30, 2013, was $17,833,350,643.(1)

The number of shares of Common Stock outstanding as of February 3, 2014 was 197,830,376.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 6, 2014, are incorporated by reference into Part III of this report.

ALXN2065
IPR2019-00739
Samsung Bioepis Exhibit No. 1002
Page 11990

(1) Excludes 1,898,588 shares of common stock held by directors and executive officers at June 30, 2013. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Samsung Bioepis Exhibit No. 1002
Page 11991

We estimate that we will pay employer contributions of approximately $3,886 in 2014. The expected future cash flows to be paid in respect of the pension plans as of December 31, 2013 were as follows:

Year	
2014	$ 2,140
2015	1,960
2016	1,910
2017	2,020
2018	1,851
2019 to 2023	8,306

17. Segment Information

We operate as one business segment, which is the innovation, development and commercialization of life-transforming therapeutic products. Therefore, our chief operating decision-maker manages our operations as a single operating segment.

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	**2013**	**2012**	**2011**
United States	$ 561,405	$ 400,483	$ 263,387
Europe	514,987	418,321	340,812
Asia Pacific (primarily Japan)	203,538	161,480	115,377
Other	271,416	153,830	63,855
	$ 1,551,346	$ 1,134,114	$ 783,431

	December 31,	
Long-lived assets (1):	**2013**	**2012**
United States	$ 190,791	$ 157,019
Europe	5,413	5,988
Other	4,905	2,622
	$ 201,109	$ 165,629

(1) Long-lived assets consist of property, plant and equipment.

18. Subsequent Events

In January 2014, we entered into an agreement with Moderna Therapeutics, Inc. (Moderna) that provides the option to purchase drug products for clinical development and commercialization of Moderna's messenger RNA (mRNA) therapeutics to treat rare diseases. Due to the early stage of these assets, we recorded expense for an upfront payment of $100,000 in 2014. We will also be responsible for funding research activities under the program. In addition, for each drug target, up to a maximum of ten targets, would could be required to make an option exercise payment of $15,000 and to pay up to an additional $120,000 with respect to a rare disease product and $400,000 with respect to a non-rare disease product in development and sales milestones if the specific milestones are met over time as well as royalties on commercial sales. In addition to the option agreement, we purchased $25,000 of preferred equity of Moderna LLC, Moderna's parent company.

In January 2014, we agreed to purchase a vialing facility in Athlone, Ireland. The closing of the acquisition is expected to occur during the first quarter of 2014 upon satisfaction of agreed upon closing conditions. Following closing and refurbishment of the facility, and after successful completion of the appropriate validation processes and regulatory approvals, such facility will become our first company-owned vialing facility for Soliris and other clinical and commercial products.

UNITED STATES
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FORM 10-K

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For the fiscal year ended December 31, 2014

or

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For the transition period from to

Commission file number: 0-27756

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352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The NASDAQ Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

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Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The NASDAQ Stock Market LLC on June 30, 2014, was $30,706,252,188.(1)

The number of shares of Common Stock outstanding as of February 3, 2015 was 202,148,509.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 6, 2015, are incorporated by reference into Part III of this report.

ALXN2066
IPR2019-00739
Samsung Bioepis Exhibit No. 1002
Page 11993

(1) Excludes 1,378,571 shares of common stock held by directors and executive officers at June 30, 2014. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Samsung Bioepis Exhibit No. 1002
Page 11994

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	**2014**	**2013**	**2012**
United States	$ 730,089	$ 561,405	$ 400,483
Europe (1)	836,134	514,987	418,321
Asia Pacific	244,059	203,538	161,480
Other	423,451	271,416	153,830
	$ 2,233,733	$ 1,551,346	$ 1,134,114

(1) As described in Note 19 "Quarterly Financial Information (unaudited)", included within the Europe revenues for 2014 is a reimbursement of $87,830 for shipments made in years prior to January 1, 2014 as a result of an agreement with the French government.

	December 31,	
Long-lived assets (2):	**2014**	**2013**
United States	$ 298,122	$ 190,791
Europe	88,543	5,413
Other	5,583	4,905
	$ 392,248	$ 201,109

(2) Long-lived assets consist of property, plant and equipment.

18. Subsequent Events

In January 2015, we entered into a license agreement with a third party to obtain certain intellectual property rights and technology related to specific therapeutic compounds. The agreement provides an exclusive research, development and commercial license for products to be developed using such compounds. Pursuant to the terms of the agreement, we made an upfront payment of $50,000 during the first quarter 2015. We could be required to pay up to an additional $213,000 in development and regulatory milestones related to a product developed under the agreement for a single disease indication. An additional $437,000 in milestone payments could be due if certain development and regulatory milestones are achieved for additional disease indications. The agreement also provides for royalty payments and potential milestone payments of up to $180,000 on commercial sales of products developed under the agreement.

In January 2015, we entered into a new lease agreement for approximately 44,000 square feet of office space in Zurich, Switzerland to support the relocation of the European headquarters. The lease is estimated to commence in the second quarter of 2015 and will expire 10 years later, with a minimum renewal option of 5 years and a maximum renewal option of 10 years. The lease provides for annual payments of $2,600 over the term of the lease.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

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For the fiscal year ended December 31, 2015

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

100 College Street, New Haven, Connecticut 06510
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**

Name of each exchange on which registered: **The NASDAQ Stock Market LLC**
Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The NASDAQ Stock Market LLC on June 30, 2015, was $39,491,560,848.(1)

The number of shares of Common Stock outstanding as of February 3, 2016 was 225,291,331.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 11, 2016, are incorporated by reference into Part III of this report.

ALXN2067
IPR2019-00739
Samsung Bioepis Exhibit No. 1002
Page 11996

(1) Excludes 7,551,963 shares of common stock held by directors and executive officers at June 30, 2015. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Samsung Bioepis Exhibit No. 1002
Page 11997

The following table presents a reconciliation of the restructuring reserve recorded within accrued expenses on the Company's condensed consolidated balance sheet for the year ended December 31, 2015 and December 31, 2014, respectively:

	December 31, 2015				December 31, 2014			
	Employee Separation Costs	Contract Termination Costs	Other Costs	Total	Employee Separation Costs	Contract Termination Costs	Other Costs	Total
Liability, beginning of period	$ 15,365	$ —	$ —	$ 15,365	$ —	$ —	$ —	$ —
Restructuring expenses	21,524	12,419	3,847	37,790	15,365	—	—	15,365
Cash settlements	(34,843)	(11,772)	(3,678)	(50,293)	—	—	—	—
Adjustments to previous estimates	4,344	35	—	4,379	—	—	—	—
Liability, end of period	$ 6,390	$ 682	$ 169	$ 7,241	$ 15,365	$ —	$ —	$ 15,365

18. Segment Information

We operate as one business segment, which is the innovation, development and commercialization of life-transforming therapeutic products. Therefore, results of our operations are reported on a consolidated basis for purposes of segment reporting, consistent with our management reporting. Disclosures about net product sales and long-lived assets by geographic area are presented below.

Net product sales

Net product sales by product are as follows:

	Year Ended December 31,		
	2015	2014	2013
Net product sales:			
Soliris (1)	$ 2,590,197	$ 2,233,733	$ 1,551,346
Strensiq	11,969	—	—
Kanuma	366	—	—
	$ 2,602,532	$ 2,233,733	$ 1,551,346

Geographical information

	Year Ended December 31,		
Net product sales:	2015	2014	2013
United States	$ 951,307	$ 730,089	$ 561,405
Europe (1)	840,465	836,134	514,987
Asia Pacific	276,350	244,059	203,538
Other	534,410	423,451	271,416
	$ 2,602,532	$ 2,233,733	$ 1,551,346

(1) As described in Note 19, "Quarterly Financial Information (unaudited)", included within the Soliris and Europe revenues for 2014 is a reimbursement of $87,830 for shipments made in years prior to January 1, 2014 as a result of an agreement with the French government.

	December 31,	
Long-lived assets (2):	2015	2014
United States	$ 444,282	$ 298,122
Europe	247,474	88,543
Other	5,269	5,583
	$ 697,025	$ 392,248

(2) Long-lived assets consist of property, plant and equipment.

Samsung Bioepis Exhibit No. 1002
Page 11998

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2016

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

100 College Street, New Haven, Connecticut 06510
(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**

Name of each exchange on which registered: **The NASDAQ Stock Market LLC**
Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

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Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The NASDAQ Stock Market LLC on June 30, 2016, was $25,314,108,813.(1)

The number of shares of Common Stock outstanding as of February 13, 2017 was 224,613,750.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 10, 2017, are incorporated by reference into Part III of this report.

(1) Excludes 7,417,897 shares of common stock held by directors and executive officers at June 30, 2016. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

ALXN2068
IPR2019-00739

Alexion Pharmaceuticals, Inc.

Table of Contents

PART I		Page
Item 1.	Business	3
Item 1A.	Risk Factors	25
Item 1B.	Unresolved Staff Comments	43
Item 2.	Properties	43
Item 3.	Legal Proceedings	44
Item 4.	Mine Safety Disclosures	44
PART II		
Item 5.	Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	45
Item 6.	Selected Financial Data	48
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	49
Item 7.A	Quantitative and Qualitative Disclosures About Market Risk	73
Item 8.	Financial Statements and Supplementary Data	74
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	74
Item 9A.	Controls and Procedures	74
Item 9A(T).	Controls and Procedures	75
Item 9B.	Other Information	76
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	77
Item 11.	Executive Compensation	77
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	77
Item 13.	Certain Relationships and Related Transactions, and Director Independence	77
Item 14.	Principle Accounting Fees and Services	77
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	78
Item 16.	Form 10-K Summary	80
SIGNATURES		81

Samsung Bioepis Exhibit No. 1002
Page 12000

Comparison of the Year Ended December 31, 2016 to the Year Ended December 31, 2015

Net Product Sales

Net product sales by significant geographic region are as follows:

	Year Ended December 31,		
	2016	2015	% Change
Net product sales:			
United States	$ 1,257	$ 951	32%
Europe	961	841	14%
Asia Pacific	318	276	15%
Rest of World	546	535	2%
	$ 3,082	$ 2,603	18%

Net product sales by product are as follows:

	Year Ended December 31,		
	2016	2015	% Change
Net product sales:			
Soliris	2,843	2,591	10%
Strensiq	210	12	-
Kanuma	29	—	-
	$ 3,082	$ 2,603	18%

The components of the increase in net product sales for the year ended December 31, 2016 are as follows:

	Year Ended December 31,
	2016
Components of change:	
Price	(1)%
Volume	22 %
Foreign exchange	(3)%
Total change in net product sales	**18 %**

The increase in net product sales for fiscal year 2016 as compared to the same period in 2015 was primarily due to an increase in unit volumes of 22% due to increased demand globally for Soliris therapy for patients with PNH or aHUS and sales of Strensiq and Kanuma during 2016.

The positive impact of volume on net product sales was partially offset by the negative impact on foreign exchange of 3%, for the year ended December 31, 2016, as compared to the same period in 2015. The negative impact on foreign exchange of $(74), or 3%, was due to changes in foreign currency exchange rates (inclusive of hedging activity) versus the U.S. dollar for the year ended December 31, 2015. The negative impact was primarily due to the weakening of the Euro, Japanese Yen, Russian Ruble, and the British Pound. We recorded a gain in revenue of $73 and $118 related to our foreign currency cash flow hedging program, for the years ended December 31, 2016 and 2015, respectively. We expect the strong dollar compared to other currencies to continue to have a negative impact on revenue into 2017.

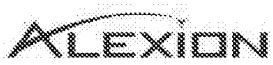
Samsung Bioepis Exhibit No. 1002
Page 12001

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

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Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐ Emerging growth company ☐
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2017, was $26,128,956,666.(1)

The number of shares of Common Stock outstanding as of February 5, 2018 was 221,681,437.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 8, 2018, are incorporated by reference into Part III of this report.

(1) Excludes 8,789,185 shares of common stock held by directors and executive officers at June 30, 2017. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Alexion Pharmaceuticals, Inc.

Table of Contents

		Page
PART I		
Item 1.	Business	4
Item 1A.	Risk Factors	27
Item 1B.	Unresolved Staff Comments	47
Item 2.	Properties	48
Item 3.	Legal Proceedings	49
Item 4.	Mine Safety Disclosures	50
PART II		
Item 5.	Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	51
Item 6.	Selected Financial Data	54
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	56
Item 7.A	Quantitative and Qualitative Disclosures About Market Risk	81
Item 8.	Financial Statements and Supplementary Data	82
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	82
Item 9A.	Controls and Procedures	82
Item 9A(T).	Controls and Procedures	83
Item 9B.	Other Information	83
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	84
Item 11.	Executive Compensation	84
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	84
Item 13.	Certain Relationships and Related Transactions, and Director Independence	84
Item 14.	Principle Accounting Fees and Services	84
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	85
Item 16.	Form 10-K Summary	88
SIGNATURES		89

Samsung Bioepis Exhibit No. 1002
Page 12003

Net Product Sales

Net product sales by product and significant geographic region are as follows:

	Year Ended December 31,			% Change	
	2017	2016	2015	2017 compared to 2016	2016 compared to 2015
Soliris					
United States	$ 1,235.0	$ 1,058.5	$ 943.6	16.7%	12.2%
Europe	985.2	939.7	838.3	4.8%	12.1%
Asia Pacific	328.1	303.8	274.0	8.0%	10.9%
Rest of World	595.8	541.2	534.3	10.1%	1.3%
	$ 3,144.1	2,843.2	2,590.2	10.6%	9.8%
Strensiq					
United States	$ 280.1	$ 177.5	$ 7.7	57.8%	**
Europe	35.6	15.3	1.7	132.7%	**
Asia Pacific	18.6	13.0	2.4	43.1%	**
Rest of World	5.5	3.6	0.1	52.8%	**
	339.8	209.4	11.9	62.3%	**
Kanuma					
United States	$ 42.4	$ 20.4	$ –	107.8%	N/A
Europe	14.6	6.3	0.4	131.7%	**
Asia Pacific	2.7	1.3	–	107.7%	N/A
Rest of World	5.9	1.1	–	**	N/A
	$ 65.6	29.1	0.4	125.4%	**
Total Net Product Sales	3,549.5	3,081.7	2,602.5	15.2%	18.4%

** Percentages not meaningful

Long-Lived Assets

Long-lived assets consist of property, plant and equipment.

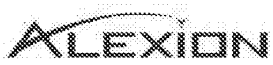
	December 31,	
	2017	2016
United States	$ 456.9	$ 489.7
Europe	864.6	538.4
Other	4.9	7.5
	$ 1,326.4	$ 1,035.6

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2018
or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to
Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210

(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company ☐ Emerging growth company ☐
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 29, 2018, was $26,514,235,288.(1)

The number of shares of Common Stock outstanding as of January 31, 2019 was 223,469,381.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its 2019 Annual Meeting of Stockholders currently anticipated to be held on May 14, 2019, are incorporated by reference into Part III of this report.

(1) Excludes 9,186,789 shares of common stock held by directors, executive officers and their respective affiliates at June 29, 2018. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Alexion Pharmaceuticals, Inc.

Table of Contents

		Page
PART I		
Item 1.	Business	5
Item 1A.	Risk Factors	29
Item 1B.	Unresolved Staff Comments	56
Item 2.	Properties	56
Item 3.	Legal Proceedings	56
Item 4.	Mine Safety Disclosures	56
PART II		
Item 5.	Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	57
Item 6.	Selected Financial Data	59
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	61
Item 7.A	Quantitative and Qualitative Disclosures About Market Risk	85
Item 8.	Financial Statements and Supplementary Data	86
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	86
Item 9A.	Controls and Procedures	86
Item 9A(T).	Controls and Procedures	87
Item 9B.	Other Information	87
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	88
Item 11.	Executive Compensation	88
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	88
Item 13.	Certain Relationships and Related Transactions, and Director Independence	88
Item 14.	Principle Accounting Fees and Services	88
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	89
Item 16.	Form 10-K Summary	91
SIGNATURES		92

Samsung Bioepis Exhibit No. 1002
Page 12006

19. Segment Information

We operate in a single segment, focusing on serving patients affected by rare diseases through the innovation, development and commercialization of life-changing therapies. Consistent with our operational structure, our chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, results of our operations are reported on a consolidated basis for purposes of segment reporting, consistent with our management reporting. Disclosures about net product sales and long-lived assets by geographic area are presented below.

Net Product Sales

Net product sales by product and geographic region are as follows:

	Year Ended December 31,			% Change	
	2018	2017	2016	2018 compared to 2017	2017 compared to 2016
SOLIRIS					
United States	$ 1,588.4	$ 1,235.0	$ 1,058.5	28.6 %	16.7%
Europe	1,036.7	985.2	939.7	5.2 %	4.8%
Asia Pacific	382.0	328.1	303.8	16.4 %	8.0%
Rest of World	555.9	595.8	541.2	(6.7)%	10.1%
	$ 3,563.0	$ 3,144.1	$ 2,843.2	13.3 %	10.6%
STRENSIQ					
United States	$ 374.3	$ 280.1	$ 177.5	33.6 %	57.8%
Europe	61.7	35.6	15.3	73.3 %	132.7%
Asia Pacific	27.9	18.6	13.0	50.0 %	43.1%
Rest of World	11.2	5.5	3.6	103.6 %	52.8%
	$ 475.1	$ 339.8	$ 209.4	39.8 %	62.3%
KANUMA					
United States	$ 51.3	$ 42.4	$ 20.4	21.0 %	107.8%
Europe	21.6	14.6	6.3	47.9 %	131.7%
Asia Pacific	3.7	2.7	1.3	37.0 %	107.7%
Rest of World	15.4	5.9	1.1	**	**
	$ 92.0	$ 65.6	$ 29.1	40.2 %	125.4%
Total Net Product Sales	4,130.1	$ 3,549.5	$ 3,081.7	16.4 %	15.2%

** Percentages not meaningful

Long-Lived Assets

Long-lived assets consist of property, plant and equipment.

	December 31,	
	2018	2017
United States	$ 468.3	$ 455.9
Europe	1,001.1	864.6
Other	2.1	4.9
	$ 1,471.5	$ 1,325.4

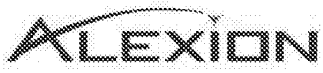
Samsung Bioepis Exhibit No. 1002
Page 12007

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q

☒ Quarterly report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934
For the quarterly period ended March 31, 2019
or

☐ Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934
For the transition period from to
Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210
(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)
N/A
(Former name, former address, and former fiscal year, if changed since last report)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company ☐ Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Common Stock, $0.0001 par value	224,237,214
Class	Outstanding as of April 23, 2019

Alexion Pharmaceuticals, Inc.

Table of Contents

			Page
PART I.		**FINANCIAL INFORMATION**	
	Item 1.	**Condensed Consolidated Financial Statements (Unaudited)**	
		Condensed Consolidated Balance Sheets as of March 31, 2019 and December 31, 2018	2
		Condensed Consolidated Statements of Operations for the three months ended March 31, 2019 and 2018	3
		Condensed Consolidated Statements of Comprehensive Income for the three months ended March 31, 2019 and 2018	4
		Condensed Consolidated Statements of Changes in Stockholders' Equity for the three months ended March 31, 2019 and 2018	5
		Condensed Consolidated Statements of Cash Flows for the three months ended March 31, 2019 and 2018	6
		Notes to Condensed Consolidated Financial Statements	7
	Item 2.	Management's Discussion and Analysis of Financial Condition and Results of Operations	32
	Item 3.	Quantitative and Qualitative Disclosures about Market Risk	53
	Item 4.	Controls and Procedures	55
PART II.		OTHER INFORMATION	57
	Item 1.	Legal Proceedings	58
	Item 1A.	Risk Factors	59
	Item 2.	Unregistered Sales of Equity Securities and Use of Proceeds	85
	Item 5.	Other Information	85
	Item 6.	Exhibits	86
SIGNATURES			

14. Revenue Recognition

Disaggregation of Revenue

The Company disaggregates revenue from contracts with customers into product and geographical regions as summarized below.

	Three months ended March 31,	
	2019	2018
SOLIRIS		
United States	$ 463.7	$ 336.0
Europe	264.5	250.8
Asia Pacific	100.9	85.5
Rest of World	132.9	127.8
Total	$ 962.0	$ 800.1
ULTOMIRIS		
United States	$ 24.6	$ —
Europe	—	—
Asia Pacific	—	—
Rest of World	—	—
Total	$ 24.6	$ —
STRENSIQ		
United States	$ 89.5	$ 89.2
Europe	17.5	14.0
Asia Pacific	9.9	5.7
Rest of World	3.2	1.8
Total	$ 130.1	$ 110.7
KANUMA		
United States	$ 13.8	$ 11.9
Europe	6.3	5.9
Asia Pacific	0.8	1.0
Rest of World	2.6	0.8
Total	$ 23.5	$ 19.6
Total Net Product Sales	$ 1,140.2	$ 930.4

Contract Balances and Receivables

Contract liabilities relate to consideration received and/or billed for goods that have not been delivered to the customer and for which the performance obligation has not yet been completed. These amounts are included within other current liabilities in the condensed consolidated balance sheets.

The following table provides information about receivables and contract liabilities from our contracts with customers.

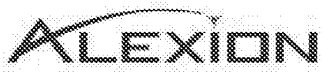
	March 31, 2019	December 31, 2018
Receivables, which are included in "Trade accounts receivable, net"	$ 1,016.3	$ 922.3
Contract liabilities, which are included in "Other current liabilities"	$ 3.0	$ 3.4

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q

☒ **Quarterly report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the quarterly period ended June 30, 2019
or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to
Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210
(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)
N/A
(Former name, former address, and former fiscal year, if changed since last report)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock $0.0001 par value	ALXN	NASDAQ Stock Market LLC

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company ☐ Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Common Stock $0.0001 par value	224,226,878
Class	Outstanding as of July 22, 2019

Alexion Pharmaceuticals, Inc.

Table of Contents

			Page
PART I.		**FINANCIAL INFORMATION**	
	Item 1.	**Condensed Consolidated Financial Statements (Unaudited)**	
		Condensed Consolidated Balance Sheets as of June 30, 2019 and December 31, 2018	2
		Condensed Consolidated Statements of Operations for the three and six months ended June 30, 2019 and 2018	3
		Condensed Consolidated Statements of Comprehensive Income for the three and six months ended June 30, 2019 and 2018	4
		Condensed Consolidated Statements of Changes in Stockholders' Equity for the three and six months ended June 30, 2019 and 2018	5
		Condensed Consolidated Statements of Cash Flows for the six months ended June 30, 2019 and 2018	7
		Notes to Condensed Consolidated Financial Statements	9
	Item 2.	Management's Discussion and Analysis of Financial Condition and Results of Operations	34
	Item 3.	Quantitative and Qualitative Disclosures about Market Risk	54
	Item 4.	Controls and Procedures	56
PART II.		OTHER INFORMATION	57
	Item 1.	Legal Proceedings	57
	Item 1A.	Risk Factors	58
	Item 2.	Unregistered Sales of Equity Securities and Use of Proceeds	86
	Item 5.	Other Information	86
	Item 6.	Exhibits	86
SIGNATURES			

14. Revenue Recognition

Disaggregation of Revenue

The Company disaggregates revenue from contracts with customers into product and geographical regions as summarized below.

	Three months ended June 30,		Six months ended June 30,	
	2019	2018	2019	2018
SOLIRIS				
United States	$ 496.3	$ 395.8	$ 960.0	$ 731.8
Europe	280.2	253.4	544.7	504.2
Asia Pacific	110.3	93.6	211.2	179.1
Rest of World	94.0	155.4	226.9	283.2
Total	$ 980.8	$ 898.2	$ 1,942.8	$ 1,698.3
ULTOMIRIS				
United States	$ 54.2	$ —	$ 78.8	$ —
Europe	—	—	—	—
Asia Pacific	—	—	—	—
Rest of World	—	—	—	—
Total	$ 54.2	$ —	$ 78.8	$ —
STRENSIQ				
United States	$ 106.2	$ 99.9	$ 205.7	$ 189.1
Europe	19.5	16.4	37.0	30.4
Asia Pacific	12.1	6.3	22.0	12.0
Rest of World	3.5	2.5	6.7	4.3
Total	$ 141.3	$ 125.1	$ 271.4	$ 235.8
KANUMA				
United States	$ 15.3	$ 13.0	$ 29.1	$ 24.9
Europe	6.8	5.8	13.1	11.7
Asia Pacific	1.3	1.1	2.1	2.1
Rest of World	2.8	1.5	5.4	2.3
Total	$ 26.2	$ 21.4	$ 49.7	$ 41.0
Total Net Product Sales	$ 1,202.5	$ 1,044.7	$ 2,342.7	$ 1,975.1

Contract Balances and Receivables

Contract liabilities relate to consideration received and/or billed for goods that have not been delivered to the customer and for which the performance obligation has not yet been completed. These amounts are included within other current liabilities in the condensed consolidated balance sheets.

The following table provides information about receivables and contract liabilities from our contracts with customers.

	June 30, 2019	December 31, 2018
Receivables, which are included in "Trade accounts receivable, net"	$ 1,123.6	$ 922.3
Contract liabilities, which are included in "Other current liabilities"	$ 3.1	$ 3.4

Samsung Bioepis Exhibit No. 1002
Page 12013

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q

Quarterly report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934

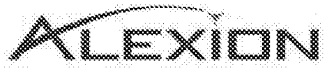
For the quarterly period ended September 30, 2019

or

Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934

For the transition period from to

Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210
(Address of Principal Executive Offices) (Zip Code)

475-230-2596
(Registrant's telephone number, including area code)

N/A
(Former name, former address, and former fiscal year, if changed since last report)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock $0.0001 par value	ALXN	NASDAQ Stock Market LLC

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No ☒

Common Stock $0.0001 par value	221,290,691
Class	Outstanding as of October 21, 2019

ALXN2073
IPR2019-00739

Alexion Pharmaceuticals, Inc.

Table of Contents

			Page
PART I.		**FINANCIAL INFORMATION**	
	Item 1.	**Condensed Consolidated Financial Statements (Unaudited)**	
		Condensed Consolidated Balance Sheets as of September 30, 2019 and December 31, 2018	2
		Condensed Consolidated Statements of Operations for the three and nine months ended September 30, 2019 and 2018	3
		Condensed Consolidated Statements of Comprehensive Income for the three and nine months ended September 30, 2019 and 2018	4
		Condensed Consolidated Statements of Changes in Stockholders' Equity for the three and nine months ended September 30, 2019 and 2018	5
		Condensed Consolidated Statements of Cash Flows for the nine months ended September 30, 2019 and 2018	7
		Notes to Condensed Consolidated Financial Statements	9
	Item 2.	Management's Discussion and Analysis of Financial Condition and Results of Operations	35
	Item 3.	Quantitative and Qualitative Disclosures about Market Risk	58
	Item 4.	Controls and Procedures	60
PART II.		OTHER INFORMATION	61
	Item 1.	Legal Proceedings	61
	Item 1A.	Risk Factors	62
	Item 2.	Unregistered Sales of Equity Securities and Use of Proceeds	90
	Item 5.	Other Information	90
	Item 6.	Exhibits	90
SIGNATURES			

Our derivative assets and liabilities include foreign exchange and interest rate derivatives that are measured at fair value using observable market inputs such as forward rates, interest rates, our own credit risk as well as an evaluation of our counterparties' credit risks. Based on these inputs, the derivative assets and liabilities are classified within Level 2 of the valuation hierarchy.

Contingent consideration liabilities related to business acquisitions and derivative liabilities associated with other contingent payments are classified as Level 3 within the valuation hierarchy and are valued based on various estimates, including probability of success, discount rates and amount of time until the conditions of the milestone payments are met.

As of September 30, 2019, there has not been any impact to the fair value of our derivative liabilities due to our own credit risk. Similarly, there has not been any significant adverse impact to our derivative assets based on our evaluation of our counterparties' credit risks.

Acquisition-Related Contingent Consideration

In connection with prior business combinations, we may be required to pay future consideration that is contingent upon the achievement of specified development, regulatory approvals or sales-based milestone events. We determine the fair value of these obligations using various estimates that are not observable in the market and represent a Level 3 measurement within the fair value hierarchy. The resulting probability-weighted cash flows were discounted using a cost of debt of 5.1% for developmental and regulatory milestones and a weighted average cost of capital of 10.0% for sales-based milestones.

Each reporting period, we adjust the contingent consideration to fair value with changes in fair value recognized in operating earnings. Changes in fair values reflect new information about the probability and timing of meeting the conditions of the milestone payments. In the absence of new information, changes in fair value will only reflect the interest component of contingent consideration related to the passage of time.

As of September 30, 2019, estimated future contingent milestone payments related to prior business combinations range from zero if no milestone events are achieved, to a maximum of $602.0 if all development, regulatory and sales-based milestones are reached. In the second quarter 2019, a sales-based milestone associated with our acquisition of Enobia Pharma Corp. was achieved. In connection with such achievement, we made a $100.0 milestone payment in the third quarter 2019.

As of September 30, 2019, the fair value of acquisition-related contingent consideration was $188.0. The following table represents a roll-forward of our acquisition-related contingent consideration:

	Nine months ended September 30, 2019
Balance at beginning of period	$ 280.8
Milestone payments	(100.0)
Changes in fair value	7.2
Balance at end of period	$ 188.0

Other Contingent Payments

In January 2019, we entered into an agreement with Caelum, a biotechnology company that is developing CAEL101 for light chain (AL) amyloidosis. Under the terms of the agreement, we acquired a minority equity interest in preferred stock of Caelum and an exclusive option to acquire the remaining equity in Caelum based on Phase II data, for pre-negotiated economics. We paid $30.0 during the first quarter 2019 and could be required to pay up to an additional $30.0 in contingent milestone-dependent fees. These contingent payments meet the definition of a derivative liability and were initially recorded at fair value of $27.1, based on the probability-weighted cash flows, discounted using a cost of debt ranging from 3.3% to 3.5%.

Each reporting period, we adjust the derivative liability associated with the contingent fees to fair value with changes in fair value recognized in other income and expense. Changes in fair values reflect new information about the probability and timing of meeting the conditions of the milestone payments. In the absence of new information, changes in fair value will only reflect the interest component of the liability related to the passage of time. As of September 30, 2019, the fair value of our contingent fees was $27.6. We recorded $(0.2) and $(0.5) in other income and (expense) during

APPENDIX T

NATURAL HISTORY OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

PETER HILLMEN, M.B., CH.B., PH.D., S.M. LEWIS, M.D., MONICA BESSLER, PH.D., LUCIO LUZZATTO, M.D., AND JOHN V. DACIE, M.D.

Abstract *Background.* Paroxysmal nocturnal hemoglobinuria (PNH), which is characterized by intravascular hemolysis and venous thrombosis, is an acquired clonal disorder associated with a somatic mutation in a totipotent hematopoietic stem cell. An understanding of the natural history of PNH is essential to improve therapy.

Methods. We have followed a group of 80 consecutive patients with PNH who were referred to Hammersmith Hospital, London, between 1940 and 1970. They were treated with supportive measures, such as oral anticoagulant therapy after established thromboses, and transfusions.

Results. The median age of the patients at the time of diagnosis was 42 years (range, 16 to 75), and the median survival after diagnosis was 10 years, with 22 patients (28 percent) surviving for 25 years. Sixty patients have died; 28 of the 48 patients for whom the cause of death is known died from either venous thrombosis or hemorrhage. Thirty-one patients (39 percent) had one or more episodes of venous thrombosis during their illness. Of the 35 patients who survived for 10 years or more, 12 had a spontaneous clinical recovery. No PNH-affected cells were found among the erythrocytes or neutrophils of the patients in prolonged remission, but a few PNH-affected lymphocytes were detectable in three of the four patients tested. Leukemia did not develop in any of the patients.

Conclusions. PNH is a chronic disorder that curtails life. A spontaneous long-term remission can occur, which must be taken into account when considering potentially dangerous treatments, such as bone marrow transplantation. Platelet transfusions should be given, as appropriate, and long-term anticoagulation therapy should be considered for all patients. (N Engl J Med 1995;333:1253-8.)

PAROXYSMAL nocturnal hemoglobinuria (PNH) is an acquired disorder of hematopoiesis characterized by intravascular hemolysis and manifested by episodes of hemoglobinuria and life-threatening venous thromboses.[1] The cellular abnormality in this disorder is caused by a somatic mutation in a totipotent hematopoietic stem cell.[2,3] The cells derived from the abnormal clone are deficient in all surface proteins normally attached to the cell membrane by a glycosylphosphatidylinositol anchor.[4,5]

PNH was first described as a distinct clinical entity in 1882.[6] The cardinal diagnostic test, introduced in the late 1930s, is Ham's test,[7] which is based on the increased sensitivity of PNH-affected erythrocytes to lysis by complement. Deficiency of an antigen known as the membrane inhibitor of reactive lysis (CD59) is largely responsible for the hemolysis[8,9] and is implicated in the tendency for patients to have thromboses.[9] In the past two years the biochemical defect underlying PNH has been pinpointed at an early step in the biosynthesis of glycosylphosphatidylinositol molecules — namely, the transfer of *N*-acetylglucosamine to phosphatidylinositol.[10-12] The protein required for this step is encoded by a gene, *PIG-A*, that is somatically mutated in patients with PNH.[13-17]

Despite the remarkable progress in our understanding of this disorder, treatment has remained largely supportive. The only potentially curative therapy currently available is bone marrow transplantation,[18,19] which is associated with substantial morbidity and mortality.[20] To determine whether the management of PNH can be improved, it is important to know its natural history. We report the results of a long-term study (up to 48 years after the diagnosis) of a group of 80 patients with PNH seen at one institution between 1940 and 1970. This study has uncovered some surprising information on the natural history of the disorder and has identified relatively simple therapies that may reduce the associated morbidity and mortality.

From the Department of Haematology, Royal Postgraduate Medical School and Hammersmith Hospital, London (P.H., S.M.L., M.B., L.L., J.V.D.); the Haematological Malignancy Diagnostic Service, Institute of Pathology, General Infirmary at Leeds, Leeds, United Kingdom (P.H.); and the Department of Human Genetics, Memorial Sloan-Kettering Cancer Center, New York (M.B., L.L.). Address reprint requests to Dr. Hillmen at the Haematological Malignancy Diagnostic Service, Institute of Pathology, General Infirmary at Leeds, Great George St., Leeds LS1 3EX, United Kingdom.

Supported by grants from the Wellcome Trust, the Annette Fox Leukaemia Research Fund, and the Friends of the Leukaemia Unit, Leeds General Infirmary.

METHODS

Patients

Eighty patients with PNH were referred to Hammersmith Hospital in London between 1940 and 1970. In all patients the diagnosis was established or confirmed by a positive Ham's test.[21] This group of patients was last described in 1972.[22] Follow-up data have been obtained by contacting the patients' primary physicians and reviewing death certificates.

Complications and Causes of Death

The complications and causes of death reported were either unequivocally diagnosable on clinical grounds or were diagnosed after death. If a complication was not confirmed, it is not reported here. Thus, the reported incidence of complications is likely to be an underestimate, because many of the patients were seen at Hammersmith Hospital only infrequently. We compared the survival of the patients with the survival of a control group matched for sex and age.

Analysis of Blood Samples

In 1993 venous blood samples were obtained from five patients in either acid–citrate–dextrose or EDTA for the performance of Ham's tests and flow cytometric studies of the expression of glycosylphosphatidylinositol-linked proteins on erythrocytes and white cells, as previously described.[23,24] By definition, normal cells express normal levels of glycosylphosphatidylinositol-linked proteins, whereas PNH-affected cells are deficient in all these proteins.

RESULTS

Follow-up Studies

Sixty of the 80 patients were known to have died, and 6 patients were lost to follow-up before 1972. The remaining 14 patients were alive when last seen between

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1975 and 1994, and 9 of the 14 were known to be alive in 1994.

Clinical Presentation

The presenting features or initial diagnoses were reported previously.[22] The median age at the time of diagnosis was 42 years (range, 16 to 75). Forty-three (84 percent) of the 51 patients for whom reliable information was available had episodes of hemoglobinuria as a chief symptom at some time during their illness.

Course of Illness and Survival

The course of the disease in each of the 80 patients is shown in Figure 1. From the actuarial survival curve for the group, we calculated a median survival of approximately 10 years (Fig. 2). Twenty-five years after the diagnosis, 58 patients (72 percent) had died, and 22 (28 percent) were alive. The median age at the time of death was 56 years (range, 20 to 84), with a median interval of 10 years (range, 0 to 48) between diagnosis and death. Patient 10 received the diagnosis of PNH in 1939, had a spontaneous remission in 1949, and died of bronchial carcinoma in 1987, 48 years after the diagnosis.

Cause of Death

For 12 of the 60 patients who died (Table 1), the cause of death was unknown. In 28 of the other 48 patients (58 percent), the cause of death (either thrombosis or hemorrhage attributable to thrombocytopenia) was directly related to PNH. In the other 20 patients (42 percent), the cause of death was unrelated to PNH.

Venous Thrombosis

Thirty-one patients (39 percent) were known to have had one or more episodes of venous thrombosis during the course of their illness (Table 2), and several patients had repeated thromboses. In many patients the thrombosis was either fatal or life-threatening, and it was often unheralded.

Spontaneous Remission

Twelve patients (15 percent) had spontaneous clinical remissions (Fig. 1), with negative Ham's tests in all nine who were tested. We later obtained blood samples from five of these nine patients; in all five the erythrocytes expressed normal levels of glycosylphosphatidylinositol-linked proteins, with no demonstrable PNH-affected erythrocytes (Fig. 3A). In addition, of the four patients tested, none had PNH-affected neutrophils (Fig. 3A), but three of the four had small numbers of PNH-affected lymphocytes (Fig. 3B). Further analysis by double fluorescent staining demonstrated a subpopulation of PNH-affected lymphocytes among CD4+

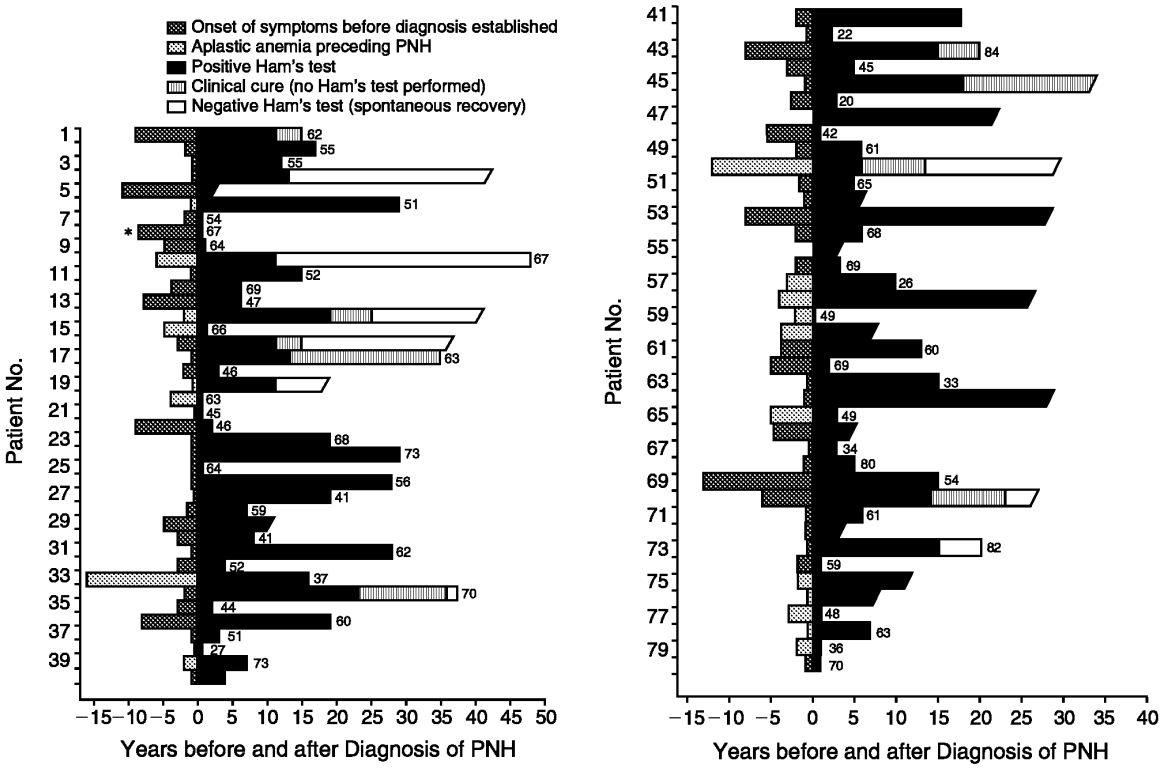


Figure 1. Course of Illness in 80 Consecutive Patients with PNH.

The x axis indicates the years before and after the diagnosis of PNH, which is denoted by the zero on the axis. Bars ending in a straight line indicate patients who died, and their ages at death are shown; bars ending in a diagonal line indicate surviving patients. Nine patients had complete clinical recovery, with negative Ham's tests. Three additional patients had protracted clinical remissions, but Ham's test was not repeated during remission. The asterisk indicates a prolonged but unspecified period of symptoms before the diagnosis was established.

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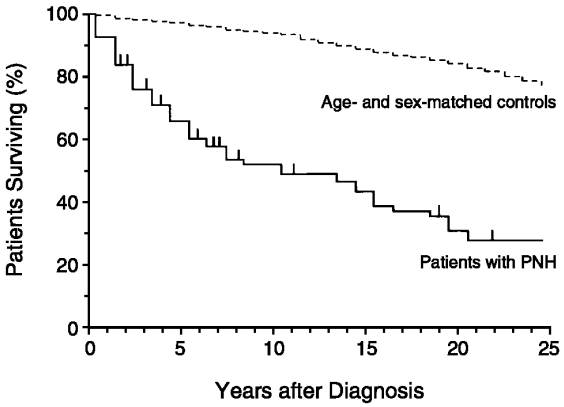


Figure 2. Actuarial Survival from the Time of Diagnosis in 80 Patients with PNH.

The median survival was 10 years. The expected survival of an age- and sex-matched control group is shown for comparison.

T cells, CD8+ T cells, and CD19+ B cells in all three patients.

Associated Disorders

Twenty-three patients (29 percent) received a diagnosis of aplastic anemia before the diagnosis of PNH. Nine of these patients subsequently had hemolytic PNH, with episodes of overt hemoglobinuria, and six did not; whether the remaining eight patients ever had hemoglobinuria could not be reliably determined.

At the time of the diagnosis, 64 of the 80 patients (80 percent) had thrombocytopenia (platelet count, <150,000 per cubic millimeter), and 38 patients (48 percent) had severe thrombocytopenia (platelet count, <50,000 per cubic millimeter). In addition, 44 patients (55 percent) had neutropenia (neutrophil count, <1500 per cubic millimeter).

In five patients the disorder progressed from hemolytic PNH to aplasia. Ham's test remained positive in four of these patients, but the fifth (Patient 34) subsequently had a negative Ham's test, with no PNH-affected erythrocytes or neutrophils. The patient died from bleeding due to severe thrombocytopenia 37 years after the diagnosis of PNH and at least 8 years after Ham's test had become negative.

Leukemia was not known to have developed in any of the patients.

Discussion

Clinical Features

In this group of 80 patients who were followed for up to 48 years, the median actuarial survival was 10 years, with 28 percent of the patients surviving for 25 years. Death was directly attributable to PNH or to bone marrow hypoplasia in 58 percent of the patients who died. Therapy with platelet concentrates should reduce mortality from hemorrhage due to thrombocytopenia.

At least 39 percent of the patients had venous thrombosis at some time during their illness. Many patients had initial thromboses that were life-threatening, but two (Patients 17 and 70), who probably had postpartum hepatic-vein thrombosis, recovered and survived for 34 and 27 years, respectively, after the thrombosis. One other patient (Patient 34) survived for 24 years after a thrombosis of the inferior mesenteric vein.

Spontaneous Remission

In some patients with PNH, the severity of the illness diminishes with time,[25] and some patients have a complete clinical remission,[22,26] although laboratory abnormalities may persist for years.[27] In this series 15 percent of the patients had spontaneous clinical remissions, and Ham's test became negative in the patients who were tested. Neither the severity of symptoms or complications nor the proportion of red cells lysed in Ham's test was correlated with an eventual remission. Among the patients with remissions, one (Patient 14) had severe, transfusion-dependent PNH and thromboses, and at

Table 1. Causes of Death in 60 Patients with PNH.

Cause of Death	No. of Patients
Probably related to PNH	
Venous thrombosis	
Hepatic vein	7
Inferior vena cava	1
Cerebral vein	1
Mesenteric vein	2
Pulmonary embolism	3
Hemorrhage	
Gastrointestinal	6
Subarachnoid	3
Intracerebral	2
Miscellaneous	
Liver failure	2
Intraabdominal event	1
Probably unrelated to PNH	
Arterial thrombosis	
Myocardial infarction	6
Cerebrovascular accident	2
Bronchopneumonia	3
Chronic obstructive airways disease plus cor pulmonale	2
Cardiac tamponade	1
Constrictive pericarditis	1
Renal failure	1
Amyloidosis	1
Lymphoma	1
Bronchial carcinoma	1
Epilepsy	1
Unknown	12

Table 2. Sites and Types of Thrombosis.

Site and Type of Thrombosis	No. of Patients
Intraabdominal	
Hepatic vein	8
Inferior vena cava	3
Mesenteric vein	4
Splenic vein	1
Renal vein	1
Unspecified	1
Other venous sites	
Cerebral vein	4
Pulmonary embolism	9
Deep vein	7
Superficial	3
Arterial	
Myocardial infarction	6
Cerebrovascular accident	2

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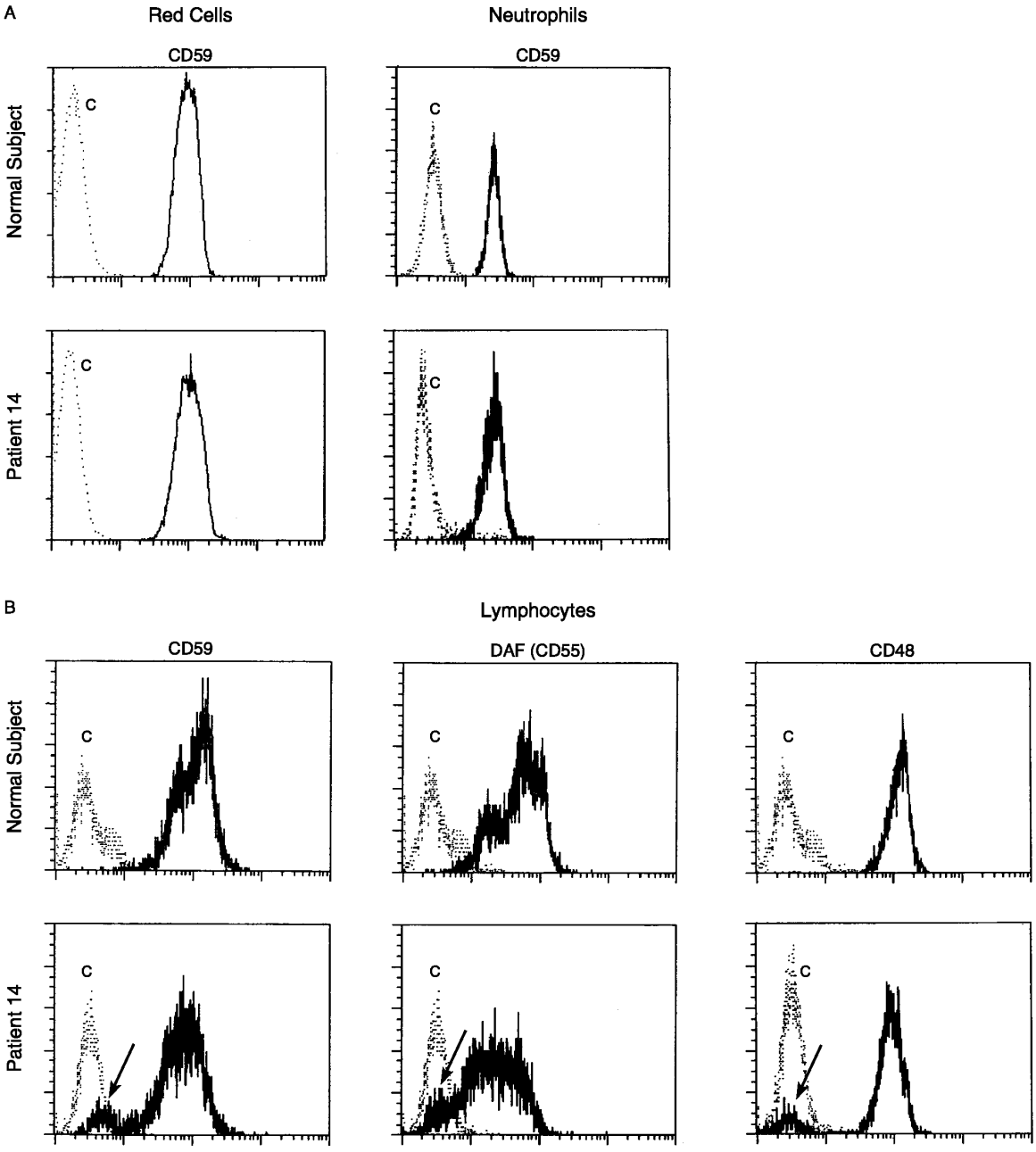


Figure 3. Flow-Cytometric Analysis of Blood Cells from a Normal Subject and Patient 14 after Spontaneous Recovery from PNH.

The analysis was carried out 20 years after the patient's clinical remission began and 17 years after her Ham's test had become negative. Panel A shows a unimodal distribution of cells with normal reactivity after reaction with anti-CD59 antibody (a molecule absent from the surface of PNH-affected cells). The distributions obtained with the patient's red cells and neutrophils are indistinguishable from those of the cells from a normal subject, demonstrating that no PNH-affected cells remain. C indicates distributions obtained in control experiments with an antibody directed against a molecule absent from normal blood cells.

Panel B shows the results of an analysis, similar to that in Panel A, carried out on peripheral-blood lymphocytes. The distributions of cells from a normal subject show that, as compared with the results of analyses with negative control antibody (C), all the lymphocytes reacted with all three antibodies used. The distribution is unimodal for CD48 and bimodal for CD59 and CD55. In contrast, the cells from Patient 14 have a small population of lymphocytes that are unreactive with all three antibodies (arrows), which indicates that these cells lack the corresponding antigen protein molecules on their surfaces. The fact that there is a peak of antigen-negative cells for three different proteins that are normally attached to the cell membrane by a glycosylphosphatidylinositol anchor means that the anchor is absent, which is characteristic of the PNH phenotype. The finding that the PNH clone was still present when there were no PNH-affected erythroid or myeloid cells in Patient 14 during a clinical and hematologic remission is consistent with the notion that this clone does not have a selective advantage once normal hematopoiesis has resumed. DAF denotes decay-accelerating factor.

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least two had over 50 percent lysis in earlier Ham's tests, suggesting that they had few residual normal stem cells at the height of their illness. The spontaneous remissions occurred between 10 and 20 years after the diagnosis of PNH. Of the 35 patients who survived 10 years or more, 12 (34 percent) eventually had remissions. A possible explanation for spontaneous remission is that the clones of PNH-affected cells have a finite life span, like normal somatic cells. Recovery may thus depend on the presence of normal stem cells capable of repopulating the bone marrow.[28]

There were no erythrocytes or neutrophils affected by PNH after recovery, but three of four patients tested had some residual abnormal lymphocytes. These results are consistent with the fact that lymphocytes have a much longer life span than myeloid and erythroid cells and that committed lymphocyte progenitor cells undergo division less frequently than the other cells. If the aging process postulated as being responsible for the gradual disappearance of clones of PNH-affected cells is related to the number of cell divisions, this may explain why abnormal lymphocytes persist for many years after the disappearance of abnormal neutrophils and erythrocytes.

PNH and Bone Marrow Failure

The data on this series of patients provide further evidence of the close relation between PNH and aplastic anemia. The coexistence of the two conditions in one patient was first reported in 1944,[29] with subsequent reports in 1952[30] and 1961.[31] Cultures of peripheral blood and bone marrow from patients with PNH consistently show reduced numbers of erythroid progenitor cells (erythroid burst-forming units) and myeloid progenitor cells (granulocyte–macrophage colony-forming units), even in the absence of pancytopenia,[32,33] as in patients with aplastic anemia.[34] In addition, PNH eventually develops in 10 to 31 percent of patients with aplastic anemia treated with immunosuppressive agents.[35] It is important to emphasize that PNH is not a complication of immunosuppressive treatment. Instead, the majority of patients with this disorder probably have an underlying aplastic process. Clones of PNH-affected cells may thus have a relative growth or survival advantage over the residual normal bone marrow in patients who have aplastic anemia.[1,28,36] It is conceivable that the mutation leading to the development of PNH occurs quite frequently but that, in the absence of marrow hypoplasia, the clone has difficulty establishing itself.[28]

PNH and Leukemia

Because of the reports of myelodysplasia and leukemia[1] — invariably, acute myeloid leukemia — in patients with PNH, it has been regarded as a preleukemic condition. Leukemia did not develop in any of our 80 patients, however, indicating that it is relatively rare in unselected patients with PNH. Acute myeloid leukemia eventually develops in approximately 5 percent of patients with aplastic anemia who survive the marrow aplasia.[35] Thus, aplastic anemia may predispose patients to both PNH and acute myeloid leukemia, but the development of PNH may not add to the risk of leukemia associated with uncomplicated aplastic anemia.

In most reported cases of leukemia in patients with PNH in whom the leukemic cells were studied,[37,38] the leukemic clone was derived from the PNH clone. According to a recent report of a patient with PNH who subsequently had a myelodysplastic syndrome, the blasts expressed normal levels of glycosylphosphatidylinositol-linked proteins,[39] indicating that the leukemic event may occur in the residual normal stem cells.

Management

The natural history of PNH is an important factor in decisions about therapy for individual patients. Thrombolytic treatment of hepatic-vein thrombosis with tissue plasminogen activator has been reported to be effective.[40] Oral anticoagulation therapy after venous thrombosis has been used since the 1950s.[25] In view of the high incidence of potentially fatal thrombosis, a strong case can be made for prophylactic anticoagulation treatment in all patients with PNH in whom there is no contraindication (such as severe thrombocytopenia). This approach may improve survival and reduce morbidity.

The only curative therapy at present is bone marrow transplantation, but it is available to only a small proportion of patients and is associated with substantial morbidity and mortality. The recent advances in the understanding of the pathogenesis of PNH and, in particular, of the molecular lesion open opportunities to explore new treatments, such as gene therapy. The possibility of spontaneous remission and of long-term survival must be taken into account when considering either bone marrow transplantation or other new treatments for this disorder.

We are indebted to the late Miss Eleanor Lloyd for her assistance in this project, to the patients, and to the physicians who originally referred the patients and provided follow-up data.

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Samsung Bioepis Exhibit No. 1002
Page 12023

APPENDIX U

bjh research paper

Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria

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Summary

Paroxysmal nocturnal haemoglobinuria (PNH) is characterized by chronic, uncontrolled complement activation resulting in elevated intravascular haemolysis and morbidities, including fatigue, dyspnoea, abdominal pain, pulmonary hypertension, thrombotic events (TEs) and chronic kidney disease (CKD). The long-term safety and efficacy of eculizumab, a humanized monoclonal antibody that inhibits terminal complement activation, was investigated in 195 patients over 66 months. Four patient deaths were reported, all unrelated to treatment, resulting in a 3-year survival estimate of 97·6%. All patients showed a reduction in lactate dehydrogenase levels, which was sustained over the course of treatment (median reduction of 86·9% at 36 months), reflecting inhibition of chronic haemolysis. TEs decreased by 81·8%, with 96·4% of patients remaining free of TEs. Patients also showed a time-dependent improvement in renal function: 93·1% of patients exhibited improvement or stabilization in CKD score at 36 months. Transfusion independence increased by 90·0% from baseline, with the number of red blood cell units transfused decreasing by 54·7%. Eculizumab was well tolerated, with no evidence of cumulative toxicity and a decreasing occurrence of adverse events over time. Eculizumab has a substantial impact on the symptoms and complications of PNH and results a significant improvement in patient survival.

Keywords: eculizumab, paroxysmal nocturnal haemoglobinuria, phase III, long-term therapy, haemolysis.

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, progressive and life-threatening haematopoietic stem cell disorder. It is characterized by complement-mediated intravascular haemolysis and a prothrombotic state (Brodsky, 2009; Hillmen *et al*, 2010). PNH may be diagnosed in patients of all ages, but the median age is in patients in their early 30s (Socié *et al*, 1996; Nishimura *et al*, 2004). Despite best historical supportive care, including transfusions and

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Page 12025

anticoagulation management, PNH is fatal in approximately 35% of patients within 5 years of diagnosis (Hillmen *et al*, 1995; Socié *et al*, 1996; Kelly *et al*, 2011).

The disease arises from a somatic mutation in the phosphatidylinositol glycan class A gene (*PIGA*), which disrupts synthesis of glycosylphosphatidylinositol (GPI), a molecule that anchors proteins to cell membranes (Takeda *et al*, 1993). The mutation results in the reduction or complete absence of the GPI-anchored complement regulatory proteins CD55 and CD59, which renders the cells sensitive to complement-mediated destruction (Rother *et al*, 2005; Kelly *et al*, 2009). All blood cells are susceptible to complement-mediated attack, although red blood cells are the most susceptible to lysis (Parker, 1991; Pu & Brodsky, 2011).

Complement activation in PNH is manifested as chronic haemolysis that leads to the release of free haemoglobin and the subsequent depletion of nitric oxide. Consumption of nitric oxide leads to vaso-occlusion and platelet activation and results in the common morbidities seen in PNH, such as fatigue, dyspnoea, recurrent abdominal pain, dysphagia, chest pain and pulmonary hypertension. More importantly, chronic haemolysis renders PNH patients at a greater risk of thrombotic events (TEs), renal insufficiency and other organ damage, and premature mortality. Compared with the general population, patients with PNH have a 62-fold higher risk of a TE (McKeage, 2011) and a six-fold greater risk of chronic kidney disease (CKD) (Hillmen *et al*, 2010). TEs have been reported to account for up to 67% of PNH-related deaths (Hillmen *et al*, 2007), while CKD has been reported to account for 8–18% of disease-related mortality (Clark *et al*, 1981; Nishimura *et al*, 2004).

Historically, supportive care measures used in PNH, such as transfusions, anticoagulation or long-term use of steroids and pain medication, leave patients with a poor quality of life and are associated with adverse events. In addition, supportive care measures do not prevent the occurrence of catastrophic events, such as thromboses and CKD, that have recently been associated with elevated risk of premature mortality (Hillmen *et al*, 2004, 2006, 2007, 2010; Rother *et al*, 2005; Brodsky *et al*, 2008; de Latour *et al*, 2009; Hill *et al*, 2010; Kelly *et al*, 2011).

Eculizumab, a humanized monoclonal antibody, inhibits the terminal complement cascade by binding uniquely to human complement protein C5, thereby inhibiting the formation of pro-inflammatory, prothrombotic C5a, and C5b, with subsequent inhibition of assembly of the membrane attack complex (Hillmen *et al*, 2006; Brodsky *et al*, 2008). Although eculizumab suppresses the terminal complement system, the proximal complement system, responsible for opsonization of microorganisms and clearance of immune complexes, remains intact and fully functional (Rother *et al*, 2007). A series of multinational clinical trials demonstrated that eculizumab therapy is well tolerated, leads to a rapid and clinically significant reduction in intravascular haemolysis and, thus, provides substantial clinical benefits (Hillmen *et al*, 2004, 2006, 2007, 2010; Rother *et al*, 2005; Brodsky *et al*, 2008; Hill *et al*, 2010). By inhibiting terminal complement activation and intravascular haemolysis, treatment with eculizumab significantly reduces TEs (Hillmen *et al*, 2007), transfusion requirements (Hillmen *et al*, 2006) and pulmonary hypertension (Hill *et al*, 2010, 2012) and significantly improves renal function (Hillmen *et al*, 2010), gastrointestinal pain (Hill *et al*, 2005a) and patient quality of life (Hillmen *et al*, 2006).

Clinical benefit occurs rapidly in patients with PNH following the initiation of eculizumab. Here we report on continuous administration of eculizumab (for up to 66 months) and the impact of long-term therapy on clinical outcomes in PNH. In addition, we provide greater insight into the safety profile of long-term eculizumab therapy for PNH.

Methods

Study design and patients

This manuscript reports on the long-term safety and efficacy of eculizumab in 195 patients with haemolytic PNH who had participated in one of three prospective parent trials: the Phase II pilot study (Hillmen *et al*, 2004; Hill *et al*, 2005b) and its extensions, the Phase III TRIUMPH (Transfusion Reduction Efficacy and Safety Clinical Investigation, a Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Haemoglobinuria) study (NCT00122330) (Hillmen *et al*, 2006), or the Phase III SHEPHERD (Safety in Hemolytic PNH Patients Treated With Eculizumab: A Multi-Center Open-Label Research Design) study (NCT00130000) (Hillmen *et al*, 2007; Brodsky *et al*, 2008). At the end of these initial studies, 187 of the 195 patients (95·9%) enrolled in an open-label extension study (Fig 1). All patients had a minimum of 10% PNH red blood cells at enrolment in the parent trials and were vaccinated with a meningococcal vaccine at least 14 d before the first eculizumab infusion in the parent studies. It was recommended that all patients be revaccinated at intervals of between 2·5 and 3 years, with meningococcal vaccine titre assays collected prior to and within 1–2 months of the revaccination. All three parent trials employed the same dosing regimen: 600-mg infusions of eculizumab every week for 4 weeks, followed 1 week later by a single 900-mg dose, and then a maintenance dose of 900 mg every 14 (±2) days until the end of the study. In the extension study patients continued to receive the maintenance dose of eculizumab.

The first clinical investigation of eculizumab was an open-label, 12-week, Phase II pilot study that enrolled 11 patients at two UK study centres, all of whom continued into two extension studies: the first of 52 weeks duration and the second of 104 weeks duration. The positive outcomes from this study (Hillmen *et al*, 2004, 2007) resulted in the initiation of two pivotal phase III studies.

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Page 12026

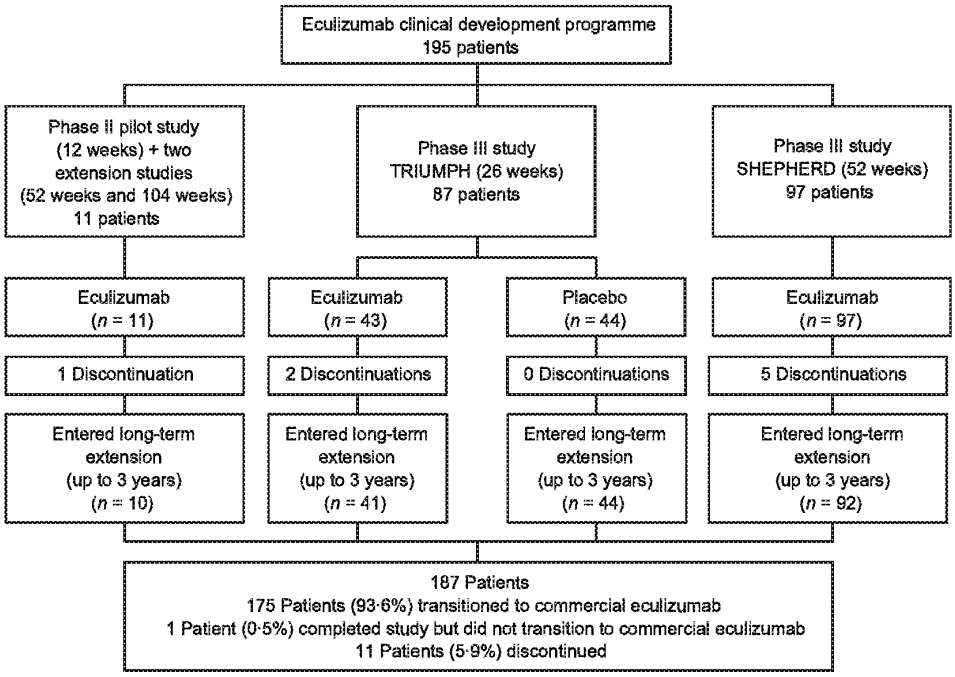


Fig 1. Phase II and III PNH clinical trials overview.

The first pivotal study, TRIUMPH, was a 26-week, double-blind placebo-controlled trial that included 87 patients randomized to either eculizumab ($n = 43$) or placebo ($n = 44$) (Hillmen *et al*, 2006). Patients were required to have had at least four transfusions during the previous 6 months for anaemia or anaemia-related symptoms, platelet counts $\geq 100 \times 10^9$/l and lactate dehydrogenase (LDH) levels $\geq$ 1·5-fold the upper limit of the normal range.

The open-label, single-arm SHEPHERD trial lasted 52 weeks and included 97 patients. The patient eligibility criteria for this study were broadened to include patients with fewer transfusion requirements (as low as one transfusion within 24 months prior to initiating eculizumab treatment) and more severe bone marrow dysfunction (platelet counts as low as 30×10^9/l) (Hillmen *et al*, 2007; Brodsky *et al*, 2008).

The long-term extension study comprised a 104-week treatment period and a 16-week post-treatment follow-up period for any patients who terminated treatment early. Patients who completed the 2-year long-term extension before eculizumab was commercially available or accessible were allowed to continue receiving the investigational product until the drug was approved in their country.

Study endpoints

Efficacy assessments were performed at least every 2 weeks from the time of initiation of eculizumab therapy in the parent study. Efficacy measures included patient survival, degree of haemolysis (as measured by blood LDH levels), TE incidence rate, mean change from baseline in haemoglobin and the number of units of transfused packed red blood cells (PRBCs) administered. Assessments of renal function were performed over the duration of the study by determining the CKD stage using formulas for estimated glomerular filtration rate (GFR) developed by the Modification of Diet in Renal Disease Study Group (Levey *et al*, 1999; Stevens *et al*, 2006). Specifically, stage 0 was defined as GFR >90 ml/min/1·73 m^2 with no evidence of kidney damage; stage 1 as GFR >90 ml/min/1·73 m^2 with evidence of kidney damage; stage 2 as GFR 60–90 ml/min/1·73 m^2 with evidence of kidney damage (proteinurea assessed by dipstick or abnormal imaging findings); stage 3 as GFR 30–60 ml/min/1·73 m^2; stage 4 as GFR 15–30 ml/min/1·73 m^2; and stage 5 as GFR <15 ml/min/1·73 m^2. The number of transfusion-independent, compared with transfusion-dependent, patients was assessed over time. The baseline period was defined as the 6 months prior to the initiation of eculizumab. At treatment evaluation, transfusion-independent patients were defined as those who did not require a blood transfusion during the previous 6 months, and transfusion-dependent patients had received at least one blood transfusion in the previous 6 months.

Safety assessments included solicited monitoring of adverse events (AEs), clinical laboratory tests and vital signs. AEs were coded using the Medical Dictionary for Regulatory Activities (MEDDRA®) version 6.1, with AEs relating to infection and infection-related serious AEs (SAEs) tabulated separately consistent

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Page 12027

with the expanded MedDRA preferred terms (http://www.meddramsso.com). In addition, all AEs were reviewed for events that could potentially be related to an infection and classified accordingly. AEs were assessed for severity and classified as mild (events requiring minimal or no treatment and not interfering with the patient's daily activities), moderate (events resulting in a low level of inconvenience or concern with the therapeutic measures and possibly causing some interference with functioning) or severe (events that are usually incapacitating and interrupting usual daily activities that may require systemic drug therapy or other treatment).

An SAE was defined as any event that resulted in death, was immediately life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. Important medical events that did not result in death or require hospitalization and were not life threatening may have been considered SAEs if, based upon appropriate medical judgment, they required medical or surgical intervention to prevent one of the outcomes listed previously.

Statistical analyses

Baseline was defined as the pre-eculizumab value collected from the parent study, except for those patients in the TRIUMPH study who received placebo where baseline was the value collected at the final visit of this study. Least-squares mean changes from baseline in LDH levels were analysed using a repeated-measure analysis of variance model, including time of treatment, parent study and parent study treatment as fixed effects. The signed-rank test was used to analyse mean changes from baseline in haemoglobin. Change in CKD stage was analysed using the Mantel–Haenszel chi-squared test. An improvement in renal function was defined as a categorical documented reduction in CKD stage, and a worsening in renal function was defined as a categorical documented increase in CKD stage.

Comparisons of the reporting of AEs by patients during the first 26 weeks of treatment with eculizumab and the last 26 weeks of treatment were tested using a one-tailed exact McNemar test using matched-pairs data. For any patient who remained in the study for <52 weeks, the incidence of AEs reported during the first 26 weeks of treatment was compared with the incidence of AEs from 26 weeks + 1 d until the patient's last dose of eculizumab.

Two patient populations were identified for statistical analyses. All patients who had completed at least 26 weeks of randomized treatment in one of the parent studies and had received at least one dose of eculizumab in the extension study were included in the safety population; patients from this population who had no major protocol violations were included in the per-protocol population. All analyses were performed on an intent-to-treat basis. A P value of <0.05 was considered to be statistically significant.

Table I. Baseline patient characteristics.

Parameter	Eculizumab (n = 195)
Age, years	
Median (range)	39·7 (18·3–85·0)
Mean (SD)	41·3 (14·37)
Median disease duration (range), months	81·5 (12·0–483·8)
Gender, n (%)	
Female	106 (54·4)
Male	89 (45·6)
Race, n (%)	
Caucasian	176 (90·2)
Black	7 (3·6)
Asian	6 (3·1)
Other	6 (3·1)
History of aplastic anaemia, n (%)	56 (28·7)
History of myelodysplastic syndrome, n (%)	3 (1·5)
Haemoglobin, g/l	
Mean (SE)	93·7 (1·14)
Range	48·0–143·0
Lactate dehydrogenase, u/l (upper limit of normal: 223 U/l)	
Mean (SE)	2293·3 (84·38)
Median	2129
Range	499–10 300

SD, standard deviation; SE, standard error.

Results

Study population and baseline characteristics

Baseline characteristics of all 195 patients at the start of the parent trials are shown in Table I. Overall median age was 39·7 years (range: 18–85 years); more than 90% of the patients were Caucasian and 54% were female. The majority of patients (92%) were <65 years of age. Twenty-nine percent of patients had a history of aplastic anaemia and 1·5% had a history of myelodysplastic syndrome.

The entire period of eculizumab administration across the parent and extension trials was 66 months, although a 36-month cut-off was used for safety and efficacy assessments to ensure that there were a sufficient number of patients for robust statistical analysis. Of the patients included in this 36-month cut-off, the overall median treatment duration was 30·3 months, with a range of 10·0–66·1 months (interquartile range: 26·2–33·1 months). During maintenance dosing, 21 patients (10·8%) deviated from the protocol dosing interval by receiving treatment <12 d apart on at least one occasion. Of the original 195 patients, 19 patients (9·7%) discontinued treatment over a period of 66 months: nine discontinued because of an AE (see 'Safety'), seven withdrew consent, two were discontinued based on the decision of the investigator and one was

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Page 12028

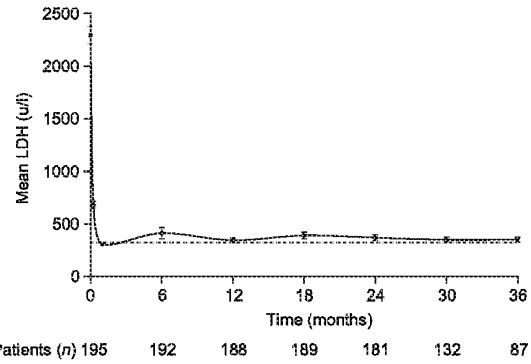


Fig 2. Lactate dehydrogenase level, a marker of intravascular haemolysis, was rapidly and consistently reduced from baseline ($P < 0{\cdot}001$ at all time points from 1 month) following initiation of eculizumab therapy. Dashed line represents the upper limit of the normal range (103–223 u/l). The decrease in number of patients was due to the transition of patients to commercially available eculizumab. LDH, lactate dehydrogenase.

noncompliant with the protocol (Fig 1). Eight of the discontinuations (six withdrawn consents and two AEs) occurred during a parent trial, and the remaining 11 discontinuations (seven AEs, two investigator's decision, one withdrawn consent, one non-compliance) occurred during the long-term extension study.

Intravascular haemolysis

All patients showed a rapid decrease from baseline in serum LDH, a marker for intravascular haemolysis, which was generally sustained with continued treatment, although throughout the course of the study some patients did have transient increases in LDH. Prior to the first administration of eculizumab, median LDH concentration was 2129 u/l (range: 499–10 300 u/l; upper limit of normal: 223 u/l). One month after eculizumab treatment initiation, median LDH decreased to 263 u/l (range: 93–1208 u/l; $P < 0{\cdot}0001$; Fig 2), a relative reduction of 87·6%. This decrease was maintained with sustained eculizumab treatment; the median LDH value at 36 months was 279 u/l (range: 88–1417 u/l), a relative reduction from baseline of 86·9%.

Plasma levels of eculizumab and haemolytic activity were reviewed for 140 patients: 43 patients from the TRIUMPH study and 97 patients from the SHEPHERD trial. Following the first dose of eculizumab, trough concentrations <35 μg/ml were observed in 49 of 135 patients (36·3%) with available samples. Overall, 36 of these 49 patients (73·5%) exhibited haemolysis as measured by a validated pharmacodynamic assay (haemolysis >20%). Multiple occurrences of trough eculizumab concentrations <35 μg/ml were observed in 14 of 140 reviewed patients (10·0%). These patients generally had more rapid eculizumab clearance (>0·4 ml/h/kg) or shorter eculizumab half-life (<130 h) than the respective median values of the trial populations as a whole.

None of the patients with breakthrough haemolysis discontinued treatment with eculizumab. In seven of the 14 patients (50·0%), the breakthrough haemolysis was successfully mitigated, as evidenced by reductions in LDH concentrations, by decreasing the eculizumab dosing interval to <14 d. None of these patients experienced SAEs relating to haemolysis. In the whole population, 21 of 195 patients (10·8%) had a median of 22 decreases (range: 3–124) in dosing intervals.

Haemoglobin levels and transfusion requirements

Treatment with eculizumab resulted in a steady increase in the serum haemoglobin concentration from baseline (93·7 g/l), including a mean increase from baseline of 5·5 g/l (range: −32·0 to 55·0 g/l) to 99·2 g/l after 2 weeks of treatment and 10·4 g/l (range: −42·0 to 81·0 g/l) to 104·7 g/l by 24 months, which was maintained at 36 months (Table II). The percentage of patients who achieved transfusion independence increased with sustained treatment (Fig 3). The percentage of patients achieving transfusion independence was 82·1% (64 of 78) by the last 6 months of treatment, compared with only 8·2% (16 of 195) in the 6 months prior to the start of treatment, a relative increase of 90.0%. Fourteen of 78 patients (17·9%) continued to require transfusions between months 30 and 36. Despite the need for transfusions, these 14 patients maintained a significant reduction in LDH from baseline levels ($P < 0{\cdot}0001$), and the number of units of PRBCs transfused over the course of the study significantly decreased from a mean of 11·2 units in the 6 months prior to starting eculizumab to 3·5 units between months 30 and 36 ($P = 0{\cdot}0001$). The change from baseline in the number of units of PRBCs administered to all patients receiving transfusions over the course of the study is presented in Table II.

Thrombotic events

Prior to initiation of eculizumab, 63 of 195 patients (32·3%) experienced 124 TEs, both venous and arterial, over a total of 1683 patient-years. These TEs included deep-vein thrombosis, hepatic vein (Budd-Chiari syndrome), cerebrovascular accident, mesenteric thrombosis and pulmonary embolism. The percentage of patients free from TEs increased from 67·7% before treatment to 96·4% during treatment: seven patients (3·6%) reported a total of 10 TEs over 467·1 patient-years. Of these seven patients, five had a history of TEs prior to starting treatment with eculizumab and four were receiving concomitant anticoagulation therapy (including warfarin and low-molecular-weight heparins). Of the 10 TEs reported during eculizumab treatment, five were reported as thrombophlebitis/deep vein thrombosis (three events occurred in the same patient), one as deep vein thrombosis, one as retinal vein thrombosis and one as a possible thrombosis in a fistula. The remaining patient experienced portal vein thrombosis and splenic infarcts. The

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Page 12029

Table II. Mean number of packed red blood cells transfused and haemoglobin concentrations throughout the study.

	Units of packed red blood cell transfused				Haemoglobin (g/l)*			
Study period, months	*n*	Mean (SE) [range]	Mean (SE) [range] change from baseline	*P* value	*n*	Mean (SE) [range]	Mean (SE) change from baseline	*P* value
Baseline	164	5·3 (0·22) [1–13]			195	93·7 (1·14) [48–143]		
0–3†	74	4·4 (0·33) [1–13]	−1·5 (0·38) [−8 to 6]	0·0001	195	99·2 (1·05) [64–136]	5·5 (0·96)† [−32 to 55]	<0·0001
3–6	76	4·7 (0·37) [1–19]	−1·5 (0·42) [−9 to 9]	0·0007	193	101·6 (1·15) [65–146]	7·7 (1·41) [−34 to 56]	<0·0001
6–9	61	4·8 (0·40) [2–14]	−1·1 (0·50) [−11 to 9]	0·0293				
9–12	58	4·6 (0·41) [2–18]	−1·7 (0·54) [1–13]	0·0025	190	100·5 (1·23) [36–152]	6·8 (1·51) [−54 to 55]	<0·0001
12–15	62	3·6 (0·29) [1–12]	−2·5 (0·49) [−9 to 10]	0·0001				
15–18	50	4·2 (0·32) [1–11]	−2·0 (0·55) [−11 to 6]	0·0006	189	103·0 (1·21) [63–168]	8·8 (1·45) [−36 to 80]	<0·0001
18–21	50	4·3 (0·51) [1–19]	−2·1 (0·65) [−11 to 15]	0·0022				
21–24	42	4·6 (0·61) [1–17]	−1·4 (0·64) [−11 to 11]	0·0333	178	104·7 (1·23) [65–169]	10·4 (1·59) [−42 to 81]	<0·0001
24–27	37	4·0 (0·49) [1–13]	−2·9 (0·65) [−11 to 4]	<0·0001				
27–30	30	4·4 (0·95) [1–24]	−1·5 (0·98) [−9 to 18]	0·1298	135	106·7 (1·44) [66–159]	11·1 (1·86) [−30 to 71]	<0·0001
30–33	10	3·1 (0·55) [1–7]	−3·0 (0·65) [−6 to 1]	0·0013				
33–36	7	2·4 (0·30) [2–4]	−3·6 (1·13) [−10 to −1]	0·0196	86	105·6 (1·79) [64–146]	9·5 (2·20) [−31 to 68]	<0·0001

SE, standard error.

*Haemoglobin assessment at the end of corresponding study period.

†Haemoglobin assessment occurred 2 weeks after treatment initiation.

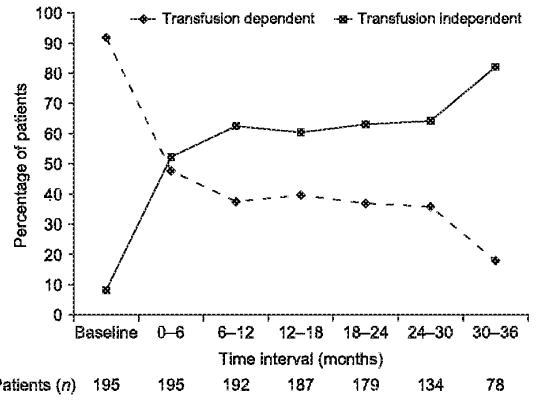


Fig 3. Percentage of transfusion-independent and transfusion-dependent patients over time. Transfusion-independent patients were those who did not require a blood transfusion during the previous 6 months; transfusion-dependent patients had received at least one blood transfusion in the previous 6 months.

median time from the first dose of eculizumab to the first TE was 646 d (approximately 21 months), with a range of 170–876 d (approximately 5·6–29·0 months).

A time-matched analysis showed that in the 467·1 patient-years prior to eculizumab treatment, there were a total of 52 TEs reported in 25 patients. The administration of eculizumab reduced the TE incidence rate from 11·13 events per 100 patient-years to 2·14 events per 100 patient-years, a relative reduction of 81·8% ($P < 0·0005$).

Overall, 98 patients (50·3%) were treated with anticoagulants prior to or coincident with eculizumab: 11 patients before the start of the study, 84 patients both before and during treatment with eculizumab and three patients during the study following a TE. Of the 95 patients who were treated with an anticoagulant prior to the start of the study, 58 (61·1%) experienced at least one TE before receiving eculizumab. Eleven patients, six of whom had a prior history of TEs, discontinued anticoagulant therapy while receiving eculizumab. None of these 11 patients experienced a TE after discontinuation of anticoagulant therapy.

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Page 12030

Chronic kidney disease

Chronic kidney disease stages (National Kidney Foundation, 2002) were assessed following each 6-month eculizumab treatment period. Previous reports on this patient population have demonstrated that prior to eculizumab treatment, 64% of patients had evidence of CKD (Hillmen *et al*, 2010). There was a time-dependent improvement in renal function. The percentage of patients showing improvement, worsening or no change in CKD was 25·4%, 6·1% and 68·5% respectively, at 6 months compared with 44·8%, 6·9% and 48·3% respectively, at 36 months. Overall, following 36 months of treatment with eculizumab, 93·1% of patients showed either an improvement or stabilization in CKD, and patients were significantly more likely to experience an improvement than a worsening in renal function ($P = 0·015$).

Patient survival

Four of the 195 patients died while on eculizumab treatment; the Kaplan–Meier estimate of patient survival at 36 months was 97·6% [95% confidence interval (CI), 93·7–99·1%], which was sustained out to 66 months (Fig 4). Mean duration of therapy with eculizumab was 399 d (range: 60–720 d). Three deaths were caused by concomitant conditions: chronic myelomonocytic leukaemia in a 71-year-old patient who had a history of myelodysplasia and died after 208 d of eculizumab therapy; metastases of pre-existing stomach adenocarcinoma in a 63-year-old patient who died after 609 d of therapy; and cerebral herniation in a 31-year-old patient who died after 60 d of therapy. During in-patient care for a pulmonary embolism, following a series of hospitalizations for a disc prolapse, pneumonia and renal failure, the patient started hyperventilating with his pupils becoming dilated. A computerized tomography scan of the brain revealed a marked left hemorrhagic cerebral arterial media infarct with clear signs of cerebral herniation and the start of cerebrospinal fluid block. The last assessment of LDH levels, almost 4 weeks prior to the event, were below the patient's chronic baseline haemolytic state, leading the investigator to conclude that no serious haemolysis was present at that time.

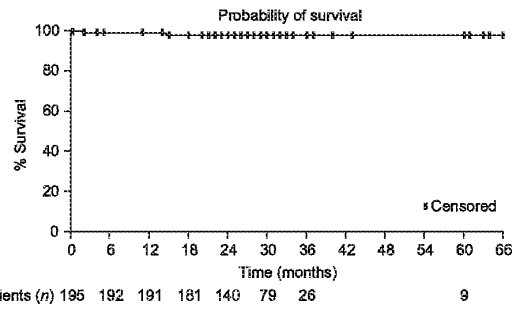


Fig 4. Long-term survival with eculizumab therapy.

The fourth patient, a 35-year-old with unconfirmed aplastic anaemia who had received therapy for 720 d, experienced an arteriovenous thrombosis of the small bowel. The investigator decided to discontinue treatment with eculizumab because of the patient's aplastic anaemia; the patient experienced the TE 19 d after the last eculizumab dose, and died with clinical symptoms of sepsis following resection of the small intestine. Further details relating to this patient have been previously reported (van Bijnen *et al*, 2012). None of the deaths were considered related to treatment with eculizumab.

Safety

Results from this study indicated that eculizumab was well tolerated by patients with PNH. Table III lists AEs that were reported in at least 10% of patients, regardless of relationship to treatment. The most frequently reported AEs were headache, nasopharyngitis and upper respiratory tract infection, each reported in more than 40% of patients. The majority of AEs (91·3%) were mild to moderate in severity.

Table III. Treatment-emergent adverse events reported in ≥10% of patients.

Adverse event	Number (%) of patients ($n = 195$)
Patients reporting at least one adverse event	194 (99·5)
Headache	107 (54·9)
Nasopharyngitis	97 (49·7)
Upper respiratory tract infection	80 (41·0)
Diarrhoea	68 (34·9)
Nausea	63 (32·3)
Vomiting	50 (25·6)
Back pain	48 (24·6)
Abdominal pain	43 (22·1)
Arthralgia	43 (22·1)
Oropharyngeal pain	42 (21·5)
Pyrexia	40 (20·5)
Cough	39 (20·0)
Dizziness	39 (20·0)
Pain in extremity	39 (20·0)
Influenza-like illness	34 (17·4)
Urinary tract infection	33 (16·9)
Viral infection	30 (15·4)
Constipation	29 (14·9)
Contusion	29 (14·9)
Myalgia	29 (14·9)
Fatigue	25 (12·8)
Abdominal pain upper	24 (12·3)
Insomnia	23 (11·8)
Sinusitis	23 (11·8)
Epistaxis	21 (10·8)
Oedema peripheral	20 (10·3)
Pruritus	20 (10·3)
Rash	20 (10·3)

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Samsung Bioepis Exhibit No. 1002
Page 12031

Serious AEs were reported in 75 of the 195 patients (38·5%), with some of the most frequently reported serious AEs, such as haemolysis, abdominal pain and anaemia, typically seen in patients with PNH. These events generally occurred at times of biological stress, most typically in conjunction with an infection. Other serious AEs reported by at least 2% of patients were pyrexia (4·6%) and viral infection (3·1%). Cholecystectomies were reported in six of the 195 patients (3·1%), and one patient developed chronic myelomonocytic leukaemia, resulting in the death of the patient.

Of the 19 patients who discontinued treatment, five (26·3%) discontinued as a result of a nonfatal AE. Two patients became pregnant, one patient developed myelodysplastic syndrome, one patient had meningococcal sepsis (see Table IV) and one patient had, in the opinion of the investigator, a worsening of PNH. This patient suffered from diabetes and had persistent anaemia and impaired renal function, but without reticulocytosis. Of note, three of these 19 patients (15·8%) experienced a TE within 8 weeks of their last dose of eculizumab, with clinical details for one of these patients having been previously described (van Bijnen *et al*, 2012). In the two patients who became pregnant, eculizumab was received for the first 4 and 5 weeks of gestation. Both pregnancies were without complication and resulted in the delivery of healthy babies without any adverse effects from eculizumab treatment (Kelly *et al*, 2010).

Three of the patients included in this study had a history of myelodysplastic syndrome (MDS) prior to treatment with eculizumab. At the time of last follow-up, one patient had spontaneous resolution of the disorder 6 years after onset, one patient was alive and had transitioned to commercially available eculizumab and, as mentioned previously, one patient developed chronic myelomonocytic leukaemia and subsequently died. A fourth patient was diagnosed with MDS during treatment with eculizumab and was withdrawn from the study prior to receiving a bone marrow transplantation; this patient did not show any signs of serious haemolysis in the 12 weeks of follow-up following discontinuation of eculizumab.

Table IV. Serious infection-related treatment-emergent adverse events reported during eculizumab therapy (n = 195).

Adverse event	Number (%) of patients	Mean onset (days)*
Pyrexia	9 (4·6)	446
Viral infection	6 (3·1)	477
Lower respiratory tract infection	3 (1·5)	833
Urinary tract infection	3 (1·5)	878
Cellulitis	2 (1·0)	235
Meningococcal sepsis	2 (1·0)†	385
Pneumonia	2 (1·0)	456
Respiratory tract infection	2 (1·0)	664
Sepsis	2 (1·0)	604
Septic shock	2 (1·0)	312
Viral gastroenteritis	2 (1·0)	419

*Mean interval between date of first eculizumab dose until the adverse event onset date.
†One patient discontinued treatment.

Forty patients (20·5%) reported a total of 67 serious infection-related treatment-emergent AEs, none of which were fatal. Table IV presents all serious infection-related events reported in two or more patients. The most frequently reported events were pyrexia (reported in nine patients) and viral infection (reported in six patients). There was one case of staphylococcal infection, which was successfully treated with cefazolin sodium and two doses of vancomycin, although the patient subsequently withdrew from the study.

Two cases of meningococcal sepsis were reported during treatment, an infection rate of 0·42 per 100 patient-years. One was a serotype B infection that occurred in a 24-year-old male patient 353 d after the initiation of eculizumab. This patient had received a quradivalent vaccine against serotypes A, C, W135 and Y. The infection was successfully treated with several antibiotics, including imipenem, vancomycin, ceftriaxone and penicillin; the range of antibiotics used was because of bacterial sensitivity and the resistance pattern in the local hospital flora. This patient remained in the study and continued to receive eculizumab. The other case occurred in a 54-year-old female patient 416 d after eculizumab treatment was initiated and was due to serotype Y or W135 (further serotyping was not possible in this patient's country). This patient had been vaccinated against serotypes A and C. This infection was successfully treated with meropenem, vancomycin, ceftriaxone and ciprofloxacin, although the patient discontinued treatment on the advice of the investigator. Of note, neither of the patients with meningococcal sepsis had received vaccination against the specific strain of their infection, at the time of the infections serum bactericidal antibody values were within an appropriate range and both infections resolved with treatment and without sequelae. In neither case was the meningococceal infection due to failure of the vaccine.

All AEs coded as pyrexia were considered related to infection even if an identifiable infection was not diagnosed at the time of the fever. Overall, there were 38 events of pyrexia reported in 22 patients, the majority of which (26 of 38; 68·4%) were mild in severity, whereas only three of 38 events (7·9%) were considered severe. As previously mentioned, nine patients (4·6%) had pyrexia events reported as SAEs, which included all the events considered to be severe. All events of pyrexia resolved without sequelae.

Adverse events related to treatment infusion were reported in 71 patients (36·4%). Peripheral oedema, pruritus and rash were the most frequently reported AEs of this type, each occurring in a total of 20 patients (10·3%). None of the AEs associated with treatment infusion resulted in the discontinuation of eculizumab.

In order to investigate if long-term treatment with eculizumab increased the incidence of any individual or category of AE or whether eculizumab was associated with

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Page 12032

Table V. Adverse events reported at a significantly different incidence in the first and last 26 weeks of treatment with eculizumab*.

Adverse event	Number of patients: First 26 weeks	Number of patients: Last 26 weeks	*P* value†
Any event	189	145	<0·001
Headache	87	20	<0·001
Nasopharyngitis	47	32	0·029
Nausea	33	21	0·029
Constipation	14	3	0·006
Back pain	20	9	0·031
Arthralgia	17	8	0·032
Muscle spasms	9	0	0·002
Dizziness	17	8	0·039
Pyrexia	18	9	0·032
Epistaxis	12	4	0·011
Fatigue	12	4	0·029
Insomnia	10	2	0·019
Respiratory tract infection	7	0	0·008
Oral herpes	8	1	0·020
Chest pain	6	1	0·031
Haematoma	6	1	0·031
Lethargy	5	0	0·031
Toothache	5	0	0·031

*For patients who received eculizumab for a total of <52 weeks, the incidence of adverse events in the first 26 weeks was compared with the period from the start of the 27th week until the last dose of treatment. Only events for which there was a statistically significant difference between the treatment periods are reported.

†*P* values determined from one-tailed exact McNemar test for matched-pairs data.

cumulative toxicity, the incidence of AEs (irrespective of relation to treatment) reported during the first 26 weeks of eculizumab treatment was compared with the last 26 weeks of treatment (Table V). Overall, significantly fewer patients reported at least one AE in the last 26 weeks of treatment ($n = 145$) than in the first 26 weeks of treatment ($n = 189$; $P < 0·001$), and no individual AE was reported by a statistically significantly greater number of patients during the last 26 weeks than during the first 26 weeks of treatment with eculizumab. Although this analysis included patients who had a total treatment duration of <52 weeks, the mean (median) observation times of 26·00 (26·0) and 25·86 (26·0) weeks for the first and last observation periods respectively, indicated that the reduction in number of AEs seen in the last 26 weeks of therapy was not due to the reporting of AEs over a shorter observation time.

Assessments of clinical laboratory tests and vital signs did not reveal any consistent or clinically significant mean changes or any obvious treatment effect on these parameters. There were small increases in direct bilirubin concentrations, although median levels of total bilirubin remained essentially unchanged.

Discussion

The results from this study demonstrate the long-term safety and efficacy of chronic eculizumab treatment in a large cohort of patients with PNH ($n = 195$). The median eculizumab treatment duration was 30·3 months, with a maximum duration of 66 months. Inhibition of terminal complement activity with eculizumab has previously been reported to rapidly and significantly reduce chronic haemolysis, leading to reductions in transfusion requirements (Hillmen *et al*, 2006) and TEs (Hillmen *et al*, 2007), as well as improvements in renal function (Hillmen *et al*, 2010). The current study shows that these results are sustained with long-term treatment.

Thrombotic events are a severe and life-threatening complication of PNH and are reportedly the most frequent cause of death in patients with PNH (Hillmen *et al*, 2007). TE has been shown to be a significant risk factor for early mortality (relative risk: 15·4; 95% CI, 9·3–25·4; $P < 0·001$) in untreated patients (de Latour *et al*, 2008). Furthermore, following the occurrence of a first TE, there is a greater risk of subsequent TEs, which places patients with a history of TE at a heightened risk of premature mortality (Nishimura *et al*, 2004; de Latour *et al*, 2008). Given that TE in PNH patients appears to be related to severe and ongoing uncontrolled terminal complement activation, management of TE is difficult in PNH patients, as many continue to report TE despite prophylactic use of anticoagulation therapies (Moyo *et al*, 2004; de Latour *et al*, 2008; Kelly *et al*, 2011). We observed an 81·8% reduction in the incidence of TEs with long-term eculizumab treatment. Eighty-four patients in this study received concomitant anticoagulant therapy, which was discontinued in 11 patients. Despite six of these 11 patients having a history of TE, none of them experienced a TE following withdrawal of anticoagulation therapy while receiving eculizumab alone. This experience is consistent with other reports (Emadi & Brodsky, 2009; Kelly *et al*, 2011).

Thrombotic events were observed in 16% (3 of 19) of patients who discontinued treatment with eculizumab, all within 8 weeks of taking their last dose. This finding highlights the importance of adherence to eculizumab treatment at the recommended dose and schedule over the long term, as continuous therapy is paramount in maintaining sustained inhibition of the underlying uncontrolled terminal complement activation. If discontinuation of eculizumab therapy becomes necessary, the potential risk of thrombosis as well as possible preventive measures should be considered.

Chronic kidney disease in PNH patients is caused by several factors, including chronic exposure to free haemoglobin, which increases renal accumulation of haemosiderin, tubulointerstitial inflammation and kidney damage (Nath *et al*, 2001). Renal impairment is known to progress over time (Hillmen *et al*, 2010) and is associated with an increase in mortality (Kim *et al*, 2011). Continued improvement in CKD was observed with sustained eculizumab treatment,

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Samsung Bioepis Exhibit No. 1002
Page 12033

with 44·8% of patients showing improvement after 36 months of treatment, compared with 24·4% showing improvement in CKD after only 6 months of treatment. The improvement in renal function in all nine patients with early-stage CKD (stage 1–2) over 36 months suggests that patients treated with eculizumab at earlier stages of kidney damage have a greater likelihood of improvement in renal function, and there is evidence that sustained long-term therapy with eculizumab can reverse early stage renal damage sustained prior to treatment initiation. These are unique findings in a patient population known to be at risk for progressive decline in renal function (Hillmen *et al*, 2010), and they suggest that eculizumab may have a protective role that can lead to improvement in, or less progression of, renal disease.

Reduction in the incidence of TE and CKD, the two major causes of death in PNH, by administration of eculizumab would be expected to lead to improved patient survival. In the current prospective, multinational study in a large cohort of 195 patients, we demonstrated a patient survival of 97·6% (95% CI, 93·7%–99·1%) at 3 years, which was maintained over 66 months of eculizumab treatment. This result is similar to the 5-year survival rate of 95·5% observed in a single-centre, retrospective analysis of 79 patients (Kelly *et al*, 2011). These survival rates seen with eculizumab therapy are a substantial improvement over historical 5-year survival rates of approximately 65% in PNH patients with evidence of haemolysis (Hillmen *et al*, 1995; Kelly *et al*, 2011) and are similar to survival rates of age- and sex-matched healthy subjects (Kelly *et al*, 2011). These results further emphasize the role of uncontrolled complement activation in the pathophysiology of PNH-related mortality.

Long-term treatment with eculizumab also resulted in sustained haematological improvement in patients. Transfusion independence was achieved by 52% (102 of 195) of patients within the first 6 months of treatment, which increased to 82% by the last 6 months of treatment. The number of units of PRBCs transfused was reduced by 55% over the 36-month period. In addition, there was a continuous improvement in haemoglobin levels, which was achieved despite the reduction in transfusions.

The standard eculizumab maintenance dose of 900 mg every 14 ± 2 d was sufficient to maintain inhibition of haemolysis in 89% of patients. In the 21 patients who did report breakthrough haemolysis, shortening the dosing interval to <14 d was sufficient to maintain inhibition of haemolysis, and none of these patients discontinued treatment because of a lack of therapeutic effect. It is important that patients be monitored for any signs or symptoms of breakthrough haemolysis so that the dosing can be adjusted accordingly or, in cases of persistent breakthroughs, to ensure the patient has not developed human anti-human antibodies (HAHA) or neutralizing antibodies to eculizumab. Subsequent to the end of the study, a more sensitive analysis became available for the identification of HAHA in patients receiving eculizumab. With this new analysis, two of the patients in the long-term extension study were found to have low positive values for neutralizing antibodies, which exceeded the prespecified threshold for the *in vitro* assay (data not shown). This finding had no impact on the clinical response to eculizumab therapy or on the pharmacokinetic and pharmacodynamic effects of eculizumab, which continued to block complement activity.

Eculizumab was well tolerated over the long term and demonstrated a positive safety profile. Although nearly all patients reported at least one AE, this is to be expected considering the duration of the study; importantly, discontinuation from treatment due to a nonfatal AE was seen in only five patients (2·6%) over the entire period of study. With no comparator group in this open-label extension, we compared the AE rate of the early treatment group with that of the later treatment group to understand the risk of long-term eculizumab treatment. The probability of a patient experiencing one or more AEs was significantly lower in the last 6 months of the eculizumab treatment period than in the first 6 months of therapy. This suggests that there is no cumulative toxicity with long-term administration of eculizumab and that the risk–benefit profile of eculizumab improves with extended use. Serious infection-related AEs were observed throughout the study, although there was no evidence that their occurrence was related to time on eculizumab treatment.

There is an increased incidence of infections with *N. meningitidis* in individuals with genetic deficiencies of C5–C9 (Figueroa & Densen, 1991). Thus, blocking terminal complement activity with eculizumab increases a patient's susceptibility to meningococcal infections. Two cases of meningococcal sepsis were reported during the approximately 467 patient-years of exposure to eculizumab. Both patients were successfully treated without sequelae. Patient education on the signs and symptoms of potential meningococcal infections remains important to ensure that any infections are identified as quickly as possible. This is particularly crucial outside of a closely monitored clinical study, where continuous vigilance and proactive antibiotic treatment are essential to avoid a potentially fatal infection (http://soliris.net/sites/default/files/assets/soliris_pi.pdf).

In conclusion, long-term treatment with eculizumab resulted in sustained improvement in patient outcomes by rapidly reducing haemolysis and significantly reducing the frequency of severe and life-threatening morbidities, such as TEs and CKD, and thus, improving patient survival. There was evidence that eculizumab improved kidney function over time and also provided sustained protection against further renal damage, particularly when administered early and prior to advanced renal impairment. Eculizumab therapy was well tolerated with a favourable safety profile; very few patients discontinued treatment during long-term therapy. Over the course of this study, survival

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Samsung Bioepis Exhibit No. 1002
Page 12034

rates were high and consistent with the improvements observed in another overlapping cohort of patients in whom survival was seen to be similar to age- and sex-matched normal control subjects (Kelly *et al*, 2011). The International PNH Registry (www.pnhregistry.com) is providing further opportunities to continue studying and understanding the long-term benefits of eculizumab in patients with PNH outside the clinical trial setting.

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Authorship contributions

All authors participated in study design, collection, analysis and interpretation of the data presented in this study, review and critical appraisal of the contents of manuscript at each stage of its preparation and provided final approval of the completed manuscript.

Conflicts of interest

P.H. served on an advisory committee for and received honoraria from Alexion Pharmaceuticals. P.M. served on an advisory committee for Alexion Pharmaceuticals. A.R. served on an advisory committee for and received honoraria and research funding from Alexion Pharmaceuticals. M.O.E. served on an advisory committee for and received honoraria from Alexion Pharmaceuticals. A.M.R. served on an advisory committee for and received honoraria from Alexion Pharmaceuticals. H.S. served on an advisory committee for and received honoraria and research funding from Alexion Pharmaceuticals and received honoraria from Genzyme. J.S. served as a consultant for and received honoraria from Alexion Pharmaceuticals, Ortho Biotech and Roche. P.B. has nothing to disclose. J.P.M. served as a consultant for Alexion Pharmaceuticals and received research funding from Celgene and Eisai. J.S. served on an advisory committee for and received honoraria from Alexion Pharmaceuticals and served on advisory committees for Celgene, Novartis and Pfizer. A.U.-I. served on an advisory committee for Alexion Pharmaceuticals. C.D. served on a speakers bureau for Alexion Pharmaceuticals. G.S. served as a consultant for Alexion Pharmaceuticals and served on advisory committees for and received honoraria from Therakos and Fresenius. R.A.B. served on an advisory committee for Alexion Pharmaceuticals.

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Samsung Bioepis Exhibit No. 1002
Page 12035

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Samsung Bioepis Exhibit No. 1002
Page 12036

APPENDIX V

Long-term effect of the complement inhibitor eculizumab on kidney function in patients with paroxysmal nocturnal hemoglobinuria

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Paroxysmal nocturnal hemoglobinuria (PNH) is a debilitating and life-threatening disease in which lysis of PNH red blood cells frequently manifests with chronic hemolysis, anemia, and thrombosis. Renal damage in PNH is associated with chronic hemosiderosis and/or microvascular thrombosis. We determined the incidence of renal dysfunction or damage, defined by stages of chronic kidney disease (CKD), in a large cohort of PNH patients and evaluated the safety and efficacy of the complement inhibitor eculizumab in altering its progression. Renal dysfunction or damage was observed in 65% of the study population at baseline with 21% of patients with later stage CKD or kidney failure (glomerular filtration rate [GFR] ≤60 ml/min/1.73 m^2; Stage 3, 4, or 5). Eculizumab treatment was safe and well-tolerated in patients with renal dysfunction or damage and resulted in the likelihood of improvement as defined as categorical reduction in CKD stage ($P < 0.001$) compared with baseline and to placebo ($P = 0.04$). Improvement in renal function was more commonly seen in patients with baseline CKD Stages 1–2 (67.1% improvement, $P < 0.001$) although improvement was also observed in patients with CKD Stages 3–4 ($P = 0.05$). Improvements occurred quickly and were sustained for at least 18 months of treatment. Patients categorized at CKD Stages 3–5 did not worsen during treatment with eculizumab. Overall, 40 (21%) of 195 patients who demonstrated renal dysfunction or damage at baseline were no longer classified as such after 18 months of treatment. Administration of eculizumab to patients with renal dysfunction or damage was well tolerated and was usually associated with clinical improvement. Am. J. Hematol. 85:553–559, 2010. © 2010 Wiley-Liss, Inc.

Introduction

Intravascular hemolysis and the presence of cell-free plasma hemoglobin cause many of the serious clinical sequelae associated with various hemolytic disorders [1]. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare and life-threatening blood disease that is clinically defined by significant intravascular hemolysis [2,3]. PNH arises from an acquired clonal genetic deficiency of glycosylphosphatidylinositol-linked proteins on the surface of blood cells [3,4]. In particular, PNH red blood cells lack complement regulatory proteins, which render them susceptible to hemolysis mediated by the terminal components of complement. The release of excessive red cell hemoglobin during intravascular hemolysis usually exceeds the capacity of the hemoglobin scavenging molecule, haptoglobin, leading to high levels of cell-free hemoglobin, and subsequently clinical manifestations of PNH [1].

Five-year mortality in patients with PNH is approximately 35%, and median survival is approximately 10–15 years [2,5]. Kidney failure contributes to 8%–18% of PNH-related deaths [6]. Virtually all patients with PNH have evidence of kidney damage by biopsy or imaging techniques or at post-mortem examination [7–16]. Previous reports showed that repetitive exposure to cell-free hemoglobin causes renal hemosiderin accumulation, tubulointerstitial inflammation, and kidney damage [17].

Cell-free plasma hemoglobin in patients with PNH has also been shown to deplete nitric oxide (NO), leading to smooth muscle dystonias and pulmonary hypertension [18,19]. NO is also a critical molecule in the regulation of vascular tone with the greatest effect on the afferent renal arterials [20]. Alterations in renal blood flow because of the sequestration of NO can have a direct effect on the glomerular filtration rate (GFR) and renal plasma flow [20–23].

Eculizumab (Soliris®) is a humanized monoclonal antibody that targets complement protein C5, thereby preventing production of the potent proinflammatory mediator C5a and the assembly of the terminal complement complex (also called the membrane attack complex) during complement activation [24]. In clinical studies, treatment of PNH patients with eculizumab resulted in a reduction in hemolysis, cell-free plasma hemoglobin, and NO depletion [19,25]. Data from treated patients also demonstrated an improvement in anemia, fatigue and quality of life, and a reduction in thrombotic events [25–28]. Herewith, we report the incidence of renal dysfunction or damage and evaluate the effect of long-term eculizumab treatment on the progression of this serious and life-threatening morbidity in a large, multinational cohort of patients with PNH enrolled in a phase 3b open-label extension study.

Hillmen has received honoraria and research funding from and served as a consultant to and member of the Advisory Board of Alexion Pharmaceuticals. Kelly has received grant support from and served on Advisory Boards for Alexion. Omine received research funding and is a consultant for Alexion. Urbano-Ispizua has served on the Alexion Advisory Board. Rother and Khursigara are employees of Alexion Pharmaceuticals and own stock in the company.

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Samsung Bioepis Exhibit No. 1002
Page 12038

Methods

Study design and patients. Kidney function and the incidence of clinical kidney damage event rates were assessed in patients from three independent parent clinical studies (the Phase 2 pilot study [26,29] and its extensions, the Phase 3 TRIUMPH study, [25] and the Phase 3 SHEPHERD study [28]) and the subsequent common Phase 3 extension study [30]. All protocols were approved by the institutional review board at each center, and all patients gave written informed consent.

The open-label, 12-week, Phase 2 pilot study was conducted in 11 patients at two study centers in the United Kingdom [26]. Patients who completed the pilot study were eligible to enroll in a 1-year extension study [29] followed by a 2-year extension study. Patients 18 years or older who had received at least four red cell transfusions in the previous 12 months and had a PNH Type III erythrocyte population ≥10% were eligible to enroll in the pilot study. Patients who were taking stable doses of immunosuppressive drugs (e.g., cyclosporine), warfarin, and iron supplements were permitted to continue them during the study. Eculizumab was dosed at 600 mg via intravenous infusion every 7 days for 4 doses, 900 mg 7 days later, and 900 mg every 14 days as a maintenance dose.

The double-blind, placebo controlled, 26-week, Phase 3 efficacy and safety study (TRIUMPH) was conducted in 87 patients in the United States, Europe, Australia, and Canada [25]. Patients 18 years or older, with at least four red cell transfusions in the previous 12 months, a PNH Type III erythrocyte population ≥10%, platelets ≥100 × 10^9/l, and lactate dehydrogenase (LDH) ≥1.5 times the upper limit of normal were eligible to enroll. Exclusion criteria were described previously [25]. Patients who were taking stable doses of immunosuppressive drugs, anticoagulants, and iron supplements were permitted to continue during the study. Patients were centrally randomized (1:1) and stratified (according to red cell units transfused in the past year) to receive either placebo or eculizumab. Study medication was dosed as follows: eculizumab (600 mg) or placebo via intravenous infusion every 7 days for 4 doses; eculizumab (900 mg) or placebo via intravenous infusion 7 days later; followed by a maintenance dose of eculizumab (900 mg) or placebo via intravenous infusion every 14 ± 2 days for a total of 26 weeks of treatment.

The open-label, 52-week, Phase 3 study (SHEPHERD) was conducted in 97 patients in the United States, Europe, Australia, and Canada [28]. Inclusion criteria for patients were broader than those for patients enrolled in TRIUMPH, as the pretreatment transfusion eligibility was adjusted to one or more red cell transfusions in the previous 24 months and the minimum platelet count requirement was lowered to 30 × 10^9/l; all patients received the identical eculizumab dose as in the TRIUMPH study.

After completion of the parent clinical studies, 187 patients enrolled in the common open-label, 102-week, Phase 3 extension study (195 patients were enrolled in parent studies) [30]. Placebo-treated TRIUMPH patients entering the Phase 3 extension study received the same eculizumab regimen outlined for the TRIUMPH and SHEPHERD studies. Eculizumab-treated patients from the pilot, TRIUMPH, or SHEPHERD studies who entered the Phase 3 extension study continued to receive the 900 mg maintenance dose of eculizumab. Doses of immunosuppressive drugs, anticoagulants, and iron supplements could be altered at the discretion of the treating physician.

Outcome measures. For each of the 195 PNH patients entered into the eculizumab clinical trials, evidence of renal dysfunction or damage, as measured by chronic kidney disease (CKD) stage, was evaluated at baseline, 6, 12, and 18 months. All patients were required to have a urinalysis and serum creatinine measures at baseline and during the trial. Patients with a positive dipstick urine protein test were considered to have evidence of proteinuria. The GFR was estimated using the modification of diet in renal disease study formula equation, as defined previously [31,32]. CKD stages were defined using the Kidney Disease Outcomes Quality Initiative as: Stage 5 CKD, GFR less than 15 ml/min/1.73 m^2; Stage 4 CKD, GFR 15–30 ml/min/1.73 m^2; Stage 3 CKD, GFR 30–60 ml/min/1.73 m^2; Stage 2 CKD, GFR 60–90 ml/min/1.73 m^2 and evidence of kidney damage, which may include spot urinalysis with proteinuria or by abnormal imaging findings; and Stage 1 CKD, GFR greater than 90 ml/min/1.73 m^2 and evidence of kidney damage, which may include spot urinalysis with proteinuria or by abnormal imaging findings. Patients were classified as not having renal dysfunction or damage if they failed to meet the criteria for Stages 1–5 CKD [33]. Initial measurements were performed at screening before study enrollment. An improvement in renal function was defined as a categorical documented reduction in CKD stage level (e.g., a change from Stage 4 to Stage 3 or Stage 3 to Stage 1) or fulfilling the criteria of no CKD. A worsening in renal function was defined as a categorical documented increase in CKD stage level (e.g., a change from Stage 3 to Stage 4 or Stage 1 to Stage 2). No change in renal status was defined as the patient remaining in the same CKD stage or the continued absence of CKD. In addition, major clinical kidney (MCK) events were determined by querying all medical history events before the use of eculizumab and all adverse events during treatment with eculizumab. Medical history events before diagnosis of PNH were excluded. By definition, all medical history events obtained in these analyses were nonfatal. MCK events were defined as event terms with severe reversible or irreversible renal damage including acute or chronic renal failure, renal insufficiency, renal impairment, dialysis, and procedures (i.e., hemodialysis and/or placement of catheters for dialysis, renal artery angioplasty, and ureteral catheterization), nephrotoxicity, scarred or necrotic kidney, pyelonephritis, glomuleropathy, or Stages 3–5 CKD (complete list described in Table V). MCK events during placebo treatment in the TRIUMPH study were considered with the group of events before eculizumab treatment. These analyses included all events during the period commencing from the first eculizumab dose in the parent studies until the last follow-up of either the last dose of eculizumab or the data base lock in July 2007.

Statistical analysis. The changes for all patients in each CKD stage were compared within each stage and across the overall treatment population with the observations at screening using chi-square analyses and the null hypothesis that the probability of worsening CKD stage was equal to the probability of improving CKD stage. The changes in CKD stage for patients treated with eculizumab in the TRIUMPH study and for patients treated with placebo in the TRIUMPH study were also each compared with the respective observations at screening using chi-square analyses and the null hypothesis that the probability of worsening CKD stage was equal to the probability of improving CKD stage for each treatment group. The changes in CKD stage for patients treated with eculizumab in the TRIUMPH study were compared with the changes in CKD stage for patients treated with placebo in the TRIUMPH study using chi-square analyses and the null hypothesis that the probability of worsening and improving with eculizumab treatment was equal to the probabilities with placebo treatment. The incidence rate of MCK events was tabulated, and the MCK event rate per patient-year was determined for the preeculizumab and the eculizumab treatment periods for the overall patient population. A time-to-event analysis was performed for MCK events before trial enrollment. The MCK event rate was determined as events per 100 patient-years before and during eculizumab treatment. Patients with a MCK event before treatment were included in the patients evaluated to have a potential MCK event during eculizumab treatment. Event rates were compared on an intention-to-treat basis with the Wilcoxon signed-rank test.

TABLE I. Baseline Demographics of Patients in All PNH Studies (N = 195)

Description	
Gender, male	89 (45.6)
History of AA or MDS	59 (30.3)
History of previous thrombosis	62 (31.8)
Use of cyclosporine	13 (6.6)
Use of NSAID	17 (8.7)
Age (yr)	39 (18–85)
Disease duration (yr)	5.5 (0.12–38.5)
PNH type III RBC proportions (%)	32.3 (2.4–96.8)
Reticulocyte counts (×10^{12}/l)	0.164 (0.036–0.757)
Lactate dehydrogenase level (U/l)	2139 (499–10,300)
Platelet count (×10^9/l)[a]	149 (23–547)

Data are represented as n (%) or median (range).
AA, aplastic anemia; MDS, myelodysplastic syndrome; RBC, red blood cell.
[a] N = 194.

Results

Patient characteristics

Baseline characteristics of patients in each of the parent clinical studies are shown in Table I. Ninety-six percent of all eligible patients chose to enroll in the common extension study.

Samsung Bioepis Exhibit No. 1002
Page 12039

TABLE II. Renal Characteristics in Patients

CKD stage	Baseline, n (%)	18-month treatment, n (%)
Stage 5	3 (1.5)[a]	1 (0.6)
Stage 4	7 (3.6)	8 (4.7)
Stage 3	30 (15.4)	25 (14.8)
Stage 2	48 (24.6)	18 (10.7)
Stage 1	36 (18.5)	14 (8.3)
No CKD	69 (35.4)	103 (60.9)

[a] One of the three patients was receiving dialysis at treatment entry.

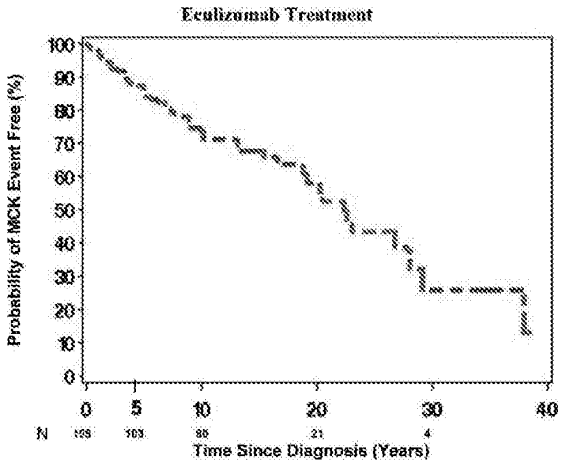


Figure 1. Time to major clinical kidney event in 195 patients with PNH prior to eculizumab treatment. The Kaplan-Meier probability of patients progressing to an MCK event. Event free; 85% (95% CI 77.9–89.6) at 5 years, 73% (95% CI 63–80) at 10 years, 56% (95% CI 42–67) at 20 years, and 25% (95% CI 10–44) at 30 years. CI, confidence interval. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Renal dysfunction or damage was a common finding in patients with PNH as 65% of the study population exhibited Stages 1–5 CKD (Table II). Approximately 21% of patients had renal insufficiency comprising CKD Stages 3, 4, or kidney failure (Stage 5). Age can play a contributing role into the development of CKD. The National Kidney Foundation (NKF) estimates the prevalence of CKD Stages 3–5 in people 65 years or older is 17%. Of the 15 patients 65 years or older who entered the trials, we found that 10 (66%) patients had CKD stages 3–5. Of the 180 patients younger than 65 years, we observed 114 (63%) had CKD and 30 (16.7%) had CKD stages 3–5 (four times higher then the general population with CKD stages 3–5) [32]. Taken together, these data suggest that patients with PNH are equally likely to have CKD at different ages, although CKD at an older age may be more likely to be more severe. In addition, there were 14 patients with a history of acute renal failure, 5 of which had required dialysis, which showed at least partial recovery and 21% (3/14) of these patients subsequently developed chronic renal insufficiency (chronic GFR < 60 ml/min/1.73 m^2).

MCK events were common in the PNH patient population, as 27% of patients (52 of 195) were diagnosed with an event, 67% of which occurred within 10 years of diagnosis. Further, the Kaplan-Meier probability of patients progressing to an MCK event was 15 of 103 (15%) at 5 years, 16 of 60 (27%) at 10 years, 9 of 21 (44%) at 20 years, and 3 of 4 (75%) at 30 years as indicated in Figure 1.

Effect of eculizumab on renal function

Eculizumab administration was associated with a reduction in median LDH from 1,832 to 292 U/l ($P < 0.0001$) at 6 months in patients with more severe renal damage (CKD Stages 3–5) and sustained out to 18 months (274 U/l; $P < 0.001$). In similar fashion, eculizumab reduced LDH levels from 2,722 to 372 U/l at 6 months in patients with CKD stages 1–2 ($P < 0.001$) and was sustained out to 18 months (318 U/l: $P < 0.001$).

TABLE III. Effect of 6-Month Eculizumab Treatment on Renal Function in the Placebo-Controlled TRIUMPH Study

	Change in stage of CKD with treatment			
Baseline stage	Improvement (%)	No change (%)	Worsening (%)	P[a]
Eculizumab				
All patients (n = 41)	29.3	65.9	4.9	0.005
Stages 3–5 (n = 9)	11.1	88.9	0.0	0.30
Stages 1–2 (n = 17)	64.7	23.5	11.8	0.006
Placebo				
All patients (n = 42)	16.7	69.0	14.3	0.78
Stages 3–5 (n = 9)	22.2	66.7	11.1	0.56
Stages 1–2 (n = 14)	35.7	50.0	14.3	0.25
Eculizumab vs. placebo				0.04[b]

[a] The comparison (except for eculizumab vs. placebo) performed for each group or for all patients, tested the null hypothesis that patients are as likely to improve as they are to worsen.

[b] The comparison of eculizumab vs. placebo tests the null hypothesis that the probability of patients improving or worsening with eculizumab is equal to the same probabilities with placebo.

In the randomized, placebo-controlled, double-blind TRIUMPH study, eculizumab treatment was associated with a significant improvement in renal function, demonstrated by improvement in CKD stages, compared with placebo treatment ($P = 0.04$; Table III). Left untreated, on balance patients were not likely to improve (16.7% improve/14.3% worsen: $P = 0.78$). In contrast, PNH patients treated with eculizumab were 6.0 times more likely to improve than worsen in renal function, showing a significant improvement at 6 months compared with baseline (29.3% of patients improved and 4.9% of patients worsened; $P = 0.005$). Patients with CKD Stages 1–2 at baseline were six times more likely to improve than worsen (Table III; $P = 0.006$) with eculizumab treatment, whereas kidney function did not change with placebo ($P = 0.25$). The improvement in kidney function with eculizumab treatment in patients with CKD Stages 3–5 at baseline in the TRIUMPH study was not significant (limited patient number, n = 9).

As indicated in Table IV, long-term eculizumab treatment significantly increased the likelihood of improved renal function in all CKD stages ($P < 0.001$). The improvements occurred early and were sustained to at least 18 months of treatment. When combining data from all three clinical trials, eculizumab-treated patients were four times more likely to improve than worsen at 6 months (31.7% improve/7.9% worsen), and this outcome improved to six times more likely to improve over 18 months of treatment (Table IV). Patients with CKD Stages 3–5 before eculizumab treatment were four times more likely to improve than worsen (22.9% improve/5.7% worsen; $P = 0.05$) with subsequent eculizumab treatment at 18 months and patients with milder renal dysfunction (Stage 1 or 2) at baseline were 25 times (67.1% improve/2.7% worsen, $P < 0.001$) more likely to improve than worsen with eculizumab treatment.

CKD Stages 3–5 is characterized by estimated GFR (eGFR; <60 ml/min/1.73 m^2). The mean eGFR across the CKD Stages 3–5 cohort demonstrated a trend in improvement at 18 months of eculizumab treatment but did not reach statistical significance. However, the mean change in eGFR in patients treated with eculizumab who improved with CKD Stages 3–5 at baseline was clinically significant: 10.3 ml/min/1.73 m^2 at 6 months, 12.8 ml/min/1.73 m^2 at

Samsung Bioepis Exhibit No. 1002
Page 12040

TABLE IV. Effect of Long-Term Eculizumab Treatment on Renal Function

Baseline stage	Change in stage of CKD with treatment: Improvement[b]	No change[b]	Worsening[b]	P^a
6 months				
All patients (n = 189)	31.7%	60.3%	7.9%	<0.001
Stages 3–5 (n = 40) (mean change in GFR, ml/min/1.73 m^2)	20.0% (+10.3)	75.0% (−0.3)	5.0% (−2.9)	0.05
Stages 1–2 (n = 81)	64.2%	24.7%	11.1%	<0.001
12 months				
All patients (n = 179)	35.2%	58.1%	6.7%	<0.001
Stages 3–5 (n = 39) (mean change in GFR, ml/min/1.73 m^2)	20.5% (12.8)	76.9% (−0.6)	2.6% (−4.2)	0.02
Stages 1–2 (n = 77)	71.4%	23.4%	5.2%	<0.001
18 months				
All patients (n = 166)	34.3%	60.2%	5.4%	<0.001
Stages 3–5 (n = 35) (mean change in GFR, ml/min/1.73 m^2)	22.9% (11.5)	71.4% (0.3)	5.7% (−6.3)	0.05
Stages 1–2 (n = 73)	67.1%	30.1%	2.7%	<0.001

[a] The comparison is performed for each group or for all patients at each time point, testing the null hypothesis that patients are as likely to improve as they are to worsen.

[b] Improvement, no change, and worsening as defined in the methods section.

TABLE V. Major Clinical Kidney Events Before and During Eculizumab Treatment

All patients, N = 195	Pretreatment	Eculizumab treatment
MCK event rate (events per 100 patient-years)	4.22	2.10
Patient years	1683.6	381.6
MCK events (n)	71	8
CKD stages 3–5[a]	22	
Renal impairment	12	5
Acute renal failure	7	
Pyelonephritis	5	
Renal failure	3	2
Hemodialysis	3	
Renal dialysis	2	
Kidney stone	2	
Other[b]	15	1
Eculizumab vs placebo		$P < 0.001$[c]

[a] Patients with CKD but no documented history of renal events.

[b] Includes bilateral atherosclerotic renal artery stenosis, calculus of kidney, hematuria, hemochromatosis, kidney abscess, nephrotic syndrome, mild secondary hydronephrosis, nephrotoxicity, proliferative glomerulonephritis, renal colic, scarred kidney, hypertension, insertion of left ureteric stent, and potassium wasting nephropathy.

[c] P value based on signed rank test.

12 months, and 11.5 ml/min/1.73 m^2 at 18 months of treatment (Table IV). Of the 46 patients with CKD Stage 2 at baseline (defined as GFR between 60 and 90 ml/min/1.73 m^2 and evidence of proteinuria), 63% improved at 6 months of treatment (vs. 13.0% deteriorated), and this improvement was sustained for 18 months (68% improved vs. 2.3% worsened). Of the 36 patients with CKD Stage 1 at baseline, 65%, 71%, and 66% showed improvement in CKD after 6, 12, and 18 months of treatment, respectively. Ninety-four percent of patients with CKD Stage 1 at baseline maintained eGFR of ≥90 ml/min/1.73 m^2 and with complete elimination of proteinuria after 18 months of treatment.

Overall, during the course of 18 months of eculizumab treatment, 40 of 195 (21%) patients classified with renal dysfunction or disease were no longer classified as having CKD. This included 5 patients initially with predialysis Stage 3, 20 patients with Stage 2, and 15 patients with Stage 1. Of the five patients with CKD Stage 3 at baseline, the median change in eGFR with eculizumab treatment was 14.6 ml/min/1.73 m^2, and all patients with proteinuria had a resolution of their proteinuria. Twenty patients with baseline CKD Stage 2 no longer had CKD (CKD Stage 0) after 18 months of eculizumab treatment. Objective evidence of renal damage, as indicated by proteinuria, was eliminated with eculizumab treatment in these patients, and 15%, 17%, and 25% of patients achieved normal eGFR (≥90 ml/min/1.73 m^2) at 6, 12, and 18 months of treatment, respectively.

In patients with either one or no transfusions in the 12 months before study entry (n = 22), the distribution of renal dysfunction or disease by stage of CKD at baseline was similar to the overall population (Stage 4, 4.5%; Stage 3, 13.6%; Stage 2, 22.7%; Stage 1, 18.2%; No CKD, 40.9%). After 6 months of treatment with eculizumab, patients with minimal or no transfusion support exhibited either an improvement in renal dysfunction stage (27%) or a stabilized renal function (73%), and no patients worsened ($P = 0.008$).

Eculizumab treatment improved CKD irrespective of patient age. An improvement with eculizumab treatment was similar in patient groups younger and older than 65 years at 18 months (no significant difference in eculizumab benefit between ≥65 and <65 years; $P = 0.10$). The likelihood of an improvement in CKD with eculizumab treatment at 18 months stratified by age quartile was statistically significant in all age quartiles (Q1 < 29 years, $P < 0.001$; Q2, 29–39 years, $P = 0.009$; Q3, 39–51 years, $P = 0.004$; Q4, >51 years, $P = 0.009$). Patients with CKD Stages 1–2 at baseline showed a significant improvement in CKD with eculizumab treatment at all age quartiles. Although there was a significant improvement in CKD in the overall study population with baseline CKD Stages 3–5, when analyzed by the smaller cohorts of age quartiles, there was a demonstrated trend in improvement but it did not reach statistical significance in the individual age quartiles (n = 0, n = 6, n = 7, and n = 22 patients with Stages 3–5 CKD at baseline in each of the age quartiles, respectively).

The effect of eculizumab treatment on clinically identified MCK events is shown in Table V. The MCK event rate was reduced 50% from 4.22 events per 100 patient-years before eculizumab treatment to 2.10 events per 100 patient-years with eculizumab treatment ($P < 0.001$).

Safety

Eculizumab was safe and well tolerated. Safety observations are consistent in all three parent studies and the open-label extension study. Most treatment-emergent Adverse Events (AEs) (95.0%) were mild or moderate in severity, and 90.8% of AEs were determined to be unrelated to study drug. The most frequently occurring treatment-emergent AEs were as follows: nasopharyngitis (39.6%), headache (36.9%), and upper respiratory tract infection (31.0%). The most frequently reported AE related to study drug by preferred term was headache (15.5%). Notably, headaches were generally mild and treated with over-the-counter analgesics. As reported previously, the frequency of headaches declined after the first two treatment doses and were similar in frequency to that observed with placebo. The most common Serious Adverse Events (SAEs) reported were associated with infections and infestations (12.8% of patients), nervous system disorders (4.3%), and blood and lymphatic disorders (8.0%). The majority of SAEs were moderate in intensity and unrelated to the study drug. Two patients experienced meningococcal infections during the study. Both patients fully recovered. One patient discontinued treatment, and one patient continued treatment with study drug. Positive tests for human anti-human antibodies (HAHA) were rare, recorded in only five patients, transient, not sustained in any patient, and not associated with any pharmacokinetic or clinical effect. Three deaths were reported during this study. Two deaths

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Page 12041

were determined to be unrelated to study drug, and in one patient, drug discontinuation could not be excluded as a contributing factor

Discussion

Because of the recognized high incidence (65%) of renal dysfunction or damage at baseline in patients from the TRIUMPH study [27] and the serious and life-threatening nature of poor renal function in patients with PNH [12], analyses were performed to assess the overall effect of eculizumab treatment on renal function. Eculizumab treatment was significantly more likely to improve CKD stage than placebo treatment through 6 months. Long-term eculizumab treatment resulted in a significant improvement and prevention of worsening of renal dysfunction or damage at all stages of baseline disease. Patients were six times more likely to improve renal function at 18 months of eculizumab treatment, rather than deteriorate, with 34% of patients showing improvement in renal function.

CKD stage was selected as the primary measure of renal outcome, as opposed to solely eGFR, to align our results with clinically validated assessments of renal function in other populations, as recommended by the NKF [33]. The assessment of CKD Stages 1–2 identifies the importance of early damage, as measured by proteinuria, because eGFR can remain at a relatively high functional level ($\geq$60 ml/min/1.73 m^2), but the presence of proteinuria indicates further objective evidence of clinically significant glomerular and/or tubular damage. Further, NKF guidelines recommend treatment of the comorbid conditions in patients with CKD Stages 1–2 that may contribute to the increase in renal damage or proteinuria to ultimately slow progression of renal dysfunction [33]. In alignment with these NKF guidelines, the results of this clinical study indicate that blocking the on-going complement-mediated hemolysis with eculizumab treatment was associated with a significant improvement in CKD and also resulted in a reduction in the percent of patients who progressed (from 11.1% at 6 months to 2.7% at 18 months of eculizumab treatment). The staging of CKD Stages 3–5 is defined by eGFR < 60 ml/min/1.73 m^2, a measure of poor renal filtration, and without the concomitant requirement for proteinuria [33]. Therefore, for patients with baseline Stages 3–5 CKD, in alignment with NKF guidelines, the current analysis focused on categorical changes in eGFR, with particular focus on maintenance of renal function and delay of deterioration. In this study, results demonstrate that 22.9% of patients with CKD Stages 3–5 improved (vs. 5.7% worsened) and 71.4% maintain stable renal function. There was a mean increase of 11.5 ml/min/1.73 m^2 eGFR in the patients with baseline CKD Stages 3–5 who improved with eculizumab treatment.

The observation that a substantial proportion of patients treated with eculizumab stabilized renal function during 18 months of treatment is clinically important. In the general population, patients without PNH with CKD Stages 1–5 followed for an average of 4.2 years, the rate of CKD stage progression has been reported as 12 patients per 100 patient-years [34]. During 1.5 years of treatment with eculizumab, the rate of CKD stage progression is 2.5 patients per 100 patient-years. Further, the rate of improvement of CKD in the general population was reported as 0.9 patients per 100 patient-years over 4.2 years [34]. In contrast, treatment with eculizumab is associated with an improvement rate of 35.2 patients per 100 patient-years. In PNH patients with more severe CKD Stages 3–5 at baseline, the rates of CKD improvement during treatment with eculizumab is 15.3 patients per 100 patient-years. The observed improvements with eculizumab treatment demonstrate the significant contribution of chronic terminal complement-mediated hemolysis to the progression of CKD in patients with PNH.

Clark et al. [12] previously reported that 32% (6/19) of patients with PNH had creatinine clearance of <60 ml/min/1.73 m^2 (CKD Stages 3–5), indicating kidney damage. The exact mechanisms responsible for kidney damage in patients with PNH are unclear, but a substantial number of investigations implicate chronic hemolysis leading to hemosiderin accumulation, inflammation, and renal scarring. Magnetic resonance imaging (MRI) studies reproducibly show that virtually all patients with PNH are observed to have renal cortical areas of low signal intensity including patients with PNH who have lower levels of hemolysis indicated by no hemoglobinuria for more than 8 years, aplastic anemia, myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML), or with smaller PNH clones [7,10,16,35]. Cortical abnormalities detected by intravenous pyelogram have been noted in patients with lower levels of hemolysis as represented by the absence of overt hemoglobinuria [12]. Autopsy or biopsy findings typically show heavy hemosiderin accumulation in the proximal tubules, hemoglobin tubular casts, signs of chronic interstitial nephritis, and fibrosis [12]. When examined, functional tubular defects are commonly found with impaired ability to concentrate urine, renal tubular acidosis, decreased reabsorption of phosphate, glucosuria with normal blood sugar, and aminoaciduria [12,36].

The renal cortical damage in PNH is typical of intravascular hemolysis and not generally found in patients with extravascular hemolysis [11]. Cell-free plasma hemoglobin can lead to progressive tubulointerstitial inflammation with upregulation of monocyte chemoattractant protein-1 and nuclear factor-κB and upregulation of both interstitial and basement membrane extracellular matrix components. In addition, hemosiderosis in the kidney with direct generation of free radicals has also been suggested as a mechanism for both acute and chronic kidney inflammation and fibrosis in PNH [14,37]. Hemosiderosis was found in 9 of 10 patients in a recent MRI study of patients with PNH [16]. The fate of iron deposits in the kidneys of these patients after resolution of hemolysis with eculizumab treatment is currently under investigation. Terminal complement inhibition with eculizumab would be expected to inhibit the direct hemolysis-mediated renal damage and the damage secondarily because of inflammation associated with kidney injury.

Eculizumab administration is associated with an immediate and sustained reduction in intravascular hemolysis in all treated patients [25,26,28]. Inhibition of terminal complement with eculizumab rapidly and consistently reduced intravascular hemolysis to near normal levels in patients from all PNH clinical studies, whereas placebo treatment in the TRIUMPH study showed no effect [25]. Moreover, the reduction in intravascular hemolysis with eculizumab treatment resulted in similar reductions in cell-free plasma hemoglobin to near normal levels [19]. In a previous study, treatment with eculizumab significantly reduced the load of cell-free plasma hemoglobin delivered to the kidneys in patients with PNH, as indicated by the 96% ($P < 0.001$) reduction in the frequency of hemoglobinuria [26].

Biochemical analyses of patients with PNH have demonstrated high levels of cell-free plasma hemoglobin and the resultant depletion of NO [1,19]. Interestingly, reduction of available NO in animal models results in an increase in renal arteriole resistance, a reduction in renal plasma flow and GFR, and subsequently poor renal function [20–23]. In addition, pooled data from 310 human subjects with normal renal function demonstrated that administration of the NO synthase inhibitor L-NG-monomethyl arginine significantly reduced renal plasma flow and that GFR was dependent

Samsung Bioepis Exhibit No. 1002
Page 12042

on NO synthase activity, suggesting a direct role of NO in glomerular hemodynamics [20]. In clinical trials, eculizumab rapidly reduced hemolysis and cell-free plasma hemoglobin, resulting in a repletion of NO in patients with PNH [19]. Although eculizumab treatment improved renal function at all stages of CKD, it was particularly noteworthy in patients classified with Stage 1 or 2 CKD at baseline. In a higher proportion of patients with Stage 1 or 2, eculizumab treatment resulted in improvement in renal function (progression to less severe CKD stage or transition to no CKD) in 67% of treated patients. In addition, the improvements in renal function in all stages of CKD occurred rapidly (within 6 months). Taken together, these data suggest the possibility that the availability of NO and subsequent changes in renal vascular tone after eculizumab treatment may play a role in the improvement of renal dysfunction or damage demonstrated in this study. Nonetheless, whether renal dysfunction is because of NO-mediated vasomotor responses in the renal arteries or renal disease because of the direct effects of cell-free plasma hemoglobin and hemosiderin, mitigation of hemolysis in these patients with eculizumab improves renal function. The impact of eculizumab on retarding progression and/or improving function may be more substantial with intervention early in the course of the disease.

It has been suggested that large vessel thrombosis or microvascular thrombosis may contribute to renal damage in patients with PNH [12]. However, clinical observations have been only infrequently supportive of large vessel thrombosis as a cause of renal dysfunction or damage in PNH with many studies demonstrating renal damage in the absence of large vessel occlusions [9,13–15]. In addition, no incidence of renal vein or renal arterial thrombosis was reported among 195 patients in this study population [30]. Nonetheless, subclinical microvascular venous or arterial thrombosis could conceivably contribute to renal insufficiency in PNH [12].

The study population presented here indicates that the overall prevalence of renal dysfunction or disease in PNH, as measured by CKD staging, is increased 6.6-fold over that observed in the general population in the United States [32]. It is possible that drug therapies occasionally used in PNH patients such as cyclosporine or non-steroidal anti-inflammatory drugs (NSAIDs) may contribute to renal dysfunction or damage. However, in our study, 6.6% of patients were taking cyclosporine and 8.7% were on NSAIDs, making it unlikely that these concomitant medications significantly impacted the analyses.

Later-stage renal dysfunction or failure is a major cause of morbidity and mortality in PNH [6,12]. In this study, of the 40 patients with later stage CKD (Stages 3–5), 10 patients had been identified as specifically having chronic renal impairment in a review of their medical histories. Eighteen of these 40 patients had been identified to have had one or more MCK event, and 22 had not been diagnosed with any renal disorder. These data suggest that kidney damage has been underappreciated as a significant symptom or clinical consequence of PNH.

Eculizumab was safe and well tolerated, consistent with the safety findings in all three parent clinical trials. In keeping with established precautions, all patients were vaccinated with a meningococcal vaccine at least 14 days before initial eculizumab treatment.

In summary, PNH is a life-threatening blood disorder in which patients are at risk for end-organ damage and organ failure because of chronic hemolysis. Renal dysfunction or damage is a common and progressive medical complication in patients with PNH that also contributes to mortality in these patients. The current findings show that long-term treatment with eculizumab in patients with hemolytic PNH requiring transfusions substantially improved kidney function or reduced progression of kidney disease as a consequence of controlling the intravascular hemolysis.

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Samsung Bioepis Exhibit No. 1002
Page 12043

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Samsung Bioepis Exhibit No. 1002
Page 12044

APPENDIX W

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CME article

Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival

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Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic disorder with increased mortality and morbidity resulting from intravascular hemolysis. Eculizumab, a monoclonal antibody against the complement protein 5, stops the intravascular hemolysis in PNH. We evaluated 79 consecutive patients treated with eculizumab in Leeds between May 2002 and July 2010. The survival of patients treated with eculizumab was not different from age- and sex-matched normal controls ($P = .46$) but was significantly better than 30 similar patients managed before eculizumab ($P = .030$). Three patients on eculizumab, all over 50 years old, died of causes unrelated to PNH. Twenty-one patients (27%) had a thrombosis before starting eculizumab (5.6 events per 100 patient-years) compared with 2 thromboses on eculizumab (0.8 events per 100 patient-years; $P < .001$). Twenty-one patients with no previous thrombosis discontinued warfarin on eculizumab with no thrombotic sequelae. Forty of 61 (66%) patients on eculizumab for more than 12 months achieved transfusion independence. The 12-month mean transfusion requirement reduced from 19.3 units before eculizumab to 5.0 units in the most recent 12 months on eculizumab ($P < .001$). Eculizumab dramatically alters the natural course of PNH, reducing symptoms and disease complications as well as improving survival to a similar level to that of the general population. (*Blood*. 2011;117(25): 6786-6792)

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Disclosures

Richard J. Kelly, Anita Hill, Louise M. Arnold, Stephen J. Richards, and Peter Hillmen have received speaker fees from Alexion Pharmaceuticals. Richard J. Kelly, Anita Hill, Stephen J. Richards, and Peter Hillmen have sat on advisory committees for Alexion Pharmaceuticals. Peter Hillmen has received research funding from Alexion Pharmaceuticals. The remaining authors; the Associate Editor Grover C. Bagby; and the CME questions author Laurie Barclay, MD, freelance writer and reviewer, Medscape, LLC, declare no competing financial interests.

Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe survival in patients with PNH treated with eculizumab, according to a case series of 79 consecutive patients treated with eculizumab in Leeds between May 2002 and July 2010.
2. Describe thrombotic episodes in patients with PNH treated with eculizumab according to that case series.
3. Describe transfusion requirements in patients with PNH treated with eculizumab according to that case series.

Release date: June 23, 2011; Expiration date: June 23, 2012

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, clonal disorder of hematopoietic stem cells in which the abnormal cells have somatic mutations of the phosphatidylinositol glycan complementation class A (*PIG-A*) gene.[1] Mutations of the *PIG-A* gene disrupt the first step of glycophosphatidylinositol (GPI) biosynthesis, leading to an absence of the GPI anchor and, in turn, a deficiency of all GPI-linked proteins.[2] CD55 and CD59 are both GPI-linked complement regulatory proteins on the surface of blood

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Samsung Bioepis Exhibit No. 1002
Page 12046

cells, and their absence from erythrocytes renders affected cells susceptible to complement attack causing intravascular hemolysis.[3] Intravascular hemolysis in PNH causes the release of free hemoglobin, leading to the development of anemia, hemoglobinuria, thrombosis, dysphagia, abdominal pain, pulmonary hypertension, renal impairment, and erectile dysfunction.[4-6] Affected persons have chronic hemolysis with exacerbations of the disease where their symptoms become more severe.

PNH can present at any age but mainly occurs in young adults, with the median age at diagnosis being in the early 30s.[7,8] Historical studies have shown the median survival to be between 10 and 15 years from the time of diagnosis.[9,10] More recently, data from a French series of patients have shown an improvement in median survival to 22 years, which is probably the result of improvements in both supportive care and in the management of disease complications.[11] Thrombosis is the main cause of death in PNH. Thrombotic events occur in approximately 50% of patients and result in the deaths of approximately one-third of patients with PNH.[9,10]

Eculizumab is a humanized monoclonal antibody that binds to complement protein 5, thereby inhibiting the formation of the terminal components of the complement cascade.[12] Eculizumab was licensed by the Food and Drug Administration in March 2007 and by the European Medicines Agency in June 2007 for the treatment of PNH after being shown to be well tolerated and highly effective for patients with PNH in clinical trials. It demonstrated a reduction in hemolysis, stabilization of hemoglobin levels, reduction in transfusion requirements, and improvement in quality of life.[13-15] Eculizumab also protects against the complications of hemolytic PNH, such as deteriorating renal function, pulmonary hypertension, and thromboembolism.[16-18]

We report on 79 patients treated with eculizumab at a single center between May 2002 and July 2010 with the first definitive evidence that eculizumab improves survival and effects a sustained improvement in symptoms.

Methods

Patients and investigations

Seventy-nine patients with PNH were treated with eculizumab at Leeds Teaching Hospitals PNH center between May 2002 and July 2010, including 34 patients from the clinical trials[13-15] and a further 45 treated since then. Funding was through the National Health Service either via central commissioning in England or local funding in Wales or Scotland. The follow-up of patients was approved through the Central Research Ethics Committee, and all patients gave signed informed consent for entry into the study in accordance with the Declaration of Helsinki. The diagnosis was established or confirmed using multicolor flow cytometry of the erythrocytes and granulocytes in all cases. Patients were assessed at a minimum of every 12 weeks by the Leeds PNH team. Data collected for analysis include age and symptoms at diagnosis, presence of a history of preceding aplastic anemia (AA) or myelodysplasia (MDS), age at the start of eculizumab, use of other medication to treat PNH, the occurrence of thrombosis before and during eculizumab treatment, blood transfusion requirement for the 12 months before starting eculizumab and after its initiation, lactate dehydrogenase (LDH) levels at the start of eculizumab and the most recent level (all of which were from May, June, or July 2010), and documentation of cause and date of death if applicable. Data were collected up until the end of July 2010 when this planned analysis was made.

In the 7 years before the availability of eculizumab, 30 patients who fulfilled our criteria for eculizumab therapy were cared for in Leeds. The mortality of these patients, up to the point at which they went on to receive eculizumab, was evaluated to provide a control group for comparison.

Eculizumab therapy

Seventy-six patients fulfilled the agreed nationally commissioned indications for treatment: Transfusion-dependent hemolysis (4 or more transfusions in 12 months). A significant PNH-related complication (ie, thrombosis or renal failure) regardless of transfusion history. In addition, 4 patients who did not fulfill these criteria were treated as agreed exceptions requiring therapy because of profound symptoms.

Eculizumab was initially delivered at the approved dosing schedule of 600-mg intravenous infusions more than 30 minutes each week for 4 doses followed by a 900-mg infusion after a further week. A 900-mg dose was then given every 14 days (± 2 days) indefinitely. After the initial 2 to 5 doses, all therapy was administered in the patient's home by homecare nurses (Healthcare-at-Home Limited) under the guidance of the Leeds PNH team. A return of a patient's symptoms (eg, red or black urine or abdominal discomfort) or increased LDH immediately before a dose of eculizumab was indicative of break-through from complement control, and these patients were treated with higher doses (usually 1200 mg) every 14 days.

The major potential complication of eculizumab is the increased risk of meningococcal infection with *Neisseria meningitidis* as terminal complement appears critical to prevent such infections. All patients were vaccinated with a tetravalent meningococcal vaccine against subgroup A, C, W, and Y, but no vaccine is currently available to serogroup B. In the United Kingdom, serotype B is the commonest serotype isolated in meningococcal sepsis. In view of this, in January 2010 our policy changed to continue with vaccination but to also recommend antibiotic prophylaxis to all patients (penicillin V 500 mg twice a day or erythromycin 500 mg twice a day for patients intolerant of penicillin). *N meningitidis* is very sensitive to penicillin; and in areas where there is a high prevalence of serotype B, the use of prophylactic antibiotics may prove to be of benefit.

Statistical analysis

Unless otherwise stated, all analysis was generated using SAS software, Version 9.2. Survival curves were derived by the Kaplan-Meier method using the log-rank test to evaluate the significance of differences between groups. Patient survival on eculizumab was compared with age- and sex-matched control averages obtained using 2001 United Kingdom census data from the United Kingdom Office of National Statistics. To enable a log-rank comparison between these data and the PNH cohort, United Kingdom individual survival data were generated to match the age and sex control averages derived from the census data. A Cox regression model with time-dependent covariates was used to assess whether the introduction of eculizumab as a new treatment strategy altered the mortality of patients with PNH. This analysis included patients with PNH treated in the 7 years before the availability of eculizumab; analysis was generated using Stata Statistical Software release 11. When drawing the survival curve for this pre-ecluzimab cohort, patients were censored at the time they first received eculizumab.

Seventy-five patients required transfusions before eculizumab therapy, and 61 of these (81%) have been on therapy for at least 12 months. Their transfusion requirements in the 12 months before eculizumab and in the most recent 12 months were compared using the Wilcoxon signed rank-sum test. The patients within this group who were not transfusion independent at the time of analysis were further evaluated using a paired t test to assess whether there was a significant difference in the number of transfusions required compared with their transfusion requirements before eculizumab.

Thrombotic event rates for pre-eculizumab and eculizumab treatment periods were calculated as the mean number of thrombotic events per year since diagnosis or start of treatment, respectively. Comparison of the occurrence of thrombosis before and after starting eculizumab was carried out using the Wilcoxon signed rank-sum test.

Platelet counts at the start of eculizumab treatment were compared with those after 12 months of treatment using a paired t test.

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Samsung Bioepis Exhibit No. 1002
Page 12047

Table 1. Patient demographics and features at diagnosis and the start of eculizumab treatment (n = 79 unless otherwise stated)

Demographics and features	Value
Presenting features	
Male, no. (%)	40 (51)
Age at diagnosis, y, median (range)	37 (12-79)
Documented history of AA/MDS,* no. (%)	24 (30)
Hemoglobinuria, no. (%)	50 (63)
Abdominal pain, no. (%)	24 (30)
Dysphagia, no. (%)	9 (11)
Thrombosis, no. (%)	4 (5)
Anemia (n = 73),† no. (%)	69 (95)
LDH,‡ IU/L, median (range)	2872 (587-10 300)
Thromboses before eculizumab (n)	
Venous	
Budd-Chiari	12
Mesenteric	4
Cerebral	3
Pulmonary embolus	3
Deep vein	4
Other	3
Arterial	
Stroke	3
Myocardial infarction	2
At start of eculizumab	
Age, y, median (range)	46 (14-84)
LDH level, IU/L, median (range)	2872 (587-10 300)
Neutrophils, $\times 10^9$/L, median (range)	2.2 (0.6-11.9)
Platelets, $\times 10^9$/L, median (range)	149 (11-507)
Reticulocytes (absolute), $\times 10^9$/L, median (range)	171 (57-415)
PNH clone sizes, % (range)	
Granulocyte	96.4 (41.8-100)
Erythrocte	34.0 (2.9-100)
Type II erythrocyte§	3.8 (0-77.4)
Type III erythrocyte§	25.0 (2.4-79.6)
Treatment at start of eculizumab, no. (%)	
Anticoagulation	46 (58)
Ciclosporin	11 (14)
Androgens	2 (3)
No transfusion support‖	4 (5)

*One patient had myelodysplasia.
†Hemoglobin at presentation was not known in 6 cases.
‡Normal value, 430 IU/L.
§Type II erythrocytes have a partial deficiency, and type III erythrocytes have a complete deficiency of GPI-linked proteins.
‖Two patients refused to have blood transfusions for religious reasons.

Results

Patient characteristics

This study includes all patients treated at our center with eculizumab between May 2002 and July 2010. There were 40 men and 39 women with the median age at diagnosis of 37 years (range, 12-79 years) and the median age at initiation of eculizumab of 46 years (range, 14-84 years). Patient characteristics, neutrophil and platelet counts, and PNH clone sizes at the initiation of eculizumab are shown in Table 1. The mean duration of eculizumab treatment was 39 months (range, 1-98 months). Eculizumab has been stopped in 2 patients: one because of predominant aplastic anemia and one with spontaneous remission of his PNH. Seventy-four patients remained on eculizumab until the end of the study date. Seventy-four patients were treated with a maintenance dose of 900 mg of eculizumab every 14 days, with 5 patients requiring higher doses. Four of these required 1200 mg and 1 required 1500 mg every 14 days.

Survival

The survival curve for the patient group compared with age- and sex-matched control averages from the United Kingdom population is shown in Figure 1. There is no significant difference between the 2 groups ($P = .46$). The difference between the curves at 5 years is 0.8% (95% confidence interval [CI], −4.2% to 5.8%). The difference at 8 years is −0.8% (95% CI, −5.8% to 4.2%). Age was significant as a continuous variable in the Cox model for survival ($P = .04$), and none of the 45 patients who commenced eculizumab under the age of 50 years has died. The survival curves for different age groups for PNH patients on eculizumab are shown in Figure 2.

The survival of 30 patients with PNH assessed between 1997 and 2004 who fulfilled the criteria for treatment with eculizumab was also compared with the treated patient group and is shown in Figure 3. The P value obtained from the time-dependent Cox model is .030, with a corresponding hazard ratio of 0.21 (95% CI, 0.05-0.88), suggesting that the risk of dying is significantly reduced on eculizumab. The 5-year survival rate for these patients is 66.8% (95% CI, 41.4%-85.1%), which is significantly worse than the 5-year survival rate for the patients treated with eculizumab, 95.5% (95% CI, 87.6%-98.5%).

Cause of death

Three patients (4%) died while on eculizumab, all from causes unrelated to their PNH. A 55-year-old man died of metastatic cecal carcinoma, which was diagnosed as disseminated disease before eculizumab treatment. A 76-year-old woman died of pneumonia after a long history of recurrent bronchopneumonia before starting eculizumab, and a 79-year-old man with a preceding history of ischemic heart disease died of congestive cardiac failure.

Complications of PNH

Three patients (4%) have undergone a clonal change in their disease. Two patients (age, 71 and 75 years) have developed MDS, 58 and 76 months, respectively, after commencing eculizumab. In both cases, the MDS occurred within the GPI-negative cells; but in each case, the majority of their myeloid series was derived from the PNH clone (granulocyte clone, 100% and 99.4%, respectively). Bone marrow examination in both these patients showed hypercellular marrows with refractory cytopenia and multilineage dysplasia. Cytogenetics in both cases were normal. Another patient (age, 50 years) developed acute myeloid leukemia, 27 years after his initial diagnosis of PNH. The leukemia also developed from GPI-deficient cells; but again, his myeloid series was largely PNH (PNH granulocyte population, 97.9%), and monosomy 7 had been identified in his marrow immediately before commencing eculizumab. The patient with acute myeloid leukemia is undergoing intensive chemotherapy for his leukemia. All 3 patients remained on eculizumab to the end of July 2010.

The relationship between PNH and AA was a prominent feature in this patient cohort, with 11 patients treated with long-term cyclosporine therapy before starting eculizumab and a further 3 patients developing aplasia after eculizumab was initiated. Two of these patients were treated with antilymphocyte globulin and cyclosporine and the third with campath and cyclosporine. All 3 continued eculizumab treatment as they all continued to have

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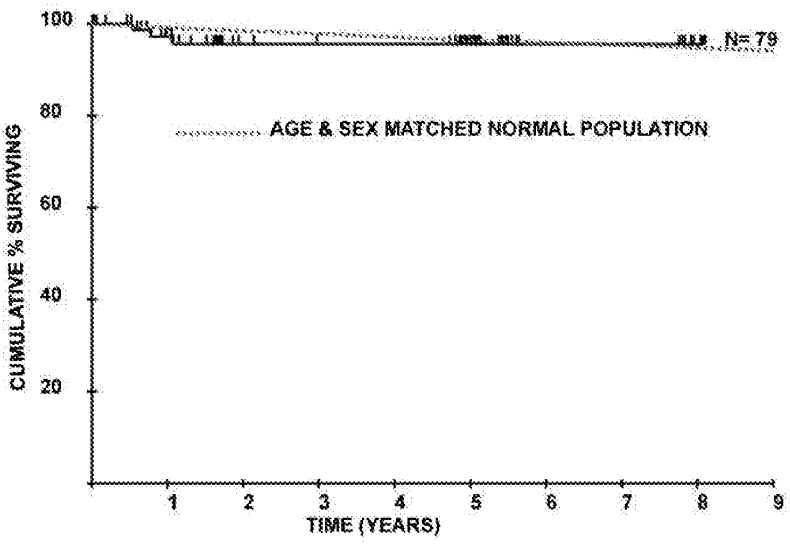


Figure 1. Overall survival of 79 patients from initiation of eculizumab treatment compared with an age- and sex-matched normal population.

significant PNH clones (all 3 had a PNH granulocyte level of > 99.5%).

There were 34 thrombotic episodes in 21 of the 79 patients (27%) before eculizumab treatment. The sites of these thromboses are shown in Table 1. Twenty-three of these were the primary thrombotic events; and in 17 of these cases, the patients were not anticoagulated (74%). Eleven thrombotic events occurred in patients who had already had a previous proven thrombosis, and all of these patients were also on therapeutic anticoagulation. Seven patients had thrombosis within the 12 months before starting eculizumab. Two patients stopped eculizumab temporarily: one because of difficulty in obtaining funding for treatment and the second to establish whether a seronegative arthropathy, which had developed, might improve off treatment (which it did not). Both patients needed to stop their prophylactic anticoagulation because of serious bleeding complications, and both developed thrombotic events within 5 months of stopping eculizumab. These thromboses are not included in the statistical analysis as they occurred in patients no longer on eculizumab.

Two patients had a thrombosis while on eculizumab. The first, who had a stroke before eculizumab, had a retinal vein thrombosis despite treatment with both eculizumab and warfarin. The second, who is on hemodialysis for end-stage renal failure and had no prior history of thrombosis, developed a thrombus in the arteriovenous fistula that had been created.

The number of thromboses occurring from the date of PNH diagnosis to the start of eculizumab treatment was compared with the number occurring while on eculizumab therapy. The mean length of time between PNH diagnosis and starting eculizumab was 7.7 years (range, 0-44 years), and the mean length of time on eculizumab was 3.3 years (range, 0-8 years). The rate of thrombotic events occurring before eculizumab was 5.6 events per 100 patient-years compared with at a rate of 0.8 events per 100 patient-years while on eculizumab ($P < .001$ by the Wilcoxon signed rank-sum test).

Before the advent of eculizumab, primary prophylaxis with warfarin before the patient's first thrombosis was usually recommended in view of the high-risk morbidity and mortality associated with thrombosis in PNH. Because eculizumab appears to be

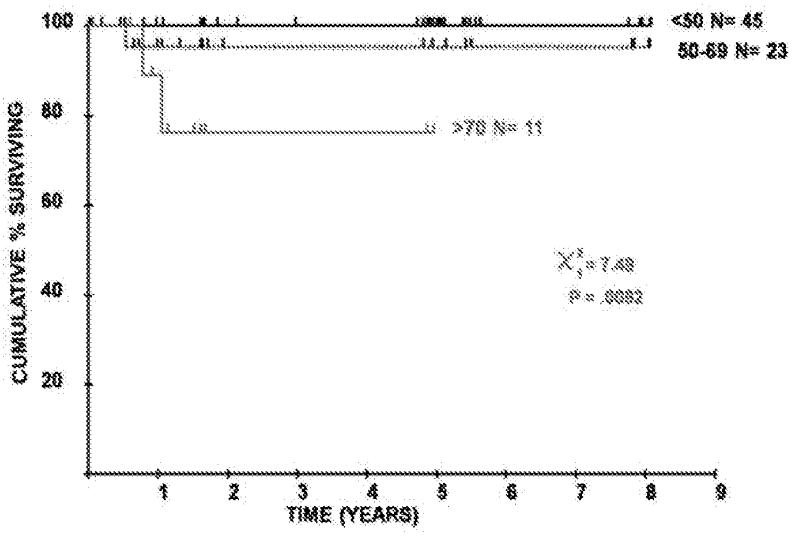


Figure 2. Overall survival of 79 patients from initiation of eculizumab treatment according to age.

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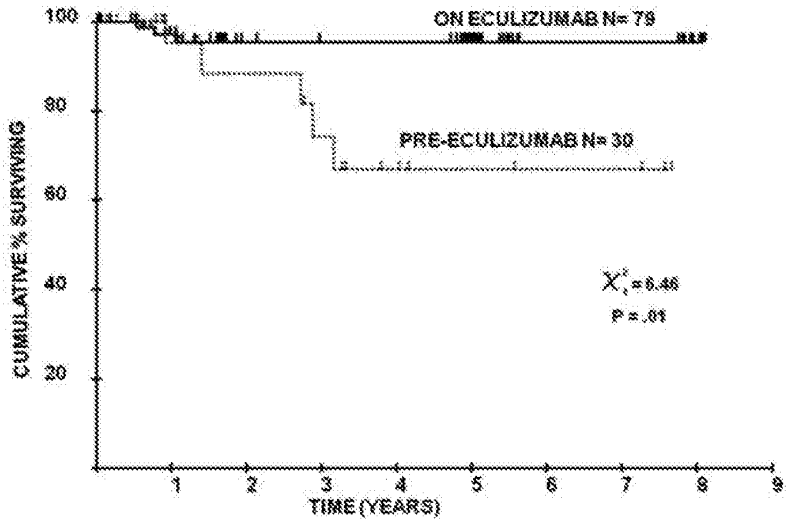


Figure 3. Overall survival of patients before and after eculizumab.

protective against thrombosis in PNH, primary prophylaxis with warfarin has now been stopped in 21 patients and secondary prophylaxis stopped in a further patient because of an episode of life-threatening bleeding. Overall, anticoagulation in patients on eculizumab has been stopped for a mean duration of 10.8 months (range, 1-60 months) and a cumulative total of more than 19 years. No thrombotic complications have been seen in these patients. Anticoagulation of patients with a previous history of thrombosis was not routinely stopped.

Two patients had proven meningococcal infection both with *N meningitidis* serogroup B, which translated to a risk of 0.9 events per 100 patient-years on eculizumab. With advice from the United Kingdom Meningococcal Reference Unit, our policy was altered in January 2010 to include a recommendation for patients to have routine antibiotic prophylaxis.

Intravascular hemolysis and transfusion requirements

The median LDH value fell from 2872 IU/L (range, 587-10 300 IU/L, upper limit of normal 430 IU/L) at the start of eculizumab treatment to the most recent average recording of 477 IU/L (range, 177-1793 IU/L).

In the 12 months before starting eculizumab, the mean number of units of blood transfused was 19.9. Sixty-one of the 75 patients (81%) required transfusions before eculizumab and have been on eculizumab for 12 months. We compared the transfusion requirements for the 12 months before eculizumab therapy with the most recent 12 months on therapy. The mean number of transfusions required fell by 74% from 19.3 units (range, 2-52 units) to 5.0 units (range, 0-50 units, $P < .001$; Figure 4), with 40 of the 61 patients (66%) becoming transfusion independent.

Looking specifically at the 21 patients of this group of 61 who still needed a transfusion in the last 12 months, there was a significant reduction in the number of transfusions needed ($P = .028$). The mean number of units transfused fell from 24.6 units (range, 4-52 units) to 14.6 units (range, 2-50 units). Two of these patients continued to require transfusions as they had developed MDS, 4 patients were transfused as they had breakthrough hemolysis and their eculizumab maintenance dose was increased to 1200 mg every 14 days, 5 patients had 2 or fewer transfusions in the 12-month period (and these were associated with infections usually viral in nature), 2 patients were transfused as they had developed aplasia, and 8 patients continued

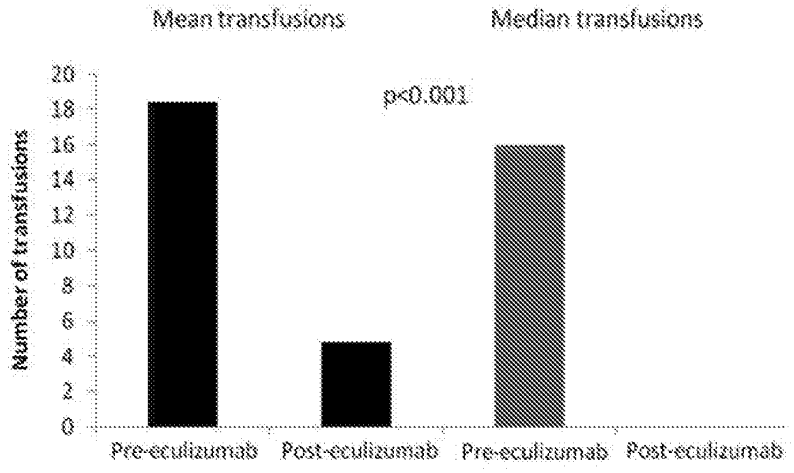


Figure 4. Blood transfusion requirements in the 12 months before eculizumab therapy and the most recent 12 months on eculizumab treatment in 64 patients.

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to need transfusions, which is probably the result of extravascular hemolysis.

Platelets

There are 61 patients who have been on treatment for 12 months and have platelet values recorded both at initiation of eculizumab therapy and after 12 months on eculizumab. There was no difference between platelet counts before or after 12 months of treatment, with the mean platelet count being 161×10^9/L and 163×10^9/L at the start of eculizumab therapy and after 12 months of treatment, respectively. As many patients had increased platelet counts as had decreased platelet counts. We also specifically assessed this in 12 patients with thrombocytopenia (platelets $< 100 \times 10^9$/L) at the start of eculizumab, but there was no difference seen (mean platelet counts, 67×10^9/L and 66×10^9/L at the start of eculizumab therapy and after 12 months of treatment, respectively).

Discussion

This is the first study to show improved survival in patients with PNH treated with eculizumab. We previously published in the era before eculizumab that there was significantly worse survival for patients with PNH compared with matched controls, with approximately 50% of patients dying as a result of their PNH.[9] In the current series, we have shown both a significantly worse survival in patients with PNH in the 7 years immediately before eculizumab ($P = .030$; Figure 3) and no difference in mortality between patients on eculizumab and the normal population ($P = .46$; Figure 1). Three of the 79 patients (4%) treated with eculizumab at our center during the past 8 years have died, all from non–PNH-related causes. There were no deaths in the 45 patients commencing eculizumab under the age of 50 years, which is a significant finding as the median age at diagnosis in PNH is in the fourth decade of life.[7,8] Two of the 11 patients more than 70 years old died as a result of comorbidities and not as a direct result of their PNH (Figure 2).

In our comparison of patients with PNH treated in the 7 years immediately before eculizumab with those patients on eculizumab, the patients effectively act as their own controls, with a period before the introduction of eculizumab and a period after the introduction of eculizumab, which is considered to be an effective analysis strategy. Selection bias is minimized because the criteria for inclusion in these groups are the same (those fulfilling the criteria for eculizumab treatment in England), all presenting patients are included, and all patients were cared for at a single center and were treated with eculizumab as soon as it was available. Although other treatments, such as supportive care and treatment of disease complications, may have improved over that period of time, it is doubtful that these improvements could have affected survival to the extent displayed (Figure 3).

Three patients (4%) developed MDS or acute leukemia, which is similar to the level reported previously.[8,10,11] Two of these patients developed MDS (age, 71 and 75 years, respectively). In both instances, the MDS occurred within the GPI-negative clone of cells. A further patient (age, 50 years) developed acute myeloid leukemia 27 years after his initial diagnosis of PNH. The leukemic blast cells were also GPI-deficient. The fact that clonal myeloid evolution occurred from the PNH clone in these patients is not surprising as the majority of hematopoiesis in these 3 patients was derived from PNH stem cells.

The most common feature at diagnosis in PNH patients is that of anemia,[19] and this is confirmed in our patient group. Hemoglobinuria, the classic symptom seen in PNH, was present in a much higher proportion of our patients at diagnosis (63%) than in previously reported series[20] but is not seen in all PNH patients and can be a contributory factor in the often lengthy delay in a diagnosis being made.[9]

Thromboembolism is the main cause of mortality in PNH, accounting for approximately 40% of deaths.[5,7,9-11] Once an initial thrombosis occurs, the risk of further thrombotic events occurring is much higher, with a 5- to 10-fold increase in mortality.[8,10] Primary prophylaxis with anticoagulation is usually successful[21]; but in cases where an initial thrombosis has occurred, anticoagulation alone is frequently not sufficient to prevent further thrombotic complications.[7,22] In addition, there are well-recognized risks of anticoagulation, particularly in a population of patients with a high incidence of thrombocytopenia and of liver abnormalities.

We observed 34 thrombotic events in 21 patients (27%) before starting eculizumab. Seventeen (50%) of these occurred while on anticoagulation, with 11 of these 17 events occurring in patients with a previous proven thrombotic event. This supports the finding that anticoagulation alone will not always prevent thromboses, especially in those with a previous history of thrombosis. We observed a dramatic reduction in thromboses occurring on eculizumab therapy with just 2 events reported. Rates of thromboses reduced from 5.6 events to 0.8 events per 100 patient-years with eculizumab treatment. Even after accounting for the shorter duration of follow-up since starting eculizumab, this difference is highly significant ($P < .001$).

Seven patients had a thrombosis in the 12 months leading up to the start of eculizumab but have had no further thrombotic events since commencing therapy. It appears that, in this setting, eculizumab in conjunction with anticoagulation is effective in preventing further thrombosis. We have also stopped primary prophylactic anticoagulation in 21 patients on eculizumab with no instances of thrombosis occurring (cumulative time period of > 19 years). We now routinely recommend the cessation of anticoagulation in patients on eculizumab with no prior history of thrombosis. This is important as there is a small but significant risk of severe bleeding on long-term anticoagulation.[23] Anticoagulation of patients with a previous history of thrombosis has not been systematically stopped.

Two patients with large PNH clones stopped eculizumab temporarily. In both cases, anticoagulation was stopped during this time because of specific bleeding complications. Within a few months, both patients had developed a thrombosis and were restarted on eculizumab. Although this has been seen in only 2 cases, if patients have to stop eculizumab but still have a significant disease burden, anticoagulation should be considered before it is stopped. Consideration should also be given to transfusions in patients stopping eculizumab to dilute the PNH red cell population, thereby decreasing the likelihood of hemolysis.

Eculizumab therapy in PNH causes a rapid reduction in intravascular hemolysis with a corresponding reduction in LDH levels,[13-15] which we now demonstrate continues to remain low beyond 8 years of therapy. Two-thirds of patients on eculizumab for at least 12 months remain transfusion independent. This is higher than the proportion of patients who remained transfusion independent in the eculizumab clinical trials, with 51% of patients being transfusion independent for both the 6-month period of the TRIUMPH study and the 12 months of the SHEPHERD study.[14,15] This may reflect an improvement in patients who are treated with eculizumab for a prolonged period, particularly in those patients

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Page 12051

who are acutely unwell when commencing therapy, and/or the patients in our study are more homogeneous because of the strict criteria for eculizumab therapy. In addition, the 21 patients who still require transfusions had a significant reduction in the amount of blood required after starting eculizumab ($P = .03$). This improvement is seen even though 2 of these patients had a marked increase in the amount of blood they required as a result of developing MDS. Patients in our study who still needed transfusions on eculizumab did so for a variety of reasons. These include breakthrough hemolysis, aplasia, and extravascular hemolysis. Extravascular hemolysis has been reported in 2 studies on patients with PNH receiving eculizumab.[24,25] In our series, we observed a dramatic reduction in transfusion requirements, indicating that the phenomenon of extravascular hemolysis is of limited clinical importance for most patients.

An increase in platelet count in patients with thrombocytopenia as a direct consequence of eculizumab treatment has previously been observed.[26] No increase in platelet count was observed in our series, either looking at all study patients or just those with thrombocytopenia.

This study underlines the pivotal role that intravascular hemolysis plays in PNH. Inhibition of the formation of the terminal complement cascade, preventing intravascular hemolysis of PNH erythrocytes and other sequelae of complement on PNH cells, not only alleviates the symptoms of the disease but also improves survival to such an extent that in our patient group there were no deaths because of the sequelae of hemolytic PNH (ie, thrombosis or renal failure). Eculizumab appears to have no effect on the development of clonal myelopathies, namely, MDS or acute myeloid leukemia, which are rare occurrences in PNH; but given this caveat, the observed survival for patients on eculizumab appears to be similar to that of the normal population.

Authorship

Contribution: R.J.K. designed the study, collected, analyzed, and interpreted the data and drafted the paper; L.M.A., G.L.B., S.J.R., M.C., and L.D.M. analyzed and interpreted the data and reviewed the paper; D.R.C. and W.M.G. analyzed, interpreted, and performed statistical analysis on the data and reviewed the paper; and A.H. and P.H. designed the study, analyzed and interpreted the data, and reviewed the paper.

Conflict-of-interest disclosure: R.J.K., A.H., L.M.A., S.J.R., and P.H. have received speaker fees from Alexion Pharmaceuticals. R.J.K., A.H., S.J.R., and P.H. have sat on advisory committees for Alexion Pharmaceuticals. P.H. has received research funding from Alexion Pharmaceuticals. The remaining authors declare no competing financial interests.

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Electronic Patent Application Fee Transmittal

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First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper/Melissa St Germain
Attorney Docket Number:	AXJ-114BUSCN5

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3	Amendment/Req. Reconsideration-After Non-Final Reject	2019_12_11_-_FINAL_FOR_FILING_Response_to_Non-Final_Office_Action_-_AXJ-114BUSCN5.pdf	731767 6b63e99ed98b0b38f247c8c44bc9a968e0762502	no	32
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Warnings:					
Information:					
13	Amendment/Req. Reconsideration-After Non-Final Reject	App_I.pdf	218047 caad397118a2fb5b623098c64ff10ef054f1a3f6	no	3
Warnings:					
Information:					

14	Amendment/Req. Reconsideration-After Non-Final Reject	App_J.pdf	477567 2ecc45cafaf3de9d6bdd19274fdb2281e23197b4	no	3
Warnings:					
Information:					
15	Amendment/Req. Reconsideration-After Non-Final Reject	App_K.pdf	196088 2b84ede3668158ad96ebd0f7148528fa18f2bb90	no	2
Warnings:					
Information:					
16	Amendment/Req. Reconsideration-After Non-Final Reject	App_L.pdf	196185 3ba763ac1424d50d93d79e9c94ba75ea6c535d3c	no	2
Warnings:					
Information:					
17	Amendment/Req. Reconsideration-After Non-Final Reject	App_M.pdf	240691 e1e0d2daaf131e7913b4593455946854b8eaf116	no	8
Warnings:					
Information:					
18	Amendment/Req. Reconsideration-After Non-Final Reject	App_N.pdf	205818 9759adc2addb4c92417c334946b49e8784723c39	no	2
Warnings:					
Information:					
19	Amendment/Req. Reconsideration-After Non-Final Reject	App_O.pdf	2595630 0a63d6e9d6d3f6e0f355e843e1fd74cee89e2a9e	no	136
Warnings:					
Information:					
20	Amendment/Req. Reconsideration-After Non-Final Reject	App_P.pdf	253076 f98d2abb08736d0052581d5f69b3f53d1ee7990a	no	2
Warnings:					
Information:					

21	Amendment/Req. Reconsideration-After Non-Final Reject	App_Q.pdf	604550 da3646f1780287e81741cad19bb01be5ab9f753b	no	13
Warnings:					
Information:					
22	Amendment/Req. Reconsideration-After Non-Final Reject	App_R.pdf	518264 6298bb08f40e6a418b28571bee455f35603840de	no	9
Warnings:					
Information:					
23	Amendment/Req. Reconsideration-After Non-Final Reject	App_S.pdf	745140 07998511eb220812bc5b1d9a0a1e74d9a3aaf041	no	46
Warnings:					
Information:					
24	Amendment/Req. Reconsideration-After Non-Final Reject	App_T.pdf	269249 5b0e9bc49b0de9af31c169c5ff5c3cc2aeaff8df	no	7
Warnings:					
Information:					
25	Amendment/Req. Reconsideration-After Non-Final Reject	App_U.pdf	321880 9507878463d07dd5dc95d78a324c60bce4634c8c	no	13
Warnings:					
Information:					
26	Amendment/Req. Reconsideration-After Non-Final Reject	App_V.pdf	280646 6ec8d17095203ac0788ce5ee9d5aab6c7f96caf9	no	8
Warnings:					
Information:					
27	Amendment/Req. Reconsideration-After Non-Final Reject	App_W.pdf	366247 9607bfb9bc8000404a3895c9d0cd452dddc427ae	no	8
Warnings:					
Information:					

28	Fee Worksheet (SB06)	fee-info.pdf	30803 2108ccb34176904ca678b65c6a77b4a211a956c1	no	2
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/22 (03-13)
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) AXJ-114BUSCN5
Application Number 15/642,096-Conf. #7606	Filed July 5, 2017
For TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	
Art Unit 1644	Examiner J. L. Rogers

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐ Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☒ Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 1,400.00
☐ Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐ Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1196 .

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 60,760 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Jill Gorny Sloper, Esq./ — Signature
December 11, 2019 — Date

Jill Gorny Sloper, Esq. — Typed or printed name
617-217-4630 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: December 11, 2019 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

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(54) **ANTI-TIM-3 ANTIBODY**

(57) The present invention provides an anti-human TIM-3 antibody which binds to the amino acid sequence of the extracellular region of TIM-3 or its three-dimensional structure thereof and exhibits higher effector activity such as an antibody-dependent cellular cytotoxicity (ADCC activity) for diseases relating to a human TIM-3 expressing cell. The present invention provides a monoclonal antibody or antibody fragment thereof which binds to the amino acid sequence of the extracellular region of TIM-3 or its three-dimensional structure and exhibits ADCC activity; a hybridoma which produces the antibody; a DNA encoding the antibody; a vector comprising the DNA; a transformant which is obtainable by introducing the vector; a method for producing the antibody or the antibody fragment thereof which comprises using the hybridoma or the transformant; a therapeutic agent and a diagnostic agent comprising the antibody or the antibody fragment thereof as an active ingredient. In addition, the present invention provides an anti-human TIM-3 antibody having high ADCC activity by screening an anti-human TIM-3 antibody which competes with the monoclonal antibody or the antibody fragment thereof.

EP 2 581 113 A1

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Description

Technical Field

[0001] The present invention relates to a monoclonal antibody or an antibody fragment thereof, which binds to the extracellular region of T-cell immunoglobulin and mucin domain containing molecule-3 (hereinafter referred to as "TIM-3") and exhibits antibody-dependent cellular cytotoxicity (hereinafter referred to as "ADCC"); a hybridoma which produces the antibody; a DNA which encodes the antibody; a vector which comprises the DNA; a transformant obtained by transforming the vector; a process for producing an antibody or an antibody fragment thereof using the hybridoma or the transformant; and a diagnostic agent or a therapeutic agent using the antibody or the antibody fragment thereof.

Background Art

[0002] TIM-3 gene family consists of eight genes in mouse and three genes in human, and each of these genes are located at chromosome 11 and at chromosome 5q33 respectively (Non-patent Document 1). These gene regions are known to be related with autoimmune diseases and allergic diseases. TIM protein is a type I transmembrane protein having a structurally conserved immunoglobulin variable (IgV) domain and a mucin domain.

[0003] TIM protein was considered to be specifically expressed on T cells and directly regulate the T cell activity, but there are recent reports on expression of TIM-3 protein in antigen-presenting cells and on their functions (Non-patent Document 2). According to the crystal structure analysis, the TIM protein has a conserved protein structure and has a ligand binding site in the IgV domain.

[0004] TIM-3 was identified as a molecule specifically expressed on mouse Th1 cells but not on Th2 cells (Non-patent Document 3). The DNA sequence, the amino acid sequence and the three-dimensional structure of TIM-3 is available in the public data base such as the GenBank accession number NM_032782 and NM_134250. TIM-3 is also known as HAVCR2.

[0005] In humans, as similar to mice, TIM-3 is expressed on T-cells as well as phagocytic cells such as macrophages and dendritic cells. Binding of TIM-3 to a protein ligand (e.g., galectin-9) can inhibit the Th1 response via mechanism of apoptosis induction, and therefore lead to such as induction of peripheral tolerance.

[0006] The reduction in expression of human TIM-3 with siRNA or the inhibition of human TIM-3 by blocking-antibody increased the secretion of interferon γ (IFN-γ) from CD4 positive T-cells, supporting the inhibitory role of TIM-3 in human T cells. In phagocytes, TIM-3 also functions as a receptor for recognizing the apoptosis cells.

[0007] Analysis of clinical samples from autoimmune disease patients showed no expression of TIM-3 in CD4 positive cells. In particular, in T cell clones derived from the cerebrospinal fluid of patients with multiple sclerosis, the expression level of TIM-3 was lower and the secretion level of IFN-γ was higher than those of clones derived from normal healthy persons (Non-patent Document 4). There are reports on relation of TIM-3 with allergic diseases or asthma (Patent Documents 1 and 2).

[0008] According to the microarray analysis of hematopoietic stem cells from acute myeloid leukemia (hereinafter referred to as "AML") patients and normal hematopoietic stem cells, TIM-3 is expressed on AML stem cells and therefore the analysis suggested involvement of TIM-3 in hematological malignancy (Non-patent Document 5 and Patent Document 3).

[0009] Examples of the anti-TIM-3 monoclonal antibodies which were established up to now include anti-human TIM-3 rat monoclonal antibody (Clone 344823, manufactured by R&D Systems) and anti-human TIM-3 mouse monoclonal antibody (Clone F38-2E2, manufactured by R&D Systems).

Related Art

Pantent Literature

[0010]

Pantent Literature 1 WO96/27603
Pantent Literature 2 WO2003/063792
Pantent Literature 3 WO2009/091547

Non-Pantent Literature

[0011]

Samsung Bioepis Exhibit No. 1002
Page 12063

Non-Pantent Literature 1 Hafler DA et al., JExp Med. 205: 2699-701 (2008)
Non-Pantent Literature 2 Anderson AC et al., Science 318: 1141-3 (2007)
Non-Pantent Literature 3 Monney L et al., Nature 415: 536-41 (2002)
Non-Pantent Literature 4 Koguchi K et al., J Exp Med. 203: 1413-8 (2006)
Non-Pantent Literature 5 Majeti R et al., Proc Natl Acad Sci USA 2009 Mar 3; 106 (9): 3396-401.

Disclosure of Invention

Problems to Be Solved by the Invention

[0012] However, there is no report on monoclonal antibody against human TIM-3 having ADCC activity. Therefore, the object of the present invention is to provide a monoclonal antibody or an antibody fragment which binds to the amino acid sequence or the three-dimensional structure of the extracellular region of TIM-3 and expresses ADCC activity. In addition, the object of the present invention is to provide an anti-human TIM-3 antibody having high ADCC activity by screening an anti-human TIM-3 antibody which competes with the monoclonal antibody or the antibody fragment thereof.
[0013] In addition, the present invention is to provide a hybridoma which produces the antibody; a DNA which encodes the antibody; a vector which comprises the DNA; a transformant obtained by transforming the vector; a process for producing an antibody or an antibody fragment thereof using the hybridoma or the transformant; and a diagnostic agent or a therapeutic agent using the antibody or the antibody fragment thereof as an active ingredient.

Means for Solving the Problems

[0014] The gist of the present invention relates to the followings.

(1) A monoclonal antibody or an antibody fragment thereof, which binds to an extracellular region of human TIM-3 while competing with one antibody selected from the following (i) to (iii):

(i) an antibody which comprises a heavy chain (hereinafter referred to as "H chain") of an antibody which comprises complementary determining regions (hereinafter referred to as "CDR") 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 1 to 3, respectively, and comprises a light chain (hereinafter referred to as "L chain") of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 4 to 6, respectively,
(ii) an antibody which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 11 to 13, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 14 to 16, respectively,
(iii) an antibody which comprises an H chain of an antibody which comprises CDRs1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 21 to 23, respectively, and comprises an L chain of an antibody which comprises CDRs1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 24 to 26, respectively.

(2) The monoclonal antibody or the antibody fragment thereof described in the above (1), wherein the monoclonal antibody binds to the same epitope to which one antibody selected from the above (i) to (iii) binds.
(3) A monoclonal antibody or an antibody fragment thereof, which binds to an extracellular region of human TIM-3 while competing with one antibody selected from the following (a) and (b):

(a) an antibody which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 8 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 10,
(b) an antibody which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 18 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 20.

(4) The monoclonal antibody or the antibody fragment thereof described in the above (3), which binds to the same epitope to which one antibody selected from the above (a) or (b) binds.
(5) The monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (4), which is a recombinant antibody.
(6) The monoclonal antibody or the antibody fragment thereof described in the above (5), which is a recombinant antibody selected from a human chimeric antibody, a humanized antibody and a human antibody.
(7) A monoclonal antibody or an antibody fragment thereof, which is one selected from the following (i) to (iii):

Samsung Bioepis Exhibit No. 1002
Page 12064

(i) a monoclonal antibody and an antibody fragment thereof which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 1 to 3, respectively, and comprises an L chain of an antibody which comprises CDRs1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 4 to 6, respectively,
(ii) a monoclonal antibody and an antibody fragment thereof which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 11 to 13, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 14 to 16, respectively,
(iii) a monoclonal antibody and an antibody fragment thereof which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 21 to 23, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 24 to 26, respectively.

(8) A monoclonal antibody and an antibody fragment thereof, which is one selected from the following (a) and (b):

(a) a monoclonal antibody and an antibody fragment thereof which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 8 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 10,
(b) a monoclonal antibody and an antibody fragment thereof which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 18 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 20.

(9) A monoclonal antibody and an antibody fragment thereof which binds to the amino acid sequences at positions 67 to 105, the amino acid sequences at positions 67 to 96 or the amino acid sequences at positions 67 to 87 in the amino acid sequence of IgV domain of human TIM-3 represented by SEQ ID NO: 53.
(10) The antibody fragment described in any one of the above (1) to (9), wherein the antibody fragment is an antibody fragment selected from Fab, Fab', $F(ab')_2$, a single chain antibody (scFv), a dimerized V region (diabody), a disulfide stabilized V region (dsFv) and a peptide comprising CDR.
(11) A DNA which encodes the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10).
(12) A recombinant vector which comprises the DNA described in the above (11).
(13) A transformant obtainable by introducing the recombinant vector described in the above (12) into a host cell.
(14) A process for producing the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10), which comprises culturing the transformant described in the above (13) in culture to form and accumulate the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10), and recovering the monoclonal antibody or the antibody fragment thereof from the culture.
(15) A method for immunologically detecting or measuring a human TIM-3 which comprises using the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10).
(16) A reagent for detecting or measuring a human TIM-3 which comprises the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10).
(17) A diagnostic agent for a disease relating to a human TIM-3 positive cell which comprises the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10).
(18) A method for diagnosing a disease relating to a human TIM-3 positive cell which comprises detect or measure a human TIM-3 positive cell using the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10).
(19) A method for diagnosing a disease relating to a human TIM-3 positive cell, which comprises ditecting or measuring a human TIM-3 using the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10).
(20) Use of the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10) for the manufacture of a diagnostic agent for a disease relating to a human TIM-3 positive cell.
(21) A therapeutic agent for a disease relating to a human TIM-3 positive cell, which comprises the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10).
(22) A therapeutic method for a disease relating to a human TIM-3 positive cell, which comprises inducing cell death of a human TIM-3 positive cell using the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10).
(23) Use of the monoclonal antibody or the antibody fragment thereof described in any one of the above (1) to (10) for the manufacture of a therapeutic agent for a disease relating to a human TIM-3 positive cell.

Samsung Bioepis Exhibit No. 1002
Page 12065

Effects of the Invention

[0015] The monoclonal antibody or the antibody fragment of the present invention specifically recognizes the amino acid sequence or the three-dimensional structure of the extracellular region of human TIM-3, and binds to the extracellular region. The amino acid sequence or the three-dimensional structure of the extracellular region of human TIM-3 which is recognized by the monoclonal antibody or the antibody fragment of the present invention is different from those recognized by known anti-TIM-3 monoclonal antibodies. Therefore, the monoclonal antibody or the antibody fragment of the present invention has higher ADCC activity. The monoclonal antibody or the antibody fragment of the present invention which specifically binds to the extracellular region of human TIM-3 and has higher ADCC activity is useful as a therapeutic agent and a diagnostic agent for a disease relating to a human TIM-3 positive cell.

[0016] The present invention may provide a hybridoma which produces the antibody; a DNA which encodes the antibody; a vector which comprises the DNA; a transformant obtained by transforming the vector; a process for producing an antibody or an antibody fragment thereof using the hybridoma or the transformant; and a diagnostic agent or a therapeutic agent using the antibody or the antibody fragment thereof.

Brief Description of the Drawings

[0017]

[Fig. 1] Fig. 1 is the amino acid sequences which represent HV0, HV3, HV4, HV5, HV6, HV7, HV8, HV10, and HV12 of the designed H chain variable regions of antibody 8213, respectively.

[Fig. 2] Fig. 2 is the amino acid sequences which represent LV0, LV2, LV4, LV5, LV6, LV7, and LV9 of the designed L chain variable regions of antibody 8213.

Embodiments for Carrying Out the Invention

[0018] The human TIM-3 of the present invention include a polypeptide comprising the amino acid sequence represented by SEQ ID NO: 53 or NCBI Accession No. NM_032782, and having a function of TIM-3; a polypeptide comprising an amino acid sequence having at least 60% homology, preferably at least 80% homology, more preferably at least 90% homology, and most preferably at least 95% homology, with the amino acid sequence represented by SEQ ID NO: 53 or NCBI Accession No. NM_032782, and having a function of TIM-3; and the like.

[0019] The polypeptide comprising an amino acid sequence wherein one or more amino acid residue(s) is/are deleted, substituted and/or added in the amino acid sequence represented by SEQ ID NO: 53 or NCBI Accession No. NM_032782 can be obtained, for example, by introducing a site-directed mutation into DNA encoding the polypeptide comprising the amino acid sequence represented by SEQ ID NO: 53 by site-directed mutagenesis described in Molecular Cloning, A Laboratory Manual, Second Edition (Cold Spring Harbor Laboratory Press, 1989), Current Protocols in Molecular Biology (John Wiley & Sons, 1987-1997), Nucleic Acids Research, 10, 6487 (1982), Proc. Natl. Acad. Sci. USA, 79, 6409 (1982), Gene, 34, 315 (1985), Proc. Natl. Acad. Sci. USA, 82, 488 (1985), or the like.

[0020] The number of amino acid residues which are deleted, substituted or added is not particularly limited, and the number is preferably, 1 to dozens, such as 1 to 20, and more preferably 1 to several, such as 1 to 5.

[0021] As a gene which encodes human TIM-3, examples include the nucleotide sequence represented by SEQ ID NO: 52 or NCBI Accession No. NM_032782. Examples also include a gene comprising a nucleotide sequence in which at least one nucleotide is deleted, substituted or added in the nucleotide sequence represented by SEQ ID NO: 52 or NCBI Accession No. NM_032782 and comprising a DNA encoding a polypeptide having a function of TIM-3; a gene comprising an nucleotide sequence having at least 60% homology, preferably at least 80% homology, and more preferably at least 95% homology, with the nucleotide sequence represented by SEQ ID NO: 52 or NCBI Accession No. NM_032782 and comprising a DNA encoding a polypeptide having a function of TIM-3; a gene which hybridizes with the DNA consisting of the nucleotide sequence represented by SEQ ID NO: 52 or NCBI Accession No. NM_032782 under stringent conditions and encodes a polypeptide having a function of TIM-3; and the like.

[0022] In the present invention, the DNA which hybridizes under stringent conditions refers to a DNA which is obtained by colony hybridization, plaque hybridization, Southern blot hybridization, DNA microarray analysis, or the like using a DNA consisting of the nucleotide sequence represented by SEQ ID NO: 52 or NCBI Accession No. NM_032782 as a probe.

[0023] A specific example of such DNA is a DNA which can be identified by performing hybridization at 65°C in the presence of 0.7 to 1.0 mol/L sodium chloride using a filter or a slide glass with colony- or plaque-derived DNA, PCR products or oligo DNA encoding the DNA sequence immobilized thereon, and then washing the filter or a slide glass at 65°C with a 0.1 to 2-fold concentration SSC solution (1-fold concentration SSC solution: 150 mmol/L sodium chloride and 15 mmol/L sodium citrate). Hybridization can be carried out according to the methods described in Molecular Cloning, A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press (1989), Current Protocols in Molecular

Samsung Bioepis Exhibit No. 1002
Page 12066

Biology, John Wiley & Sons (1987-1997); DNA Cloning 1: Core Techniques, A Practical Approach, Second Edition, Oxford University (1995); and the like.

[0024] Specifically, the DNA capable of hybridization includes DNA having at least 60% or more homology, preferably 80% or more homology, and more preferably 95% or more homology to the nucleotide sequence represented by SEQ ID NO: 52 or NCBI Accession No. NM_032782.

[0025] In the nucleotide sequence of the gene encoding a protein of a eukaryote, genetic polymorphism is often recognized. The TIM-3 gene used in the present invention also includes a gene in which small modification is generated in the nucleotide sequence by such polymorphism.

[0026] The number of the homology described in the present invention may be a number calculated by using a homology search program known by the skilled person, unless otherwise indicated. Regarding the nucleotide sequence, the number may be calculated by using a default parameter in BLAST [J. Mol. Biol., 215, 403 (1990)] or the like, and regarding the amino acid sequence, the number may be calculated by using a default parameter in BLAST2 *[*Nucleic Acids Res., 25, 3389 (1997); Genome Res., 7, 649 (1997); http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/information3.html] or the like.

[0027] As the default parameter, G (cost to open gap) is 5 for the nucleotide sequence and 11 for the amino acid sequence; -E (cost to extend gap) is 2 for the nucleotide sequence and 1 for the amino acid sequence; -q (penalty for nucleotide mismatch) is -3; -r (reward for nucleotide match) is 1; -e (expect value) is 10; -W (wordsize) is 11 residues for the nucleotide sequence and 3 residues for the amino acid sequence;.-y (Dropoff (X) for blast extensions in bits) is 20 for blastn and 7 for a program other than blastn; -X (X dropoff value for gapped alignment in bits) is 15; and Z (final X dropoff value for gapped alignment in bits) is 50 for blastn and 25 for a program other than blastn (http://www.ncbi.nlm.nih.gov/blast/html/blastcgihelp.html).

[0028] The polypeptide comprising a partial sequence of the amino acid sequence represented by SEQ ID NO: 53 or NCBI Accession No. NM_032782 can be prepared according to a method known by the skilled person. For example, it can be prepared by deleting a part of DNA encoding the amino acid sequence represented by SEQ ID NO: 52 and culturing a transformant into which an expression vector containing the DNA is introduced.

[0029] Also, based on the thus prepared polypeptide or DNA, a polypeptide comprising an amino acid sequence in which one or more amino acid(s) is/are deleted, substituted or added in a partial sequence of the amino acid sequence represented by SEQ ID NO: 53 or NCBI Accession No. NM_032782 can be prepared in the same manner as described above.

[0030] The polypeptide comprising a parcial sequence of the amino acid sequence represented by SEQ ID NO: 53 or NCBI Accession No. NM_032782; or the polypeptide comprising an amino acid sequence in which at least one amino acid is deleted, substituted or added in a parcial sequence of the amino acid sequence represented by SEQ ID NO: 53 or NCBI Accession No. NM_032782 can also be produced by a chemical synthesis method such as fluorenylmethoxycarbonyl (Fmoc) method or t-butyloxycarbonyl (tBoc) method.

[0031] The extracellular region of human TIM-3 of the present invention includes, for example, regions predicted by using the amino acid sequence of the polypeptide represented by SEQ ID NO: 53 with conventionally known transmembrane region prediction program SOSUI (http://bp.nuap.nagoya-u.ac.jp/sosui/sosui submit.html), TMHMM ver. 2 (http://www.cbs.dtu.dk/services/TMHMM-2.0/), ExPASy Proteomics Server (http://Ca.expasy.org/) or SMART (http://smart.embl-heidelberg.de/).

[0032] In the present invention, the amino acid sequence of extracellular region of human TIM-3 includes the amino acid sequence at positions 1 to 201 in the amino acid sequence represented by SEQ ID NO: 53, which is the region of the extracellular region predicted by SMART.

[0033] In the present invention, the three-dimensional structure of the extracellular region of human TIM-3 is not limited, so long as the extracellular region of human TIM-3 comprising the amino acid sequence represented by SEQ ID NO: 53 or GenBank accession number NM_032782 has the same structure as in the natural state. The three-dimensional structure of the extracellular region of human TIM-3 in the natural state is a natural type of the three-dimensional structure of human TIM-3 expressed on the surface of the cell membrane.

[0034] Regarding the function of human TIM-3, binding of TIM-3 with a protein ligand (e.g., galectin 9) can inhibit the Th1 response thorough mechanism such as apoptosis induction in Th1 cells, therefore leading to induction of peripheral tolerance. In phagocytes, human TIM-3 functions as a receptor for recognizing the apoptosis cells.

[0035] Binding of the antibody or antibody fragment thereof in the present invention to an amino acid sequence of an extracellular region of human TIM-3 or a three-dimensional structure thereof can be confirmed by a conventionally known immunological immunological detection method using human TIM-3 expressing cells such as a radioimmuno assay with a solid phase sandwich method or enzyme-linked immunosorbent assay (ELISA), and preferably a fluorescent cell staining method in which the binding ability of a cell expressing a specified antigen and an antibody for the specific antigen is confirmed.

[0036] Specific examples include a fluorescent antibody staining method using an FMAT8100HTS System (manufactured by Applied Biosystems) [Cancer Immunol. Immunother, 36, 373 (1993)] or the like, a fluorescent cell staining

Samsung Bioepis Exhibit No. 1002
Page 12067

method using flow cytometry, surface plasmon resonance using a Biacore System (manufactured by GE Healthcare) or the like, and the like.

[0037] Furthermore, a known immunological detection methods [Monoclonal Antibodies - Principles and practice, Third edition, Academic Press (1996), Antibodies - A Laboratory Manual, Cold Spring Harbor Laboratory (1988), Monoclonal Antibody Experimental Manual, Kodan-sha Scientific (1987)] and the like can be combined to confirm the binding.

[0038] In the present invention, the cell expressing human TIM-3 may be any cell, so long as it expresses human TIM-3, and examples include a cell which is naturally present in the human body, a cell line established from the cell which is naturally present in the human body, a cell obtained by a recombinant technique and the like.

[0039] Example of the cell which is naturally present in the human body includes a cell expressing the TIM-3 in the body of a patient suffering from cancer, autoimmune disease or allergic disease, concretely, the cells are Th1 cells, macropharges, dendritic cells, and the like.

[0040] Example of a cell line established from the cell which is naturally present in the human body include a cell line expressing human TIM-3, among cell lines prepared by establishing the human TIM-3-expressing cells obtained from the above cancer patients, and examples include human acute myeloid leukemia cell line KG-1 (ATCC Accession No: CCL-246), human Burkitt's lymphoma cell line Daudi (ATCC Accession No: CCL-213) which are established from a human cell and the like.

[0041] Specific examples of the cell obtained by a recombinant technique may include a human TIM-3-expressing cell obtained by introducing an expression vector comprising a human TIM-3-encoding cDNA into an insect cell, an animal cell or the like, and others.

[0042] In addition, the present invention relates to a monoclonal antibody which recognizes an amino acid sequence or a three-dimensional structure of an extracellular region of human TIM-3 and exhibits ADCC activity.

[0043] The ADCC activity of the present invention is a reaction in which an antibody which is bound to human TIM-3 on the cell surface is bound to FcγRIIIa on the surface of mainly a natural killer cell (hereinafter referred to as NK cell) through Fc region and therefore a cytotoxic molecule such as molecules perforin, and granzyme released from an NK cell leads to cell lysis [Clark M, Chemical Immunology, 65, 88 (1997); Gorter A *et al.,* Immunol. Today, 20, 576 (1999)].

[0044] The antibody of the present invention may be any antibodies as long as it is an antibody or antibody fragment thereof which recognizes an amino acid sequence of an extracellular region of human TIM-3 or a three-dimensional structure thereof and binds to the extracellular region; or an antibody or antibody fragment thereof which binds an extracellular region of human TIM-3 or a three-dimensional structure thereof and have ADCC activity.

[0045] Specific example of the antibody of the present invention may include an antibody which binds to the amino acid sequence selected from sequences preferably at positions 67 to 105, more preferably at positions 67 to 96, and most preferably at positions 67 to 87 among the amino acid sequence of extracellular region of human TIM-3 comprising of the sequence at positions 1 to 201 in the sequence represented by SEQ ID NO: 53, or the three-dimensional structure thereof.

[0046] The example of the antibody includes the monoclonal antibody and the antibody fragment thereof as described in the following (i) to (iii):

(i) a monoclonal antibody or an antibody fragment thereof which comprises a heavy chain (hereinafter referred to as "H chain") of an antibody which comprises complementary determining regions (hereinafter referred to as "CDR") 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 1 to 3, respectively, and comprises a light chain (hereinafter referred to as "L chain") of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 4 to 6, respectively.

(ii) a monoclonal antibody or an antibody fragment thereof which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 11 to 13, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 14 to 16, respectively.

(iii) a monoclonal antibody or an antibody fragment thereof which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 21 to 23, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 24 to 26, respectively.

[0047] The example of the monoclonal antibody includes a monoclonal antibody and an antibody fragment thereof as described in the following (a) and (b):

(a) a monoclonal antibody and an antibody fragment thereof which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 8 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 10,

(b) a monoclonal antibody and an antibody fragment thereof which comprises VH of an antibody comprising the

Samsung Bioepis Exhibit No. 1002
Page 12068

amino acid sequence represented by SEQ ID NO: 18 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 20.

[0048] In addition, the antibody of the present invention include a monoclonal antibody or an antibody fragment thereof which competes with the above monoclonal antibody in the binding of an amino acid sequence of an extracellular region of human TIM-3 or a three-dimensional structure thereof; and a monoclonal antibody or an antibody fragment thereof which binds to the same epitope existing on the extracellular region of human TIM-3 to which the above monoclonal antibody binds.

[0049] In the present invention, an antibody which compete with a monoclonal antibody means an antibody which recognizes the same or a part of the same epitope (also referred to as antigen determinant) on the extracellular region of human TIM-3 as the monoclonal antibody of the present invention, and binds to the epitope. The antibody which binds to the same epitope as the monoclonal antibody of the present invention means an antibody which recognizes and binds to an amino acid sequence of human TIM-3 which the monoclonal antibody of the present invention recognizes.

[0050] The monoclonal antibody of the present invention includes an antibody produced by a hybridoma and a recombinant antibody produced by a transformant transformed with an expression vector containing a gene encoding an antibody.

[0051] The monoclonal antibody is an antibody secreted by a single clone antibody-producing cell, and recognizes only one epitope (also called antigen determinant) and has uniform amino acid sequence (primary structure).

[0052] Examples of the epitope include a single amino acid sequence, a three-dimensional structure comprising the amino acid sequence, a sugar chain-bound amino acid sequence, a three-dimensional structure comprising a sugar chain-bound amino acid sequence, and the like, recognized and bound by a monoclonal antibody.

[0053] The monoclonal antibody of the present invention binds preferably to the amino acid sequence at positions 22 to 131 of the IgV domain of human TIM-3 in the extracellular regions of human TIM-3 represented by SEQ ID NO: 53. Specifically, the amino acid sequence to which the monoclonal antibody of the present invention binds is preferably the amino acid sequence at positions 67 to 105, more preferably the amino acid sequence at positions 67 to 96, and most preferably the amino acid sequence at positions 67 to 87 in the amino acid sequence represented by SEQ ID NO: 53.

[0054] The epitope to which the monoclonal antibody of the present invention binds may preferably be included in the IgV domain of human TIM-3 represented by the amino acid sequence at positions 22 to 131 in the extracellular region of human TIM-3 represented by SEQ ID NO: 53. Specifically, the epitope to which the monoclonal antibody of the present invention binds is preferably included in the amino acid sequence at positions 67 to 105, more preferably included in the amino acid sequence at positions 67 to 96, and most preferably included in the amino acid sequence at positions 67 to 87 in the amino acid sequence represented by SEQ ID NO: 53.

[0055] The amino acid sequence of the epitope to which the monoclonal antibody of the present invention binds may preferably include at least one amino acid selected from the amino acid sequence at positions 67 to 87 in the amino acid sequence represented by SEQ ID NO: 53 in the IgV domain of human TIM-3, and more preferably include at least one amino acid selected from the amino acids at position 67, position 74, position 76, position 78, position 79, position 81, position 83 and position 85.

[0056] The amino acid sequence of the epitope to which the monoclonal antibody of the present invention binds may preferably include at least two or more continuous amino acids selected from positions 67 to 87 of the human TIM-3 IgV domain; and more preferably may include at least one amino acid selected from the amino acids at position 67, position 74, position 76, position 78, position 79, position 81, position 83 and position 85 and include at least two or more continuous amino acids selected from the amino acid sequence at positions 67 to 87 in the amino acid sequence represented by SEQ ID NO: 53.

[0057] Specifically, examples of the amino acid sequence of the epitope to which the monoclonal antibody of the present invention binds include the amino acid sequence comprising the amino acids at positions 67 to 74, the amino acid sequence comprising the amino acids at positions 67 to 76, the amino acid sequence comprising the amino acids at positions 67 to 78, the amino acid sequence comprising the amino acids at positions 67 to 79, the amino acid sequence comprising the amino acids at positions 67 to 81, the amino acid sequence comprising the amino acids at positions 67 to 83, the amino acid sequence comprising the amino acids at positions 67 to 85,

the amino acid sequence comprising the amino acids at positions 74 to 76, the amino acid sequence comprising the amino acids at positions 74 to 78, the amino acid sequence comprising the amino acids at positions 74 to 79, the amino acid sequence comprising the amino acids at positions 74 to 81, the amino acid sequence comprising the amino acids at positions 74 to 83, the amino acid sequence comprising the amino acids at positions 74 to 85,

the amino acid sequence comprising the amino acids at positions 76 to 78, the amino acid sequence comprising the amino acids at positions 76 to 79, the amino acid sequence comprising the amino acids at positions 76 to 81, the amino acid sequence comprising the amino acids at positions 76 to 83, the amino acid sequence comprising the amino acids at positions 76 to 85, the amino acid sequence comprising the amino acids at positions 78 to 79, the amino acid sequence comprising the amino acids at positions 78 to 81, the amino acid sequence comprising the amino acids at positions 78

Samsung Bioepis Exhibit No. 1002
Page 12069

to 83, the amino acid sequence comprising the amino acids at positions 78 to 85,
the amino acid sequence comprising the amino acids at positions 79 to 81, the amino acid sequence comprising the amino acids at positions 79 to 83, the amino acid sequence comprising the amino acids at positions 79 to 85,
the amino acid sequence comprising the amino acids at position 81 to 83, the amino acid sequence comprising the amino acids at positions 81 to 85,
the amino acid sequence comprising the amino acids at positions 83 to 85, and the like,
in the amino acid sequence represented by SEQ ID NO: 53.

[0058] The hybridoma can be prepared, for example, by preparing the above cell expressing TIM-3 as an antigen, inducing an antibody-producing cell having antigen specificity from an animal immunized with the antigen, and fusing the antibody-producing cell with a myeloma cell. The anti-TIM-3 antibody can be obtained by culturing the hybridoma or administering the hybridoma cell into an animal to cause ascites tumor in the animal and separating and purifying the culture or the ascites.

[0059] The animal immunized with an antigen may be any animal, so long as a hybridoma can be prepared, and mouse, rat, hamster, chicken, rabbit or the like is suitably used. Also, the cell having antibody-producing activity can be obtained from such an animal, and the antibody of the present invention includes an antibody produced by a hybridoma obtained by fusion of the cell after *in vitro* immunization with a myeloma cell.

[0060] In the present invention, the recombinant antibody includes an antibody produced by gene recombination, such as a human chimeric antibody, a human CDR grafted antibody, a human antibody and an antibody fragment thereof. Among the recombinant antibodies, one having character of a common monoclonal antibody, low immunogenecity and prolonged half-life in blood is preferable as a therapeutic agent. Examples of the recombinant antibody include an antibody which is prepared by modifying the above monoclonal antibody of the present invention using a recombinant technique.

[0061] The human chimeric antibody is an antibody comprising VH and VL of an antibody of a non-human animal, and a heavy chain constant region (hereinafter referred to as CH) and a light chain constant region (hereinafter referred to as CL) of a human antibody. Specifically, the human chimeric antibody of the present invention can be produced by obtaining cDNAs encoding VH and VL from a hybridoma which produces a monoclonal antibody which specifically recognizes human TIM-3 and binds to an amino acid sequence of extracellular region or a three-dimensional structure thereof, inserting each of them into an expression vector for animal cell comprising DNAs encoding CH and CL of human antibody to thereby construct a vector for expression of human chimeric antibody, and then introducing the vector into an animal cell to express the antibody.

[0062] As the CH of the human chimeric antibody, any CH can be used, so long as it belongs to human immunoglobulin (hereinafter referred to as "hIg"), and those belonging to the hIgG class are preferred, and any one of the subclasses belonging to the hIgG class, such as hIgG1, hIgG2, hIgG3 and hIgG4, can be used. As the CL of the human chimeric antibody, any CL can be used, so long as it belongs to the hIg class, and those belonging to κ class or λ class can be used.

[0063] Specific examples of the human chimeric antibody of the present invention includes a chimeric antibody which comprises VH of the antibody comprising the amino acid sequence represented by SEQ ID NO: 28 and comprises VL of the antibody comprising the amino acid sequence represented by SEQ ID NO: 30.

[0064] In addition, the chimeric antibody of the present invention include a chimeric antibody which competes with the above monoclonal antibody in the binding of an extracellular region of human TIM-3 or a three-dimensional structure thereof; and a chimeric antibody which binds to the same epitope existing on the extracellular region of human TIM-3 to which the above chimeric antibody binds.

[0065] The human CDR grafted antibody is also called as a humanized antibody and is an antibody in which CDR of VH and VL of a non-human animal antibody were grafted into the appropriate site of VH and VL of a human antibody. The human CDR grafted antibody of the present invention can be produced by constructing cDNAs encoding an antibody V region in which the amino acid sequences of CDRs of VH and VL of an antibody derived from a non-human animal produced by a hybridoma which produces a monoclonal antibody which specifically recognizes three-dimensional structure of TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof are grafted into frameworks (hereinafter referred to as "FR") of VH and VL of a suitable human antibody, inserting each of them into an expression vector for animal cell comprising genes encoding CH and CL of a human antibody to thereby construct a vector for expression of humanized antibody, and introducing it into an animal cell to thereby express and produce the humanized antibody.

[0066] As the CH of the human CDR grafted antibody, any CH can be used, so long as it belongs to human immunoglobulin (hereinafter referred to as "hIg"), and those belonging to the hIgG class are preferred, and any one of the subclasses belonging to the hIgG class, such as hIgG1, hIgG2, hIgG3 and hIgG4, can be used. As the CL of the human CDR grafted antibody, any CL can be used, so long as it belongs to the hIg class, and those belonging to κ class or λ class can be used.

[0067] Examples of the CDR grafted antibody of the present invention include a humanized antibody in which CDRs 1 to 3 of VH of the antibody comprises the amino acid sequences represented by SEQ ID NO: 21, 22, and 23, respectively,

Samsung Bioepis Exhibit No. 1002
Page 12070

and CDRs 1 to 3 ofVL of the antibody comprises the amino acid sequences represented by SEQ ID NO: 24, 25, and 26, respectively.

[0068] Specific examples of the humanized antibody include a humanized antibody comprising at least one of the following (a) VH and (b) VL:

(a) VH of the antibody comprising the amino acid sequence represented by SEQ ID NO: 67, or an amino acid sequence in which at least one amino acid residue selected from Lys at position 12, Val at position 20, Arg at position 38, Ala at position 40, Met at position 48, Arg at position 67, Val at position 68, Ile at position 70, Ala at position 72, Thr at position 74, Arg at position 98 and Val at position 113 in the amino acid sequence represented by SEQ ID NO: 67 is substituted with other amino acid residue(s),

(b) VL of the antibody comprising the amino acid sequence represented by SEQ ID NO: 69, or an amino acid sequence in which at least one amino acid residue selected from Leu at position 11, Ala at position 13, Val at position 15, Tyr at position 36, Ala at position 43, Pro at position 44, Leu at position 46, Phe at position 71 and Thr at position 85 in the amino acid sequence represented by SEQ ID NO: 69 is substituted with other amino acid residue(s).

[0069] As the VH comprised in the humanized antibody, the following (1) to (8) are preferable:

(1) VH comprising an amino acid sequence in which Lys at position 12, Val at position 20, Arg at position 38, Ala at position 40, Met at position 48, Arg at position 67, Val at position 68, Ile at position 70, Ala at position 72, Thr at position 74, Arg at position 98 and Val at position 113 in the amino acid sequence represented by SEQ ID NO: 67 are substituted with other amino acid residues;

(2) VH comprising an amino acid sequence in which Lys at position 12, Arg at position 38, Ala at position 40, Met at position 48, Arg at position 67, Val at position 68, Ile at position 70, Ala at position 72, Thr at position 74 and Arg at position 98 in the amino acid sequence represented by SEQ ID NO: 67 are substituted with other amino acid residues;

(3) VH comprising an amino acid sequence in which Val at position 20, Arg at position 38, Met at position 48, Val at position 68, Ile at position 70, Ala at position 72, Arg at position 98 and Val at position 113 in the amino acid sequence represented by SEQ ID NO: 67 are substituted with other amino acid residues;

(4) VH comprising an amino acid sequence in which Arg at position 38, Ala at position 40, Met at position 48, Arg at position 67, Ala at position 72, Thr at position 74 and Arg at position 98 in the amino acid sequence represented by SEQ ID NO: 67 are substituted with other amino acid residues;

(5) VH comprising an amino acid sequence in which Lys at position 12, Arg at position 67, Val at position 68, Ala at position 72, Thr at position 74 and Arg at position 98 in the amino acid sequence represented by SEQ ID NO: 67 are substituted with other amino acid residues;

(6) VH comprising an amino acid sequence in which Arg at position 38, Ala at position 40, Met at position 48, Arg at position 67 and Arg at position 98 in the amino acid sequence represented by SEQ ID NO: 67 are substituted with other amino acid residues,

(7) VH comprising an amino acid sequence in which Arg at position 38, Met at position 48, Arg at position 67 and Thr at position 74 in the amino acid sequence represented by SEQ ID NO: 67 are substituted with other amino acid residues; and

(8) VH comprising an amino acid sequence in which Arg at position 38, Met at position 48 and Arg at position 98 in the amino acid sequence represented by SEQ ID NO: 67 are substituted with other amino acid residues.

[0070] The amino acid sequence of the above VH obtained by the amino acid modifications includes an amino acid sequence in which at least one modification among amino acid modifications for substituting Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly or Val at position 113 with Leu is introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0071] Specific examples of the amino acid sequence of VH in which twelve modifications are introduced include an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0072] Examples of the amino acid sequence of VH in which eleven modifications are introduced include the following amino acid sequence (1) to (12):

(1) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Ala at

Samsung Bioepis Exhibit No. 1002
Page 12071

position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(2) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(3) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(4) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(5) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(6) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(7) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(8) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(9) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(10) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(11) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67; and

(12) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0073] Specific examples of the amino acid sequence of VH in which ten modifications are introduced include the following amino acid sequence (1) to (8):

(1) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;

(2) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced

Samsung Bioepis Exhibit No. 1002
Page 12072

in the amino acid sequence represented by SEQ ID NO: 67;
(3) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(4) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(7) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(8) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0074] Examples of the amino acid sequence of VH in which eight modifications are introduced include the following amino acid sequence (1) to (13):

(1) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(2) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(3) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(4) an amino acid sequence in which substitutions ofArg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Arg at position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(7) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(8) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(9) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(10) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Arg at

Samsung Bioepis Exhibit No. 1002
Page 12073

position 98 with Gly and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(11) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(12) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(13) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0075] Specific examples of the amino acid sequence of VH in which seven modifications are introduced include the following amino acid sequence (1) to (11):

(1) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(2) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(3) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(4) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitutions ofArg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(7) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Val at position 68 with Ala, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(8) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(9) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(10) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Ile at position 70 with Leu, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(11) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0076] Specific Examples of the amino acid sequence of VH in which six modifications are introduced include the following amino acid sequence (1) to (16):

(1) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 67 with Lys, Val at position 68 with Ala, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;

Samsung Bioepis Exhibit No. 1002
Page 12074

(2) an amino acid sequence in which substitutions of Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(3) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(4) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(7) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(8) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(9) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(10) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(11) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(12) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(13) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(14) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(15) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(16) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Ala at position 72 with Val, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0077] Specific examples of the amino acid sequence of VH in which five modifications are introduced include the following amino acid sequence (1) to (7):

(1) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(2) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(3) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;

Samsung Bioepis Exhibit No. 1002
Page 12075

(4) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitutions ofArg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Ile at position 70 with Leu and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Ala at position 72 with Val and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(7) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys, Thr at position 74 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0078] Specific examples of the amino acid sequence of VH in which four modifications are introduced include the following amino acid sequence (1) to (8):

(1) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys and Thr at position 74 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(2) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys, Met at position 48 with Ile and Arg at position 67 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(3) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys, Met at position 48 with Ile and Arg at position 67 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(4) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile and Arg at position 67 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys and Val at position 68 with Ala are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys and Ile at position 70 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(7) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys and Ala at position 72 with Val are introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(8) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile, Arg at position 67 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0079] Specific examples of the amino acid sequence of VH in which three modifications are introduced include the following amino acid sequence (1) to (9):

(1) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(2) an amino acid sequence in which substitutions of Lys at position 12 with Val, Arg at position 38 with Lys and Met at position 48 with Ile are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(3) an amino acid sequence in which substitutions of Val at position 20 with Leu, Arg at position 38 with Lys and Met at position 48 with Ile are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(4) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Ala at position 40 with Arg and Met at position 48 with Ile are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile and Arg at position 67 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile and Val at position 68 with Ala are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(7) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile and Ile at position 70 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;

Samsung Bioepis Exhibit No. 1002
Page 12076

(8) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile and Ala at position 72 with Val are introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(9) an amino acid sequence in which substitutions of Arg at position 38 with Lys, Met at position 48 with Ile and Thr at position 74 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;

[0080] Specific examples of the amino acid sequence of VH in which two modifications are introduced include the following amino acid sequence (1) to (21):

(1) an amino acid sequence in which substitutions of Lys at position 12 with Val and Arg at position 38 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(2) an amino acid sequence in which substitutions of Val at position 20 with Leu and Arg at position 38 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(3) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Ala at position 40 with Arg are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(4) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Met at position 48 with Ile are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Arg at position 67 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Val at position 68 with Ala are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(7) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Ile at position 70 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(8) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Ala at position 72 with Val are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(9) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Thr at position 74 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(10) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(11) an amino acid sequence in which substitutions of Arg at position 38 with Lys and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(12) an amino acid sequence in which substitutions of Lys at position 12 with Val and Met at position 48 with Ile are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(13) an amino acid sequence in which substitutions of Val at position 20 with Leu and Met at position 48 with Ile are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(14) an amino acid sequence in which substitutions of Ala at position 40 with Arg and Met at position 48 with Ile are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(15) an amino acid sequence in which substitutions of Met at position 48 with Ile and Arg at position 67 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(16) an amino acid sequence in which substitutions of Met at position 48 with Ile and Val at position 68 with Ala are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(17) an amino acid sequence in which substitutions of Met at position 48 with Ile and Ile at position 70 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(18) an amino acid sequence in which substitutions of Met at position 48 with Ile and Ala at position 72 with Val are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(19) an amino acid sequence in which substitutions of Met at position 48 with Ile and Thr at position 74 with Lys are introduced in the amino acid sequence represented by SEQ ID NO: 67;
(20) an amino acid sequence in which substitutions of Met at position 48 with Ile and Arg at position 98 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(21) an amino acid sequence in which substitutions of Met at position 48 with Ile and Val at position 113 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0081] Specific examples of the amino acid sequence of VH in which one modification is introduced include the following amino acid sequence (1) to (12):

(1) an amino acid sequence in which substitution of Lys at position 12 with Val is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(2) an amino acid sequence in which substitution of Val at position 20 with Leu is introduced in the amino acid sequence represented by SEQ ID NO: 67;

Samsung Bioepis Exhibit No. 1002
Page 12077

(3) an amino acid sequence in which substitution of Arg at position 38 with Lys is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(4) an amino acid sequence in which substitution of Ala at position 40 with Arg is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(5) an amino acid sequence in which substitution of Met at position 48 with Ile is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(6) an amino acid sequence in which substitution of Arg at position 67 with Lys is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(7) an amino acid sequence in which substitution of Val at position 68 with Ala is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(8) an amino acid sequence in which substitution of Ile at position 70 with Leu is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(9) an amino acid sequence in which substitution of Ala at position 72 with Val is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(10) an amino acid sequence in which substitution of Thr at position 74 with Lys is introduced in the amino acid sequence represented by SEQ ID NO: 67;
(11) an amino acid sequence in which substitution of Arg at position 98 with Gly is introduced in the amino acid sequence represented by SEQ ID NO: 67; and
(12) an amino acid sequence in which substitution of Val at position 113 with Leu is introduced in the amino acid sequence represented by SEQ ID NO: 67.

[0082] As the VL comprised in the humanized antibody, the following (1) to (6) are preferable:

(1) VL comprising an amino acid sequence in which Leu at position 11, Ala at position 13, Val at position 15, Tyr at position 36, Ala at position 43, Pro at position 44, Leu at position 46, Phe at position 71 and Thr at position 85 in the amino acid sequence represented by SEQ ID NO: 69 are substituted with other amino acid residues.
(2) VL comprising an amino acid sequence in which Leu at position 11, Val at position 15, Tyr at position 36, Pro at position 44, Leu at position 46, Phe at position 71 and Thr at position 85 in the amino acid sequence represented by SEQ ID NO: 69 are substituted with other amino acid residues.
(3) VL comprising an amino acid sequence in which Val at position 15, Tyr at position 36, Pro at position 44, Leu at position 46, Phe at position 71 and Thr at position 85 in the amino acid sequence represented by SEQ ID NO: 69 are substituted with other amino acid residues.
(4) VL comprising an amino acid sequence in which Tyr at position 36, Ala at position 43, Pro at position 44, Leu at position 46 and Thr at position 85 in the amino acid sequence represented by SEQ ID NO: 69 are substituted with other amino acid residues.
(5) VL comprising an amino acid sequence in which Val at position 15, Tyr at position 36, Leu at position 46 and Phe at position 71 in the amino acid sequence represented by SEQ ID NO: 69 are substituted with other amino acid residues.
(6) VL comprising an amino acid sequence in which Tyr at position 36 and Pro at position 44 in the amino acid sequence represented by SEQ ID NO: 69 are substituted with other amino acid residues.

[0083] The amino acid sequence of the above VL obtained by the amino acid modifications includes an amino acid sequence in which at least one modification among amino acid modifications for substituting Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr, and Thr at position 85 with Asp is introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0084] Examples of the amino acid sequence of VL in which nine modifications are introduced include an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr, and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0085] Specific examples of the amino acid sequence of VL in which eight modifications are introduced include the following amino acid sequence (1) to (9):

(1) an amino acid sequence in which substitutions of Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

Samsung Bioepis Exhibit No. 1002
Page 12078

(2) an amino acid sequence in which substitutions of Leu at position 11 with Met, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(3) an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(4) an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(5) an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(6) an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(7) an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(8) an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69; and

(9) an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0086] Specific example of the amino acid sequence of VL in which seven modifications are introduced include the following amino acid sequence (1) to (9):

(1) an amino acid sequence in which substitutions of Leu at position 11 with Met, Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(2) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(3) an amino acid sequence in which substitutions of Leu at position 11 with Met, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(4) an amino acid sequence in which substitutions of Leu at position 11 with Met, Val at position 15 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(5) an amino acid sequence in which substitutions of Leu at position 11 with Met, Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(6) an amino acid sequence in which substitutions of Leu at position 11 with Met, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(7) an amino acid sequence in which substitutions of Leu at position 11 with Met, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;

(8) an amino acid sequence in which substitutions of Leu at position 11 with Met, Val at position 15 with Leu, Tyr at

Samsung Bioepis Exhibit No. 1002
Page 12079

position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69; and
(9) an amino acid sequence in which substitutions of Leu at position 11 with Met, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0087] Specific example of the amino acid sequence of VL in which six modifications are introduced include the following amino acid sequence (1) to (6):

(1) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(2) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(3) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(4) an amino acid sequence in which substitutions of Leu at position 11 with Met, Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(5) an amino acid sequence in which substitutions of Leu at position 11 with Met, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69; and
(6) an amino acid sequence in which substitutions of Leu at position 11 with Met, Ala at position 13 with Val, Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0088] Specific example of the amino acid sequence of VL in which five modifications are introduced include the following amino acid sequence (1) to (7):

(1) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Ala at position 43with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(2) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe and Leu at position 46 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(3) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(4) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(5) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(6) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Ala at position 43 with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69; and
(7) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0089] Specific example of the amino acid sequence of VL in which four modifications are introduced include the following amino acid sequence (1) to (10):

(1) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Leu at position 46 with Gly and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ

Samsung Bioepis Exhibit No. 1002
Page 12080

ID NO: 69;
(2) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe and Leu at position 46 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(3) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(4) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Pro at position 44 with Phe and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(5) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(6) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(7) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(8) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Pro at position 44 with Phe, Leu at position 46 with Gly and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(9) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Pro at position 44 with Phe, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69; and
(10) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0090] Specific example of the amino acid sequence ofVL in which three modifications are introduced include the following amino acid sequence (1) to (7):

(1) an amino acid sequence in which substitutions of Leu at position 11 with Met, Tyr at position 36 with Leu and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(2) an amino acid sequence in which substitutions of Ala at position 13 with Val, Tyr at position 36 with Leu and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(3) an amino acid sequence in which substitutions of Val at position 15 with Leu, Tyr at position 36 with Leu and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(4) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Ala at position 43 with Ser and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(5) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Pro at position 44 with Phe and Leu at position 46 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(6) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Pro at position 44 with Phe and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69; and
(7) an amino acid sequence in which substitutions of Tyr at position 36 with Leu, Pro at position 44 with Phe and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0091] Specific example of the amino acid sequence of VL in which two modifications are introduced include the following amino acid sequence (1) to (15):

(1) an amino acid sequence in which substitutions of Tyr at position 36 with Leu and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(2) an amino acid sequence in which substitutions of Leu at position 11 with Met and Tyr at position 36 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(3) an amino acid sequence in which substitutions of Ala at position 13 with Val and Tyr at position 36 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(4) an amino acid sequence in which substitutions of Val at position 15 with Leu and Tyr at position 36 with Leu are introduced in the amino acid sequence represented by SEQ ID NO: 69;

Samsung Bioepis Exhibit No. 1002
Page 12081

(5) an amino acid sequence in which substitutions of Tyr at position 36 with Leu and Ala at position 43 with Ser are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(6) an amino acid sequence in which substitutions of Tyr at position 36 with Leu and Leu at position 46 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(7) an amino acid sequence in which substitutions of Tyr at position 36 with Leu and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(8) an amino acid sequence in which substitutions of Tyr at position 36 with Leu and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(9) an amino acid sequence in which substitutions of Leu at position 11 with Met and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(10) an amino acid sequence in which substitutions of Ala at position 13 with Val and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(11) an amino acid sequence in which substitutions of Val at position 15 with Leu and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(12) an amino acid sequence in which substitutions of Ala at position 43 with Ser and Pro at position 44 with Phe are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(13) an amino acid sequence in which substitutions of Pro at position 44 with Phe and Leu at position 46 with Gly are introduced in the amino acid sequence represented by SEQ ID NO: 69;
(14) an amino acid sequence in which substitutions of Pro at position 44 with Phe and Phe at position 71 with Tyr are introduced in the amino acid sequence represented by SEQ ID NO: 69; and
(15) an amino acid sequence in which substitutions of Pro at position 44 with Phe and Thr at position 85 with Asp are introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0092] Specific example of the amino acid sequence of VH in which one modification is introduced include the following amino acid sequence (1) to (9):

(1) an amino acid sequence in which substitution of Leu at position 11 with Met is introduced in the amino acid sequence represented by SEQ ID NO: 69;
(2) an amino acid sequence in which substitution of Ala at position 13 with Val is introduced in the amino acid sequence represented by SEQ ID NO: 69;
(3) an amino acid sequence in which substitution of Val at position 15 with Leu is introduced in the amino acid sequence represented by SEQ ID NO: 69;
(4) an amino acid sequence in which substitution of Tyr at position 36 with Leu is introduced in the amino acid sequence represented by SEQ ID NO: 69;
(5) an amino acid sequence in which substitution of Ala at position 43 with Ser is introduced in the amino acid sequence represented by SEQ ID NO: 69;
(6) an amino acid sequence in which substitution of Pro at position 44 with Phe is introduced in the amino acid sequence represented by SEQ ID NO: 69;
(7) an amino acid sequence in which substitution of Leu at position 46 with Gly is introduced in the amino acid sequence represented by SEQ ID NO: 69;
(8) an amino acid sequence in which substitution of Phe at position 71 with Tyr is introduced in the amino acid sequence represented by SEQ ID NO: 69; and
(9) an amino acid sequence in which substitution of Thr at position 85 with Asp is introduced in the amino acid sequence represented by SEQ ID NO: 69.

[0093] In addition, examples of the humanized antibody of the present invention include a humanized antibody in which VH of the antibody comprises the amino acid sequence represented by SEQ ID NO: 67 and/or VL of the antibody comprises the amino acid sequence represented by SEQ ID: 69, a humanized antibody in which VH of the antibody comprises the amino acid sequence represented by SEQ ID NO: 67 and/or VL of the antibody comprises any one of the amino acid sequences shown in Fig. 2, or a humanized antibody in which VH of the antibody comprises any one of the amino acid sequences shown in Fig. 1 and/or VL of the antibody comprises the amino acid sequence represented by SEQ ID: 69.

[0094] Furthermore, examples of the humanized antibody of the present invention include a humanized antibody which competes with the monoclonal antibody of the present invention in the binding of an amino acid sequence of an extracellular region of human TIM-3 or a three-dimensional structure thereof; and a humanized antibody which binds to the same epitope existing on the extracellular region of human TIM-3 to which the above humanized antibody binds.

[0095] A human antibody is originally an antibody naturally existing in the human body, and it also includes an antibody obtained from a human antibody phage library or a human antibody-producing transgenic animal, which is prepared

Samsung Bioepis Exhibit No. 1002
Page 12082

based on the recent advanced techniques in genetic engineering, cell engineering and developmental engineering.

[0096] The antibody existing in the human body can be prepared, for example, by isolating a human peripheral blood lymphocyte, immortalizing it by infecting with EB virus or the like, and then cloning it to thereby obtain lymphocytes capable of producing the antibody, culturing the lymphocytes thus obtained, and purifying the antibody from the supernatant of the culture.

[0097] The human antibody phage library is a library in which antibody fragments such as Fab and scFv are expressed on the phage surface by inserting a gene encoding an antibody prepared from a human B cell into a phage gene. A phage expressing an antibody fragment having the desired antigen binding activity can be recovered from the library, using its activity to bind to an antigen-immobilized substrate as the index. The antibody fragment can be converted further into a human antibody molecule comprising two full H chains and two full L chains by genetic engineering techniques.

[0098] A human antibody-producing transgenic animal is an animal in which a human antibody gene is integrated into cells. Specifically, a human antibody-producing transgenic animal can be prepared by introducing a gene encoding a human antibody into a mouse ES cell, grafting the ES cell into an early embryo of mouse and then developing it. A human antibody is prepared from the human antibody-producing transgenic non-human animal by obtaining a human antibody-producing hybridoma by a hybridoma preparation method usually carried out in non-human mammals, culturing the obtained hybridoma and forming and accumulating the human antibody in the supernatant of the culture.

[0099] In the amino acid sequence constituting the above antibody or antibody fragment thereof, an antibody or antibody fragment thereof in which one or more amino acids are deleted, substituted, inserted or added, having activity similar to the above antibody or antibody fragment thereof is also included in the antibody or antibody fragment of the present invention.

[0100] The number of amino acids which are deleted, substituted, inserted and/or added is one or more, and is not specifically limited, but it is within the range where deletion, substitution or addition is possible by known methods such as the site-directed mutagenesis described in *Molecular Cloning,* Second Edition, Cold Spring Harbor Laboratory Press (1989); *Current Protocols in Molecular Biology,* John Wiley & Sons (1987-1997); *Nucleic Acids Research,* 10, 6487 (1982), *Proc. Natl. Acad. Sci. USA,* 79, 6409 (1982); *Gene,* 34, 315 (1985), *Nucleic Acids Research,* 13, 4431 (1985); *Proc. Natl. Acad. Sci. USA,* 82, 488 (1985) or the like. For example, the number is preferably 1 to dozens, more preferably 1 to 20, furthermore preferably 1 to 10, and most preferably 1 to 5.

[0101] The expression "one or more amino acid residue(s) is/are deleted, substituted, inserted and/or added" in the amino acid sequence of the above antibody means the followings. That is, it means there is deletion, substitution, insertion or addition of one or plural amino acids at optional positions in the same sequence and in one or plural amino acid sequences. Also, the deletion, substitution, insertion or addition may occur at the same time and the amino acid which is substituted, inserted or added may be either a natural type or a non-natural type.

[0102] The natural type amino acid includes L-alanine, L-asparagine, L-aspartic acid, L-glutamine, L-glutamic acid, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, L-valine, L-cysteine and the like.

[0103] Preferable examples of mutually substitutable amino acids are shown below. The amino acids in the same group are mutually substitutable.

Group A: leucine, isoleucine, norleucine, valine, norvaline, alanine, 2-aminobutanoic acid, methionine, O-methylserine, t-butylglycine, t-butylalanine, cyclohexylalanine

Group B: aspartic acid, glutamic acid, isoaspartic acid, isoglutamic acid, 2-aminoadipic acid, 2-aminosuberic acid

Group C: asparagine, glutamine

Group D: lysine, arginine, ornithine, 2,4-diaminobutanoic acid, 2,3-diaminopropionic acid

Group E: proline, 3-hydroxyproline, 4-hydroxyproline

Group F: serine, threonine, homoserine

Group G: phenylalanine, tyrosine

[0104] The antibody fragment of the present invention includes Fab, $F(ab')_2$, Fab', a single chain antibody (scFv), a dimerized V region (diabody), a disulfide stabilized V region (dsFv), a peptide comprising CDR and the like.

[0105] An Fab is an antibody fragment among fragments obtained by treating an IgG antibody molecule with a protease, papain (cleaved at an amino acid residue at position 224 of the H chain), having a molecular weight of about 50,000 and having antigen binding activity, in which about a half of the N-terminal side of H chain and the entire L chain are bound together through a disulfide bond.

[0106] The Fab of the present invention can be produced by treating the monoclonal antibody of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof with papain. Also, the Fab can be produced by inserting DNA encoding Fab of the antibody into an expression vector for prokaryote or an expression vector for eukaryote, and introducing the vector into a prokaryote or eukaryote to express the Fab.

[0107] An $F(ab')_2$ is an antibody fragment having a molecular weight of about 100,000 and having antigen binding

Samsung Bioepis Exhibit No. 1002
Page 12083

activity and comprising two Fab regions which are bound in the hinge position obtained by digesting the lower part of two disulfide bonds in the hinge region of IgG with an enzyme, pepsin.

[0108] The $F(ab')_2$ of the present invention can be produced by treating the monoclonal antibody of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof with pepsin. Also, the $F(ab')_2$ can be produced by binding Fab' described below via a thioether bond or a disulfide bond.

[0109] An Fab' is an antibody fragment having a molecular weight of about 50,000 and antigen binding activity, which is obtained by cleaving a disulfide bond at the hinge region of the above $F(ab')_2$. The Fab' of the present invention can be produced by treating the $F(ab')_2$ of the present invention which specifically recognizes TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof with a reducing agent, such as dithiothreitol. Also, the Fab' can be produced by inserting DNA encoding Fab' fragment of the antibody into an expression vector for prokaryote or an expression vector for eukaryote, and introducing the vector into a prokaryote or eukaryote to express the Fab'.

[0110] An scFv is a VH-P-VL or VL-P-VH polypeptide in which one chain VH and one chain VL are linked using an appropriate peptide linker (hereinafter referred to as "P") and is an antibody fragment having antigen binding activity.

[0111] The scFv of the present invention can be produced by obtaining cDNAs encoding VH and VL of the monoclonal antibody of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof, constructing DNA encoding scFv, inserting the DNA into an expression vector for prokaryote or an expression vector for eukaryote, and then introducing the expression vector into a prokaryote or eukaryote to express the scFv.

[0112] A diabody is an antibody fragment wherein scFv is dimerized, is an antibody fragment having divalent antigen binding activity. In the divalent antigen binding activity, two antigens may be the same or different.

[0113] The diabody of the present invention can be produced by obtaining cDNAs encoding VH and VL of the monoclonal antibody of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof, constructing DNA encoding scFv so that the length of the amino acid sequence of the peptide linker is 8 or less residues, inserting the DNA into an expression vector for prokaryote or an expression vector for eukaryote, and then introducing the expression vector into a prokaryote or eukaryote to express the diabody.

[0114] A dsFv is obtained by binding polypeptides in which one amino acid residue of each of VH and VL is substituted with a cysteine residue via a disulfide bond between the cysteine residues. The amino acid residue to be substituted with a cysteine residue can be selected based on a three-dimensional structure estimation of the antibody in accordance with a known methods *[*Protein Engineering, 7, 697 (1994)].

[0115] The dsFv of the present invention can be produced by obtaining cDNAs encoding VH and VL of the monoclonal antibody of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof, constructing DNA encoding dsFv, inserting the DNA into an expression vector for prokaryote or an expression vector for eukaryote, and then introducing the expression vector into a prokaryote or eukaryote to express the dsFv.

[0116] A peptide comprising CDR is constituted by including one or more regions of CDRs of VH or VL. Peptide comprising plural CDRs can be bound directly or via an appropriate peptide linker.

[0117] The peptide comprising CDR of the present invention can be produced by constructing DNA encoding CDRs of VH and VL of the monoclonal antibody of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof, inserting the DNA into an expression vector for prokaryote or an expression vector for eukaryote, and then introducing the expression vector into a prokaryote or eukaryote to express the peptide. The peptide comprising CDR can also be produced by a chemical synthesis method such as Fmoc method or tBoc method.

[0118] The monoclonal antibody of the present invention includes an antibody conjugate in which the monoclonal antibody or the antibody fragment of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof is chemically or genetically bound to a radioisotope, an agent having a low molecular weight, an agent having a high molecular weight, a protein, a therapeutic antibody or the like.

[0119] The antibody conjugate of the present invention can be produced by chemically conjugating a radioisotope, an agent having a low molecular weight, an agent having a high molecular weight, an adjuvant, a protein, a therapeutic antibody or the like to the N-terminal side or C-terminal side of an H chain or an L chain, adequate substituent or sidechain, sugarchain, and the like of the monoclonal antibody or the antibody fragment of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof *[*Kotai Kogaku Nyumon, published by Chijin Shokan (1994)].

[0120] Also, the antibody conjugate can be genetically produced by linking a DNA encoding the monoclonal antibody or the antibody fragment of the present invention which specifically recognizes human TIM-3 and binds to an amino acid

Samsung Bioepis Exhibit No. 1002
Page 12084

sequence of the extracellular region or three-dimensional structure thereof to other DNA encoding a protein or a therapeutic antibody to be conjugated, inserting the DNA into a vector for expression, and introducing the expression vector into an appropriate host cell.

[0121] The radioisotope includes ^{131}I, ^{125}I, ^{90}Y, ^{64}Cu, ^{199}Tc, ^{77}Lu, ^{211}At and the like. The radioisotope can directly be conjugated with the antibody by Chloramine-T method or the like. Also, a substance chelating the radioisotope can be conjugated with the antibody. The chelating agent includes 1-isothiocyanatobenzyl-3-methyldiethylenetriaminepentaacetic acid (MX-DTPA) and the like.

[0122] The agent having a low molecular weight includes an anti-tumor agent such as an alkylating agent, a nitrosourea agent, a metabolism antagonist, an antibiotic substance, an alkaloid derived from a plant, a topoisomerase inhibitor, an agent for hormonotherapy, a hormone antagonist, an aromatase inhibitor, a P glycoprotein inhibitor, a platinum complex derivative, an M-phase inhibitor and a kinase inhibitor *[*Rinsho Syuyo-gaku (Clinical Oncology), Gan to Kagakuryoho-Sha (1996)], a steroid agent such as hydrocortisone and prednisone, a nonsteroidal agent such as aspirin and indomethacin, immunomodulatory agent such as aurothiomalate, penicillamine, immuno-suppressing agent such as cyclophosphamide and azathioprine, antiinflammatory agent such as anti-histamine agent, for example, chlorpheniramine maleate and clemastine *[*Ensho to Kouensho-Ryoho (Inflammation and Anti-inflammation Therapy), Ishiyaku Shuppann (1982)] and the like.

[0123] Examples of the antitumor agent include amifostine (Ethyol), cisplatin, dacarbazine (DTIC), dactinomycin, mecloretamin (nitrogen mustard), streptozocin, cyclophosphamide, iphosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), epirubicin, gemcitabine (Gemsal), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, fluorouracil, vinblastine, vincristine, bleomycin, daunomycin, peplomycin, estramustine, paclitaxel (Taxol), docetaxel (Taxotea), aldesleukin, asparaginase, busulfan, carboplatin, oxaliplatin, nedaplatin, cladribine, camptothecin, 10-hydroxy-7-ethylcamptothecin (SN38), floxuridine, fludarabine, hydroxyurea, iphosphamide, idarubicin, mesna, irinotecan (CPT-11), nogitecan, mitoxantrone, topotecan, leuprolide, megestrol, melfalan, mercaptopurine, hydroxycarbamide, plicamycin, mitotane, pegasparagase, pentostatin, pipobroman, streptozocin, tamoxifen, goserelin, leuprorelin, flutamide, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil, hydrocortisone, prednisolone, methylprednisolone, vindesine, nimustine, semustine, capecitabine, Tomudex, azacytidine, UFT, oxaliplatin, gefitinib (Iressa), imatinib (STI571), elrotinib, FMS-like tyrosine kinase 3 (Flt3) inhibitor, vascular endothelial growth facotr receptor (VEGFR) inhibitor, fibroblast growth factor receptor (FGFR) inhibitor, Epidermal Growth Factor Receptor (EGFR) inhibitor such as Iressa and Tarceva, radicicol, 17-allylamino-17-demethoxygeldanamycin, rapamycin, amsacrine, all-trans-retinoic acid, thalidomide, anastrozole, fadrozole, letrozole, exemestane, gold thiomalate, D-penicillamine, bucillamine, azathioprine, mizoribine, cyclosporine, rapamycin, hydrocortisone, bexarotene (Targretin), tamoxifen, dexamethasone, progestin substances, estrogen substances, anastrozole (Arimidex), Leuplin, aspirin, indomethacin, celecoxib, azathioprine, penicillamine, gold thiomalate, chlorpheniramine maleate, chlorpheniramine, clemastine, tretinoin, bexarotene, arsenic, voltezomib, allopurinol, calicheamicin, ibritumomab tiuxetan, Targretin, ozogamine, clarithromycin, leucovorin, ifosfamide, ketoconazole, aminoglutethimide, suramin, methotrexate, maytansinoid and derivatives thereof.

[0124] The method for conjugating the agent having low molecular weight with the antibody includes a method in which the agent and an amino group of the antibody are conjugated through glutaraldehyde, a method in which an amino group of the agent and a carboxyl group of the antibody are conjugated through water-soluble carbodiimide, and the like.

[0125] The agent having a high molecular weight includes polyethylene glycol (hereinafter referred to as "PEG"), albumin, dextran, polyoxyethylene, styrene-maleic acid copolymer, polyvinylpyrrolidone, pyran copolymer, hydroxypropylmethacrylamide, and the like. By binding these compounds having a high molecular weight to an antibody or antibody fragment, the following effects are expected: (1) improvement of stability against various chemical, physical or biological factors, (2) remarkable prolongation of half life in blood, (3) disappearance of immunogenicity or suppression of antibody production, and the like *[*Bioconjugate Drug, Hirokawa Shoten (1993)]. For example, the method for binding PEG to an antibody includes a method in which an antibody is allowed to react with a PEG-modifying reagent [Bioconjugate Drug, Hirokawa Shoten (1993)]. The PEG-modifying reagent includes a modifying agent of ε-amino group of lysine (Japanese Published Unexamined Patent Application No. 178926/86), a modifying agent of a carboxyl group of aspartic acid and glutamic acid (Japanese Published Unexamined Patent Application No. 23587/81), a modifying agent of a guanidino group of arginine (Japanese Published Unexamined Patent Application No. 117920/90) and the like.

[0126] The immunostimulator may be any natural products known as immunoadjuvants. Examples of an agent enhancing immunogen include β(1→3)glucan (lentinan, schizophyllan), α-galactosylceramide and the like.

[0127] The protein includes a cytokine or a growth factor which activates a immunocompetent cell, such as NK cell, macrophage or neutrophil, a toxic protein, and the like.

[0128] Examples of the cytokine or the growth factor include interferon (hereinafter referred to as "IFN")-α, IFN-β, IFN-γ, interleukin (hereinafter referred to as "IL")-2, IL-12, IL-15, IL-18, IL-21, IL-23, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF) and the like.

Samsung Bioepis Exhibit No. 1002
Page 12085

[0129] The toxic protein includes ricin, diphtheria toxin, ONTAK and the like, and also includes a toxic protein wherein mutation is introduced into a protein in order to control the toxicity.

[0130] The therapeutic antibody includes an antibody against an antigen in which apoptosis is induced by binding of the antibody, an antibody against an antigen participating in formation of pathologic state of tumor, an antibody against an antigen regulating immunological function and an antibody against an antigen relating to angiogenesis in the pathologic part.

[0131] The antigen in which apoptosis is induced by binding of the antibody includes cluster of differentiation (hereinafter "CD") 19, CD20, CD21, CD22, CD23, CD24, CD37, CD53, CD72, CD73, CD74, CDw75, CDw76, CD77, CDw78, CD79a, CD79b, CD80 (B7.1), CD81, CD82, CD83, CDw84, CD85, CD86 (B7.2), human leukocyte antigen (HLA)-Class II, epidermal growth factor receptor (EGFR) and the like.

[0132] The antigen participating in formation of pathologic state of tumor or the antigen regulating immunological function includes CD40, CD40 ligand, B7 family molecule (CD80, CD86, CD274, B7-DC, B7-H2, B7-H3, B7-H4), ligand of B7 family molecule (CD28, CTLA-4, ICOS, PD-1, BTLA), OX-40, OX-40 ligand, CD137, tumor necrosis factor (TNF) receptor family molecule (DR4, DR5, TNFR1, TNFR2), TNF-related apoptosis-inducing ligand receptor (TRAIL) family molecule, receptor family of TRAIL family molecule (TRAIL-R1, TRAIL-R2, TRAIL-R3, TRAIL-R4), receptor activator of nuclear factor kappa B (RANK), RANK ligand, CD25, folic acid receptor 4, cytokine [IL-1α, IL-1β, IL-4, IL-5, IL-6, IL-10, IL-13, transforming growth factor (TGF) β, TNFα, etc.], receptors of these cytokines, chemokine (SLC, ELC, I-309, TARC, MDC, CTACK, *etc.*) and receptors of these chemokines.

[0133] The antigen for the antibody which inhibits angiogenesis in the pathologic part includes vascular endothelial growth factor (VEGF), angiopoietin, fibroblast growth factor (FGF), EGF, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), erythropoietin (EPO), TGFβ, IL-8, Ephilin, SDF-1, receptors thereof and the like.

[0134] A fusion antibody with a protein or therapeutic antibody can be produced by linking a cDNA encoding a monoclonal antibody or antibody fragment to a cDNA encoding the protein, constructing a DNA encoding the fusion antibody, inserting the DNA into an expression vector for prokaryote or eukaryote, and then introducing the expression vector into a prokaryote or eukaryote to express the fusion antibody.

[0135] In the case where the above antibody conjugate is used for the detection method, method for quantitative determination, detection reagent, reagent for quantitative determination or diagnostic agent in the present invention, examples of the agent to which the monoclonal antibody or the antibody fragment of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof is bound includes a label used in routine immunological detecting or measuring method.

[0136] The label includes enzymes such as alkaline phosphatase, peroxidase and luciferase, luminescent materials such as acridinium ester and lophine, fluorescent materials such as fluorescein isothiocyanate (FITC) and tetramethyl rhodamine isothiocyanate (RITC), and the like.

[0137] Furthermore, the present invention includes an agent for treating a disease relating to a TIM-3 positive cell, comprising the monoclonal antibody of the present invention or the antibody fragment thereof as an active ingredient.

[0138] The disease relating to the TIM-3 positive cell is not limited, so long as it is a disease relating to a cell expressing TIM-3, such as cancer, autoimmune disease, and allergic disease.

[0139] The cancer includes blood cancer, breast cancer, uterine cancer, colorectal cancer, esophageal cancer, gastric cancer, ovarian cancer, lung cancer, renal cancer, rectal cancer, thyroid cancer, uterine cervix cancer, small intestinal cancer, prostate cancer and pancreatic cancer. Preferable examples of the cancer include blood cancer, esophageal cancer, gastric cancer, colorectal cancer, liver cancer and prostate cancer.

[0140] Examples of the blood cancer include acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplasticsyndromes (MDS), multiple myeloma, cutaneous T cell lymphoma (CTCL), peripheral T-cell lymphoma (PT-CL), anaplastic large cell lymphoma (ALCL), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), other lymphoid leukemia, NK cell lymphoma, Hodgkin lymphoma, non-Hodgkin's lymphoma such as Burkitt's lymphoma, and the like.

[0141] Specific examples of the autoimmune diseases include rheumatoid arthritis, psoriasis, Crohn's disease, Ankylosing spondylitis, multiple sclerosis, type I diabetes, hepatitis, myocarditis, Sjogren's syndrome, autoimmune hemolytic anemia after transplant rejection, blisters pemphigoid, Graves disease, Hashimoto's thyroiditis, systemic lupus erythematosus (SLE), myasthenia gravis, pemphigus, pernicious anemia, and the like.

[0142] Examples of the allergic diseases include acute or chronic reactive airway disease, bronchial asthma, atopic dermatitis, allergic rhinitis, urticaria, PIE syndrome, food allergies, hay fever, allergic nose, bronchial asthma, atopic dermatitis, anaphylactic shock and the like.

[0143] The therapeutic agent of the present invention comprises the above monoclonal antibody or the antibody fragment of the present invention as an active ingredient.

[0144] The therapeutic agent comprising the monoclonal antibody of the present invention or antibody fragment thereof, or conjugate thereof may comprise only the antibody or antibody fragment thereof, or conjugate thereof as an active ingredient. It is generally preferred that the therapeutic agent is prepared as a pharmaceutical preparation produced by

Samsung Bioepis Exhibit No. 1002
Page 12086

an appropriate method well known in the technical field of pharmaceutics, and by mixing it with one or more pharmaceutically acceptable carriers.

[0145] It is preferred to administer the therapeutic agent by the route that is most effective for the treatment. Examples include oral administration and parenteral administration, such as buccal, tracheal, rectal, subcutaneous, intramuscular or intravenous administration and intravenous administration is preferred.

[0146] The pharmaceutical preparation includes sprays, capsules, tablets, powders, granules, syrups, emulsions, suppositorys, injections, ointments, tapes and the like.

[0147] Although the dose or the frequency of administration varies depending on the objective therapeutic effect, administration method, treating period, age, body weight and the like, it is usually 10 μg/kg to 10 mg/kg per day and per adult.

[0148] Further, the present invention relates to a method for immunologically detecting or measuring TIM-3, a reagent for immunologically detecting or measuring TIM-3, a method for immunologically detecting or measuring a cell expressing TIM-3, and a diagnostic agent for diagnosing a disease relating to a TIM-3 positive cell, comprising the monoclonal antibody or the antibody fragment of the present invention which specifically recognizes human TIM-3 and binds to an amino acid sequence of the extracellular region or three-dimensional structure thereof as an active ingredient.

[0149] In the present invention, the method for detecting or measuring the amount of TIM-3 may be any known method. For example, it includes an immunological detecting or measuring method.

[0150] The immunological detecting or measuring method is a method in which an antibody amount or an antigen amount is detected or determined using a labeled antigen or antibody. Examples of the immunological detecting or measuring method include radioactive substance-labeled immunoantibody method (RIA), enzyme immunoassay (EIA or ELISA), fluorescent immunoassay (FIA), luminescent immunoassay, Western blotting method, physicochemical method and the like.

[0151] The above disease relating to a TIM-3 positive cell can be diagnosed by detecting or measuring a cell expressing TIM-3 by using the monoclonal antibody or antibody fragment of the present invention.

[0152] For the detection of the cell expressing the polypeptide, known immunological detection methods can be used, and an immunoprecipitation method, a fluorescent cell staining method, an immune tissue staining method and the like are preferably used. Also, a fluorescent antibody staining method using FMAT 8100 HTS system (Applied Biosystem) and the like can be used.

[0153] In the present invention, the living body sample to be used for detecting or measuring TIM-3 is not particularly limited, so long as it has a possibility of containing a cell expressing TIM-3, such as tissue cells, blood, blood plasma, serum, pancreatic fluid, urine, fecal matter, tissue fluid or culture fluid.

[0154] The diagnostic agent containing the monoclonal antibody of the present invention or antibody fragment thereof, or conjugate thereof may further contain a reagent for carrying out an antigen-antibody reaction or a reagent for detection of the reaction depending on the desired diagnostic method. The reagent for carrying out the antigen-antibody reaction includes a buffer, a salt, and the like. The reagent for detection includes a reagent generally used for the immunological detecting or measuring method, such as labeled secondary antibody which recognizes the monoclonal antibody, antibody fragment thereof or conjugates thereof and substrate corresponding to the labeling and the like.

[0155] A process for producing the antibody of the present invention, a method for treating the disease and a method for diagnosing the disease are specifically described below.

1. Preparation method of monoclonal antibody

(1) Preparation of antigen

[0156] TIM-3 or a cell expressing TIM-3 as an antigen can be obtained by introducing an expression vector comprising cDNA encoding a full length of TIM-3 or a partial length thereof is introduced into *Escherichia coli,* yeast, an insect cell, an animal cell or the like. In addition, TIM-3 can be purified and obatained from various human tumor cell lines, human tissue and the like which express a large amount of TIM-3. The tumor cell line and the tissue can be directly allowed to use as antigens. Furthermore, a synthetic peptide having a partial sequence of the TIM-3 can be prepared by a chemical synthesis method such as Fmoc method or tBoc method and used as an antigen.

[0157] TIM-3 used in the present invention can be produced, for example, by expressing a DNA encoding TIM-3 in a host cell using a method described in Molecular Cloning, A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press (1989), Current Protocols in Molecular Biology, John Wiley & Sons (1987-1997) or the like according to the following method.

[0158] Firstly, a recombinant vector is prepared by inserting a full length cDNA comprising the region encoding TIM-3 into downstream of a promoter of an appropriate expression vector. At this time, if necessary, a DNA fragment having an appropriate length containing a region encoding the polypeptide prepared based on the full length cDNA may be used instead of the above full length cDNA. Next, a transformant producing polypeptide can be obtained by introducing

Samsung Bioepis Exhibit No. 1002
Page 12087

the recombinant vector into a host cell suitable for the expression vector.

[0159] The expression vector may be any one, so long as it can replicate autonomously in the host cell to be used or it can be integrated into a chromosome comprising an appropriate promoter at such a position that the DNA encoding the polypeptide can be transcribed.

[0160] The host cell may be any one, so long as it can express the objective gene. Examples include a microorganism which belongs to the genera *Escherichia,* such as *Escherichia coli,* yeast, an insect cell, an animal cell and the like.

[0161] When a prokaryote such as *Escherichia coli* is used as the host cell, it is preferred that the recombinant vector used in the present invention is autonomously replicable in the prokaryote and comprising a promoter, a ribosome binding sequence, the DNA encoding TIM-3 and a transcription termination sequence. The recombinant vector is not necessary to have a transcription termination sequence, but a transcription termination sequence is preferably set just below the structural gene. The recombinant vector may further comprise a gene regulating the promoter.

[0162] Also, the above recombinant vector is preferably a plasmid in which the space between Shine-Dalgarno sequence, which is the ribosome binding sequence, and the initiation codon is adjusted to an appropriate distance (for example, 6 to 18 nucleotides).

[0163] Furthermore, the nucleotide sequence of the DNA encoding TIM-3 can be substituted with another base so as to be a suitable codon for expressing in a host cell, thereby improve the productivity of the objective TIM-3.

[0164] Any expression vector can be used, so long as it can function in the host cell to be used. Examples of the expression vector includes pBTrp2, pBTac1, pBTac2 (all manufactured by Roche Diagnostics), pKK233-2 (manufactured by Pharmacia), pSE280 (manufactured by Invitrogen), pGEMEX-1 (manufactured by Promega), pQE-8 (manufactured by QIAGEN), pKYP10 (Japanese Published Unexamined Patent Application No. 110600/83), pKYP200 [Agricultural Biological Chemistry, 48, 669 (1984)], pLSA1 [Agric. Biol. Chem., 53, 277 (1989)], pGEL1 [Proc. Natl. Acad Sci. USA, 82, 4306 (1985)], pBluescript II SK(-) (manufactured by Stratagene), pTrs30 [prepared from *Escherichia coli* JM109/pTrS30 (FERM BP-5407)], pTrs32 [prepared from *Escherichia coli* JM109/pTrS32 (FERM BP-5408)], pGHA2 [prepared from *Escherichia coli* IGHA2 (FERM BP-400), Japanese Published Unexamined Patent Application No. 221091/85], pGKA2 [prepared from *Escherichia coli* IGKA2 (FERM BP-6798), Japanese Published Unexamined Patent Application No. 221091/85], pTerm2 (US4686191, US4939094, US5160735), pSupex, pUB110, pTP5, pC194, pEG400 [J. Bacteriol., 172, 2392 (1990)], pGEX (manufactured by Pharmacia), pET system (manufactured by Novagen), pME18SFL3 and the like.

[0165] Any promoter can be used, so long as it can function in the host cell to be used. Examples include promoters derived from *Escherichia coli,* phage and the like, such as trp promoter (Ptrp), lac promoter, PL promoter, PR promoter and T7 promoter and the like. Also, artificially designed and modified promoters, such as a promoter in which two Ptrp are tandemly linked, tac promoter, lacT7 promoter and letI promoter, can be used.

[0166] Examples of host cell include *Escherichia coli* XL1-Blue, *Escherichia coli* XL2-Blue, *Escherichia coli* DH1, *Escherichia coli* MC1000, *Escherichia coli* KY3276, *Escherichia coli* W1485, *Escherichia coli* JM109, *Escherichia coli* HB101, *Escherichia coli* No. 49, *Escherichia coli* W3110, *Escherichia coli* NY49, *Escherichia coli* DH5α and the like.

[0167] Any introduction method of the recombinant vector can be used, so long as it is a method for introducing DNA into the host cell, and examples include a method using a calcium ion described in Proc. Natl. Acad. Sci. USA, 69, 2110 (1972), Gene, 17, 107 (1982) and Molecular & General Genetics, 168, 111 (1979) and the like.

[0168] When an animal cell is used as the host cell, any expression vector can be used, so long as it can function in the animal cell. Examples include pcDNAI, pcDM8 (manufactured by Funakoshi), pAGE107 [Japanese Published Unexamined Patent Application No. 22979/91; Cytotechnology, 3, 133 (1990)], pAS3-3 (Japanese Published Unexamined Patent Application No. 227075/90), pCDM8 [Nature, 329, 840,(1987)], pcDNAI/Amp (manufactured by Invitrogen), pcDNA3.1 (manufactured by Invitrogen), pREP4 (manufactured by Invitrogen), pAGE103 [J. Biochemistry, 101, 1307 (1987)], pAGE210, pME18SFL3, pKANTEX93 (WO 97/10354) and the like.

[0169] Any promoter can be used, so long as it can function in an animal cell. Examples include a promoter of immediate early (IE) gene of cytomegalovirus (CMV), SV40 early promoter, a promoter of retrovirus, a metallothionein promoter, a heat shock promoter, SRα promoter, Molony murine leukemia virus promoter or enhancer, and the like. Also, the enhancer of the IE gene of human CMV can be used together with the promoter.

[0170] The host cell includes human Namalwa leukemia cell, monkey COS cell, Chinese hamster ovary (CHO) cell [Journal of Experimental Medicine, 108, 945 (1958); Proc.Natl.Acad.Sci. USA, 60, 1275 (1968); Genetics, 55, 513(1968); Chromosoma, 41, 129 (1973); Methods in Cell Science, 18, 115 (1996); Radiation Research, 148, 260 (1997); Proc.Natl.Acad.Sci. USA, 77, 4216 (1980); Proc.Natl.Acad.Sci. USA, 60, 1275 (1968); Cell, 6, 121 (1975); Molecular Cell genetics, Appendix I, II (pp.883-900)], CHO/DG44, CHO-K1 (ATCC accession NO: CCL-61), DUkXB11 (ATCC accession NO:CCL-9096), Pro-5 (ATCC accession NO: CCL-1781), CHO-S (Life Technologies, Cat#11619), Pro-3, rat myeloma cell YB2/3HL.P2.G11.16Ag.20 (also called as YB2/0), mouse myeloma cell NSO, mouse myeloma cell SP2/0-Ag14, Syrian hamster cell BHK or HBT5637 (Japanese Published Unexamined Patent Application No. 299/88) and the like.

[0171] Any introduction method of the recombinant vector can be used, so long as it is a method for introducing DNA

Samsung Bioepis Exhibit No. 1002
Page 12088

into an animal cell, and examples include electroporation [Cytotechnology, 3, 133 (1990)], the calcium phosphate method (Japanese Published Unexamined Patent Application No. 227075/90), the lipofection method [Proc. Natl. Acad. Sci. USA, 84, 7413 (1987)], and the like.

[0172] TIM-3 can be produced by culturing the transformant derived from a microorganism, an animal cell or the like having a recombinant vector comprising the DNA encoding TIM-3 in a medium to form and accumulate TIM-3 in the culture, and recovering it from the culture. The method for culturing the transformant in the medium is carried out according to the usual method used in culturing of hosts.

[0173] When TIM-3 is expressed in a cell derived from eukaryote, TIM-3 to which sugars or sugar chains bind can be obtained.

[0174] When a microorganism transformed with a recombinant vector containing an inducible promoter is cultured, an inducer can be added to the medium, if necessary. For example, isopropyl-β-D-thiogalactopyranoside or the like can be added to the medium when a microorganism transformed with a recombinant vector using *lac* promoter is cultured; or indoleacrylic acid or the like can be added thereto when a microorganism transformed with a recombinant vector using trp promoter is cultured.

[0175] When a transformant obtained using an animal cell as the host cell is cultured, the medium includes generally used RPMI 1640 medium [The Journal of the American Medical Association, 199, 519 (1967)], Eagle's MEM medium [Science, 122, 501 (1952)], Dulbecco's modified MEM medium [Virology, 8, 396 (1959)] and 199 medium [Proceeding of the Society for the Biological Medicine, 73, 1 (1950)], Iscove's modified Dulbecco's medium (IMDM), the media to which fetal calf serum, *etc.* is added, and the like. Culture is carried out generally at a pH of 6 to 8 and 30 to 40°C for 1 to 7 days in the presence of 5% CO_2. If necessary, an antibiotic such as kanamycin or penicillin can be added to the medium during the culturing.

[0176] Regarding the expression method of the gene encoding TIM-3, in addition to direct expression, secretory production, fusion protein expression and the like can be carried out according to the method described in Molecular Cloning, A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press (1989).

[0177] The process for producing TIM-3 includes a method of intracellular expression in a host cell, a method of extracellular secretion from a host cell, a method of producing on a host cell outer membrane, and the like. The appropriate method can be selected by changing the host cell used and the structure of the TIM-3 produced.

[0178] When the TIM-3 is produced in a host cell or on a host cell membrane outer envelope, TIM-3 can be positively secreted extracellularly in accordance with the method of Paulson et al. [J. Biol. Chem., 264, 17619 (1989)], the method of Lowe et al. [Proc. Natl. Acad. Sci. USA, 86, 8227 (1989), Genes Develop., 4, 1288 (1990)], the methods described in Japanese Published Unexamined Patent Application No. 336963/93 and WO 94/23021, and the like.

[0179] Also, the production amount of TIM-3 can be increased in accordance with the method described in Japanese Published Unexamined Patent Application No. 227075/90 utilizing a gene amplification system using a dihydrofolate reductase gene.

[0180] The resulting TIM-3 can be isolated and purified, for example, as follows.

[0181] When TIM-3 is intracellularly expressed in a dissolved state, the cells after culturing are recovered by centrifugation, suspended in an aqueous buffer and then disrupted using ultrasonicator, French press, Manton Gaulin homogenizer, dynomill or the like to obtain a cell-free extract.

[0182] The cell-free extract is centrifuged to obtain a supernatant, and a purified preparation can be obtained by subjecting the supernatant to a general protein isolation and purification techniques such as solvent extraction; salting out with ammonium sulfate etc.; desalting; precipitation with an organic solvent; anion exchange chromatography using a resin such as diethylaminoethyl (DEAE)-sepharose, DIAION HPA-75 (manufactured by Mitsubishi Chemical); cation exchange chromatography using a resin such as S-Sepharose FF (manufactured by Pharmacia); hydrophobic chromatography using a resin such as butyl-Sepharose or phenyl-Sepharose; gel filtration using a molecular sieve; affinity chromatography; chromatofocusing; electrophoresis such as isoelectric focusing; and the like which may be used alone or in combination.

[0183] When TIM-3 is expressed intracellularly by forming an inclusion body, the cells are recovered, disrupted and centrifuged in the same manner, and the inclusion body of TIM-3 are recovered as a precipitation fraction. The recovered inclusion body of the TIM-3 protein is solubilized with a protein denaturing agent. The protein is made into a normal three-dimensional structure by diluting or dialyzing the solubilized solution, and then a purified preparation of polypeptide is obtained by the same isolation purification method as above.

[0184] When TIM-3 or the derivative such as a glycosylated product is secreted extracellularly, TIM-3 or the derivative such as a glycosylated product can be recovered from the culture supernatant. That is, the culture is treated by a method such as centrifugation in the same manner as above to obtain a soluble fraction, a purified preparation of TIM-3 can be obtained from the soluble fraction by the same isolation purification method as above.

[0185] Also, TIM-3 used in the present invention can be produced by a chemical synthesis method, such as Fmoc method or tBoc method. Also, it can be chemically synthesized using a peptide synthesizer manufactured by Advanced ChemTech, Perkin-Elmer, Pharmacia, Protein Technology Instrument, Synthecell-Vega, PerSeptive, Shimadzu Corpo-

Samsung Bioepis Exhibit No. 1002
Page 12089

ration, or the like.

(2) Immunization of animal and preparation of antibody-producing cell for fusion

[0186] A mouse, rat or hamster and the like which is 3 to 20-weeks-old is immunized with the antigen prepared in the above (1), and antibody-producing cells within the spleen, lymph node or peripheral blood of the animal are collected. Also, when the increase of a sufficient titer in the above animal is not recognized due to low immunogenecity, a TIM-3 knockout mouse may by used as an animal to be immunized.

[0187] The immunization is carried out by administering the antigen to the animal through subcutaneous, intravenous or intraperitoneal injection together with an appropriate adjuvant (for example, complete Freund's adjuvant, combination of aluminum hydroxide gel with pertussis vaccine, or the like). When the antigen is a partial peptide, a conjugate is produced with a carrier protein such as BSA (bovine serum albumin), KLH (keyhole limpet hemocyanin) or the like, which is used as the antigen.

[0188] The administration of the antigen is carried out 5 to 10 times every one week or every two weeks after the first administration. On the 3rd to 7th day after each administration, a blood sample is collected from the fundus of the eye, the reactivity of the serum with the antigen is tested, for example, by enzyme immunoassay [Antibodies-A Laboratory Manual, Cold Spring Harbor Laboratory (1988)] or the like. An animal showing a sufficient antibody titer in their sera against the antigen used for the immunization is used as the source of antibody-producing cells for fusion.

[0189] Three to seven days after final administration of the antigen, tissue containing the antibody-producing cells such as the spleen is excised from the immunized animal to collect the antibody-producing cells. When the spleen cells are used, the spleen is cut out and loosened, followed by centrifugation. Then, antibody-producing cells for fusion are obtained by removing erythrocytes.

(3) Preparation of myeloma cell

[0190] An established cell line obtained from mouse is used as myeloma cells. Examples include 8-azaguanine-resistant mouse (derived from BALB/c) myeloma cell line P3-X63Ag8-U1 (P3-U1) [Current Topics in Microbiology and Immunology, 18, 1 (1978)], P3-NS1/1-Ag41 (NS-1) [European J. Immunology, 6, 511 (1976)], SP2/0-Ag14 (SP-2) [Nature, 276, 269 (1978)], P3-X63-Ag8653 (653) [J. Immunology, 123, 1548 (1979)], P3-X63-Ag8 (X63) [Nature, 256, 495 (1975)] and the like.

[0191] The myeloma cells are subcultured in a normal medium [a medium in which glutamine, 2-mercaptoethanol, gentamicin, FBS and 8-azaguanine are added to RPMI-1640 medium] and they are subcultured in the normal medium 3 or 4 days before cell fusion to ensure the cell number of 2×10^7 or more on the day for fusion.

(4) Cell fusion and preparation of hybridoma for producing monoclonal antibody

[0192] The antibody-producing cells for fusion obtained by the above (2) and myeloma cells obtained by the above (3) were sufficiently washed with a minimum essential medium (MEM) or PBS (1.83 g of disodium hydrogen phosphate, 0.21 g of potassium dihydrogen phosphate, 7.65 g of sodium chloride, 1 liter of distilled water, pH 7.2) and mixed to give a ratio of the antibody-producing cells: the myeloma cells = 5 to 10: 1, followed by centrifugation. Then, the supernatant is discarded.

[0193] The precipitated cell group is sufficiently loosened. After loosening the precipitated cell, the mixture of polyethylene glycol-1000 (PEG-1000), MEM and dimethylsulfoxide is added to the cell under stirring at 37°C. In addition, 1 to 2 mL of MEM medium is added several times every one or two minutes, and MEM is added to give a total amount of 50 mL. After centrifugation, the supernatant is discarded. After the cells are gently loosened, the cells are gently suspended in HAT medium [a normal medium containing hypoxanthine, thymidine and aminopterin]. The suspension is cultured in a 5% CO_2 incubator for 7 to 14 days at 37°C.

[0194] After the culturing, a portion of the culture supernatant is sampled and a hybridoma which is reactive to an antigen containing TIM-3 and is not reactive to an antigen not containing TIM-3 is selected by binding assay as described below. Then, cloning is carried out twice by a limiting dilution method [Firstly, HT medium (HAT medium from which aminopterin is removed) is used, and secondly, the normal medium is used], and a hybridoma which stably shows a high antibody titer is selected as the monoclonal antibody-producing hybridoma.

(5) Preparation of purified monoclonal antibody

[0195] The hybridoma cells producing a monoclonal antibody obtained by the above (4) are administered by intraperitoneal injection into 8- to 10-week-old mice or nude mice treated with 0.5 mL of pristane (2,6,10,14-tetramethylpentadecane (pristane) is intraperitoneally administered, followed by feeding for 2 weeks). The hybridoma develops ascites

Samsung Bioepis Exhibit No. 1002
Page 12090

tumor in 10 to 21 days. The ascitic fluid is collected from the mice, centrifuged to remove solids, subjected to salting out with 40 to 50% ammonium sulfate and then precipitated by caprylic acid, passed through a DEAE-Sepharose column, a protein A column or a gel filtration column to collect an IgG or IgM fraction as a purified monoclonal antibody.

[0196] Furthermore, a monoclonal antibody-producing hybridoma obtained by the above (4) is cultured in RPMI1640 medium containing 10% FBS or the like and the supernatant is removed by centrifugation. The precipitated cells are suspended in Hybridoma-SFM medium and cultured for 3 to 7 days. The purified monoclonal antibody can be obtained by centrifusing the obtained cell suspension, followed by purification from the resulting supernatant with Protein A column or Protein G column to collect the IgG fractions. Additionally, Hybridoma-SFM medium can contain 5% DIGO GF21.

[0197] The subclass of the antibody can be determined using a subclass typing kit by enzyme immunoassay. The amount of the protein can be determined by the Lowry method or from the absorbance at 280 nm.

(6) Selection of monoclonal antibody

[0198] Selection of monoclonal antibody is carried out by the following binding assay using an enzyme immunoassay method and inhibition assay of intracellular uptake of amino acids.

(6-a) Binding assay

[0199] As the antigen, a gene-introduced cell obtained by introducing an expression vector containing a cDNA encoding TIM-3 obtained in (1) into *Escherichia coli,* yeast, an insect cell, an animal cell or the like, a recombinant protein, or a purified polypeptide or partial peptide obtained from a human tissue is used. When the antigen is a partial peptide, a conjugate is prepared with a carrier protein such as BSA or KLH is prepared and is used.

[0200] After making these antigens into a solid layer by dispensing in a 96-well plate, a substance to be tested such as serum, a culture supernatant of a hybridoma or a purified monoclonal antibody is dispensed therein as the primary antibody and allowed to react. After thoroughly washing with PBS, PBS-Tween and the like, an anti-immunoglobulin antibody labeled with biotin, an enzyme, a chemiluminescent material, a radiation compound or the like is dispensed therein as the secondary antibody and allowed to react. After thoroughly washing with PBS-Tween, the reaction appropriate to the label of the secondary antibody is carried out to select a monoclonal antibody which specifically reacts with the antigen.

[0201] In addition, a monoclonal antibody which competes with the anti-TIM-3 monoclonal antibody of the present invention in the binding of an extracellular region of human TIM-3 can be obtained by adding a subject antibody to the above binding assay system to allow to react. Namely, a monoclonal antibody which competes with the obtained monoclonal antibody in the binding of an amino acid sequence of the extracellular region of human TIM-3 or a three-dimensional structure thereof can be obtained by screening a subject antibody which inhibits the binding of the monoclonal antibody upon adding to the antibody.

[0202] Furthermore, an antibody which binds to the same epitope to which the monoclonal antibody of the present invention which binds to an amino acid sequence of the extracellular region of TIM-3 or three-dimensional structure thereof can be obtained by identifying an epitope of the antibody obtained by the above binding assay system, preparing a partial synthetic peptide of the epitope or a synthetic peptide which mimics the three-dimensional structure of the epitope and immunizing with the peptide.

(6-b) Kinetic analysis with Biacore

[0203] The kinetics between an antigen and a test substance is measured using Biacore T100 and then the obtained results are analyzed using analysis software accompanied with the apparatus. After anti-mouse IgG antibody is immobilized onto to a CM 5 sensor chip by an amine coupling method, a test substance such as culture supernatant of a hybridoma, a purified monoclonal antibody is allowed to flow and bind at an appropriate amount, and an antigen at plural known concentrations is further allowed to flow. And then, the binding and dissociation are measured.

[0204] Using the obtained data and the software accompanied with the apparatus, the kinetics analysis is carried out using the 1:1 binding model to obtain necessary parameters. Otherwise, after human TIM-3 is immobilized onto the sensor chip by an amino coupling method, a purified monoclonal antibody is allowed to flow at plural known concentrations followed by measuring the binding and dissociation. Using the obtained data and the software accompanied with the apparatus, the kinetics analysis is carried out using bivalent analyte model to obtain necessary parameters.

2. Preparation of recombinant antibody

[0205] As production examples of recombinant antibodies, processes for producing a human chimeric antibody and a human CDR grafted antibody are shown below.

Samsung Bioepis Exhibit No. 1002
Page 12091

(1) Construction of vector for expression of recombinant antibody

[0206] A vector for expression of recombinant antibody is an expression vector for animal cell into which DNAs encoding CH and CL of a human antibody have been inserted, and is constructed by cloning each of DNAs encoding CH and CL of a human antibody into an expression vector for animal cell.

[0207] The C region of a human antibody may be used CH and CL of any human antibody. Examples include CH belonging to γ1 subclass, CL belonging to κ class, and the like. As the DNAs encoding CH and CL of a human antibody, the cDNA may be generally used and a chromosomal DNA comprising an exon and an intron can be also used.

[0208] As the expression vector for animal cell, any expression vector can be used, so long as a gene encoding the C region of a human antibody can be inserted thereinto and expressed therein. Examples include pAGE107 *[*Cytotechnol., 3, 133 (1990)], pAGE103 [J. Biochem., 101, 1307 (1987)], pHSG274 [Gene, 27, 223 (1984)], pKCR *[*Proc. Natl. Acad. Sci. USA, 78, 1527 (1981)], pSG1bd2-4 [Cytotechnol., 4, 173 (1990)], pSE1UK1Sed1-3 [Cytotechnol., 13, 79 (1993)] and the like.

[0209] Examples of a promoter and enhancer used for an expression vector for animal cell include an SV40 early promoter [J. Biochem., 101, 1307 (1987)], a Moloney mouse leukemia virus LTR [Biochem. Biophys. Res. Commun., 149, 960 (1987)], an immunoglobulin H chain promoter [Cell, 41, 479 (1985)] and enhancer [Cell, 33, 717 (1983)] and the like.

[0210] The vector for expression of recombinant antibody may be either of a type in which a gene encoding an antibody H chain and a gene encoding an antibody L chain exist on separate vectors or of a type in which both genes exist on the same vector (tandem type). In respect of easiness of construction of a vector for expression of recombinant antibody, easiness of introduction into animal cells, and balance between the expression amounts of antibody H and L chains in animal cells, a tandem type of the vector for expression of recombinant antibody is more preferred [J. Immunol. Methods, 167, 271 (1994)]. Examples of the tandem type of the vector for expression of recombinant antibody include pKANTEX93 (WO 97/10354), pEE18 [Hybridoma, 17, 559 (1998)], and the like.

(2) Obtaining of cDNA encoding V region of antibody derived from non-human animal and analysis of amino acid sequence

[0211] Obtaining of cDNAs encoding VH and VL of a non-human antibody and analysis of amino acid sequence are carried out as follows.

[0212] mRNA is extracted from hybridoma cells producing a non-human antibody to synthesize cDNA. The synthesized cDNA is cloned into a vector such as a phage or a plasmid, to prepare a cDNA library.

[0213] Each of a recombinant phage or recombinant plasmid containing cDNA encoding VH or VL is isolated from the library using DNA encoding a part of the C region or V region of a mouse antibody as the probe. The full length of the nucleotide sequences of VH and VL of a mouse antibody of interest on the recombinant phage or recombinant plasmid are determined, and the full length of the amino acid sequences of VH and VL are deduced from the nucleotide sequences, respectively.

[0214] Examples of the non-human animal for preparing a hybridoma cell which produces a non-human antibody include mouse, rat, hamster, rabbit or the like. Any animals can be used so long as a hybridoma cell can be produced therefrom.

[0215] Examples of the method for preparing total RNA from a hybridoma cell include a guanidine thiocyanate-cesium trifluoroacetate method [Methods in Enzymol., 154, 3 (1987)], the use of a kit such as RNA easy kit (manufactured by Qiagen) and the like.

[0216] Examples of the method for preparing mRNA from total RNA include an oligo (dT) immobilized cellulose column method [Molecular Cloning, A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press (1989)], a method using a kit such as Oligo-dT30 <Super> mRNA Purification Kit (manufactured by Takara Bio) and the like. Additionary, examples of the method for preparing mRNA include method using a kit Fast Track mRNA Isolation kit (manufactured by Invitrogen) or QuickPrep mRNA Purification Kit (manufactured by Pharmacia) and the like.

[0217] Examples of the method for synthesizing cDNA and preparing a cDNA library include known methods *[Molecular Cloning, A Laboratory Manual,* Second Edition, Cold Spring Harbor Laboratory Press (1989); *Current Protocols in Molecular Biology,* Supplement 1, John Wiley & Sons (1987-1997)]; a method using a kit such as Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning (manufactured by Invitrogen), ZAP-cDNA Synthesis Kit (manufactured by Stratagene), *etc.;* and the like.

[0218] The vector into which the synthesized cDNA using mRNA extracted from a hybridoma cell as the template is inserted for preparing a cDNA library may be any vector, so long as the cDNA can be inserted. Examples include ZAP ExPress *[Strategies, 5,* 58 (1992)], pBluescript II SK(+) [*Nucleic Acids Research,* 17, 9494 (1989)], λZAPII (manufactured by Stratagene), λgt10 and λgt11 [*DNA Cloning: A Practical Approach,* I, 49 (1985)], Lambda BlueMid (manufactured by Clontech), λExCell and pT7T3-18U (manufactured by Pharmacia), pcD2 [*Mol. Cell. Biol.,* 3, 280 (1983)], pUC18 [*Gene,* 33, 103 (1985)], and the like.

Samsung Bioepis Exhibit No. 1002
Page 12092

[0219] Any *Escherichia coli* for introducing the cDNA library constructed by a phage or plasmid vector may be used, so long as the cDNA library can be introduced, expressed and maintained. Examples include XL1-Blue MRF' [*Strategies,* 5, 81 (1992)], C600 [*Genetics,* 39, 440 (1954)], Y1088 and Y1090 [*Science, 222:* 778 (1983)], NM522 [*J. Mol. Biol.,* 166, 1 (1983)], K802 [*J. Mol. Biol.,* 16, 118 (1966)], JM105 [*Gene,* 38, 275 (1985)], and the like.

[0220] A colony hybridization or plaque hybridization method using an isotope- or fluorescence-labeled probe may be used for selecting cDNA clones encoding VH or VL of a non-human antibody or the like from the cDNA library [*Molecular Cloning, A Laboratory Manual,* Second Edition, Cold Spring Harbor Laboratory Press (1989)].

[0221] Also, the cDNAs encoding VH and VL can be prepared through polymerase chain reaction (hereinafter referred to as "PCR"; *Molecular Cloning, A Laboratory Manual,* Second Edition, Cold Spring Harbor Laboratory Press (1989); *Current Protocols in Molecular Biology,* Supplement 1, John Wiley & Sons (1987-1997)) by preparing primers and using cDNA prepared from mRNA or a cDNA library as the template.

[0222] The nucleotide sequence of the cDNA can be determined by digesting the cDNA selected with appropriate restriction enzymes and the like, cloning the fragments into a plasmid such as pBluescript SK(-) (manufactured by Stratagene), carrying out the reaction by a usually used nucleotide sequence analyzing method. For example, a nucleotide sequence analyzing method is carried out by using an automatic nucleotide sequence analyzer such as ABI PRISM3700 (manufactured by PE Biosystems) and A.L.F. DNA sequencer (manufactured by Pharmacia) after a reaction such as the dideoxy method *[*Proc. Natl. Acad. Sci. USA, 74, 5463 (1977)].

[0223] Whether the obtained cDNAs encode the full amino acid sequences of VH and VL of the antibody containing a secretory signal sequence can be confirmed by estimating the full length of the amino acid sequences of VH and VL from the determined nucleotide sequence and comparing them with the full length of the amino acid sequences of VH and VL of known antibodies [A.L.F. DNA sequencer, US Dept. Health and Human Services (1991)].

[0224] With regard to the full amino acid sequences of VH and VL of the antibody containing a secretory signal sequence, the length of the secretory signal sequence and N-terminal amino acid sequence can be estimated by comparing them with the full length of the amino acid sequences ofVH and VL of known antibodies [A.L.F. DNA sequencer, US Dept. Health and Human Services (1991)], and furthermore the subgroup to which they belong can be determined. In addition, the amino acid sequence of each CDR of VH and VL can be determined by comparing them with the full length of the amino acid sequences of VH and VL of known antibodies [A.L.F. DNA sequencer, US Dept. Health and Human Services (1991)].

[0225] Moreover, the novelty of the full length of the amino acid sequence of VH and VL can be examined by carrying out a homology search with sequences in any database, for example, SWISS-PROT, PIR-Protein or the like using the obtained full length of the amino acid sequences of VH and VL, for example, according to the BLAST method [J. Mol. Biol., 215, 403 (1990)] or the like.

(3) Construction of vector for expression of human chimeric antibody

[0226] cDNA encoding each of VH and VL of antibody of non-human animal is cloned in the upstream of genes encoding CH or CL of human antibody of vector for expression of recombinant antibody mentioned in the above (1) to thereby construct a vector for expression of human chimeric antibody.

[0227] In order to ligate cDNA comprising a nucleotide sequence of 3'-terminal of VH or VL of antibody of non-human animal and a nucleotide sequence of 5'-terminal of CH or CL of human antibody, each cDNA encoding VH or VL of a non-human animal antibody is prepared so as to encodes appropriate amino acids and have an appropriate recognition sequence of a restriction enzyme at a linkage portion.

[0228] The prepared cDNAs encoding VH and VL of antibody are respectively cloned so that each of them is expressed in an appropriate form in the upstream of gene encoding CH or CL of the human antibody of the vector for expression of the human CDR-grafted antibody mentioned in the above (1) to construct a vector for expression of human chimeric antibody.

[0229] In addition, cDNA encoding VH or VL of a non-human animal antibody is amplified by PCR using a synthetic DNA having a recognition sequence of an appropriate restriction enzyme at both ends and each of them is cloned to the vector for expression of recombinant antibody obtained in the above (1).

(4) Construction of cDNA encoding V region of human CDR-grafted antibody

[0230] cDNAs encoding VH or VL of a human CDR-grafted antibody can be obtained as follows.

[0231] Amino acid sequences of framework region (hereinafter referred to as "FR") in VH or VL of a human antibody to which amino acid sequences of CDRs in VH or VL of an antibody derived from a non-human animal antibody are transplanted are respectively selected. Any amino acid sequences of FR of a human antibody can be used, so long as they are derived from human.

[0232] Examples include amino acid sequences of FRs of human antibodies registered in database such as Protein

Samsung Bioepis Exhibit No. 1002
Page 12093

Data Bank or the like, and amino acid sequences common to subgroups of FRs of human antibodies [Sequences of Proteins of Immunological Interest, US Dept. Health and Human Services (1991)], and the like. In order to inhibit the decrease in the binding activity of the antibody, amino acid sequences having high homology (at least 60% or more) with the amino acid sequence of FR in VH or VL of the original antibody is selected.

[0233] Then, amino acid sequences of CDRs of the original antibody are grafted to the selected amino acid sequence of FR in VH or VL of the human antibody, respectively, to design each amino acid sequence of VH or VL of a humanized antibody. The designed amino acid sequences are converted to DNA sequences by considering the frequency of codon usage found in nucleotide sequences of genes of antibodies [Sequence of Proteins of Immunological Interest, US Dept. Health and Human Services (1991)], and the DNA sequence encoding the amino acid sequence of VH or VL of a humanized antibody is designed.

[0234] Based on the designed nucleotide sequences, several synthetic DNAs having a length of about 100 nucleotides are synthesized, and PCR is carried out using them. In this case, it is preferred that 6 synthetic DNAs per each of the H chain and the L chain are designed in view of the reaction efficiency of PCR and the lengths of DNAs which can be synthesized.

[0235] Furthermore, the cDNA encoding VH or VL of a human CDR-grafted antibody can be easily cloned into the vector for expression of human CDR-grafted antibody constructed in (1) by introducing the recognition sequence of an appropriate restriction enzyme to the 5' terminal of the synthetic DNAs existing on the both ends.

[0236] Otherwise, it can be carried out using a synthetic DNA as one DNA encoding each of the full-length H chain and the full-length L chain based on the designed DNA sequence.

[0237] After the PCR, an amplified product is cloned into a plasmid such as pBluescript SK (-) (manufactured by Stratagene) or the like, and the nucleotide sequence is determined according to a method similar to the method described in (2) to obtain a plasmid having a DNA sequence encoding the amino acid sequence of VH or VL of a desired humanized antibody.

(5) Modification of amino acid sequence of V region of human CDR-grafted antibody

[0238] It is known that when a human CDR-grafted antibody is produced by simply grafting only CDRs in VH and VL of an antibody derived from a non-human animal into FRs of VH and VL of a human antibody, its antigen binding activity is lower than that of the original antibody derived from a non-human animal [BIO/TECHNOLOGY, 9, 266 (1991)].

[0239] In human CDR-grafted antibodies, among the amino acid sequences of FRs in VH and VL of a human antibody, an amino acid residue which directly relates to binding to an antigen, an amino acid residue which interacts with an amino acid residue in CDR, and an amino acid residue which maintains the three-dimensional structure of an antibody and indirectly relates to binding to an antigen are identified and modified to an amino acid residue which is found in the original non-humanized antibody to thereby increase the antigen binding activity which has been decreased.

[0240] In order to identify the amino acid residues relating to the antigen binding activity in FR, constructing the three-dimensional structure of an antibody and analyzing can be done by X-ray crystallography [J. Mol. Biol., 112, 535 (1977)], computer-modeling [Protein Engineering, 7, 1501 (1994)] or the like. In addition, modified human CDR-grafted antibody having sufficient binding activity against antigen can be obtained by various attempts, such as producing several modified antibodies of each antibody and examining their binding activities.

[0241] The modification of the amino acid sequence of FR in VH and VL of a human antibody can be accomplished using various synthetic DNA for modification according to PCR as described in (4). With regard to the amplified product obtained by the PCR, the nucleotide sequence is determined according to the method as described in (2) so that whether the objective modification has been carried out is confirmed.

(6) Construction of vector for expression of human CDR-grafted antibody

[0242] A vector for expression of human CDR-grafted antibody can be constructed by cloning each cDNA encoding VH or VL of a constructed recombinant antibody into upstream of each gene encoding CH or CL of the human antibody in the vector for expression of recombinant antibody as described in (1).

[0243] For example, when recognizing sequences of an appropriate restriction enzymes are introduced to the 5'-terminal of synthetic DNAs positioned at both ends among synthetic DNAs used in the construction of VH or VL of the human CDR-grafted antibody in (4) and (5), cloning can be carried out so that they are expressed in an appropriate form in the upstream of each gene encoding CH or CL of the human antibody in the vector for expression of a human CDR-grafted antibody as described in (1).

(7) Transient expression of recombinant antibody

[0244] In order to efficiently evaluate the antigen binding activity of various human CDR-grafted antibodies produced,

Samsung Bioepis Exhibit No. 1002
Page 12094

the recombinant antibodies can be expressed transiently using the vector for expression of antibody as described in (3) and (6) or the modified expression vector thereof.

[0245] Any cell can be used as a host cell, so long as the host cell can express a recombinant antibody. For example, COS-7 cell (ATCC CRL1651) is used in view of its high expression amount *[*Methods in Nucleic Acids Res., CRC Press, 283 (1991)].

[0246] Examples of the method for introducing the expression vector into COS-7 cell include a DEAE-dextran method *[Methods in Nucleic Acids Res.,* CRC Press, 283 (1991)], a lipofection method *[Proc. Natl. Acad. Sci. USA,* 84, 7413 (1987)], and the like.

[0247] After introduction of the expression vector, the expression amount and antigen binding activity of the recombinant antibody in the culture supernatant can be determined by the enzyme immunoassay [Monoclonal Antibodies-Principles and practice, Third edition, Academic Press (1996), Antibodies-A Laboratory Manual, Cold Spring Harbor Laboratory (1988), Monoclonal Antibody Experiment Manual, Kodansha Scientific (1987)] and the like.

(8) Obtaining transformant which stably expresses recombinant antibody and preparation of recombinant antibody

[0248] A transformant which stably expresses a recombinant antibody can be obtained by introducing the vector for expression of recombinant antibody described in (3) and (6) into an appropriate host cell.

[0249] Examples of the method for introducing the expression vector into a host cell include electroporation [Japanese Published Unexamined Patent Application No. 257891/90, Cytotechnology, 3, 133 (1990)] and the like.

[0250] As the host cell into which a vector for expression of a recombinant antbody is introduced, any cell can be used, so long as it is a host cell which can produce the recombinant antibody. Examples include CHO-K1 (ATCC CCL-61), DUkXB11 (ATCC CCL-9096), Pro-5 (ATCC CCL-1781), CHO-S (Life Technologies, Cat # 11619), rat myeloma cell YB2/3HL.P2.G11.16Ag.20 (also referred to as YB2/0), mouse myeloma cell NSO, mouse myeloma cell SP2/0-Ag14 (ATCC No. CRL1581), mouse P3X63-Ag8653 cell (ATCC No. CRL1580), CHO cell in which a dihydrofolate reductase gene (hereinafter referred to as "dhfr") is defective [Proc. Natl. Acad. Sci. U.S.A., 77, 4216 (1980)], lection resistance-acquired Lec 13 [Somatic Cell and Molecular genetics, 12, 55 (1986)], CHO cell in which α1,6-fucosyltransaferse gene is defected (WO 2005/35586, WO 02/31140), rat YB2/3HL.P2.G11.16Ag.20 cell (ATCC No. CRL1662), and the like.

[0251] In addition, host cells in which activity of a protein such as an enzyme relating to synthesis of an intracellular sugar nucleotide, GDP-fucose, a protein such as an enzyme relating to the modification of a sugar chain in which 1-position of fucose is bound to 6-position of N-acetylglucosamine in the reducing end through α-bond in a complex type N-glycoside-linked sugar chain, or a protein relating to transport of an intracellular sugar nucleotide, GDP-fucose, to the Golgi body is decreased or deleted, preferably CHO cell in which α1,6-fucosyltransferase gene is defected as described in W02005/35586, WO02/31140 or the like, can also be used.

[0252] After introduction of the expression vector, transformants which express a recombinant antibody stably are selected by culturing in a medium for animal cell culture containing an agent such as G418 sulfate (hereinafter referred to as "G418") or the like (Japanese Published Unexamined Patent Application No. 257891/90).

[0253] Examples of the medium for animal cell culture include RPMI1640 medium (manufactured by Invitrogen), GIT medium (manufactured by Nihon Pharmaceutical), EX-CELL301 medium (manufactured by JRH), IMDM medium (manufactured by Invitrogen), Hybridoma-SFM medium (manufactured by Invitrogen), media obtained by adding various additives such as FBS to these media, and the like.

[0254] The recombinant antibody can be produced and accumulated in a culture supernatant by culturing the obtained transformants in a medium. The expression amount and antigen binding activity of the recombinant antibody in the culture supernatant can be measured by ELISA or the like. Also, in the transformant, the expression amount of the recombinant antibody can be increased by using DHFR amplification system or the like according to the method disclosed in Japanese Published Unexamined Patent Application No. 257891/90.

[0255] The recombinant antibody can be purified from the culture supernatant of the transformant by using a protein A column [Monoclonal Antibodies-Principles and practice, Third edition, Academic Press (1996), Antibodies-A Laboratory Manual, Cold Spring Harbor Laboratory (1988)]. In addition, the recombinant antibody can be purified by a combination of the methods for purification such as gel filtration, ionexchange chromatography, ultrafiltration and the like.

[0256] The molecular weight of the H chain or the L chain of the purified recombinant antibody or the antibody molecule as a whole is determined by polyacrylamide gel electrophoresis (hereinafter referred to as "SDS-PAGE") *[*Nature, 227, 680 (1970)], Western blotting [Monoclonal Antibodies-Principles and practice, Third edition, Academic Press (1996), Antibodies-A Laboratory Manual, Cold Spring Harbor Laboratory (1988)], and the like.

3. Activity evaluation of the monoclonal antibody or antibody fragment

[0257] The activity of the purified monoclonal antibody or antibody fragment of the present invention can be evaluated in the following manner.

Samsung Bioepis Exhibit No. 1002
Page 12095

[0258] The binding activity to TIM-3-expressing cell is evaluated by the binding assay described in the above 1-(6a) and a surface plasmon resonance method using such as the Biacore system described in the above (6b). Furthermore, it can be measured by fluorescent antibody technique [Cancer Immunol. Immunother, 36, 373 (1993)] and the like.

[0259] Complement-Dependent Cytotoxicity (hereinafter, referred to as "CDC activity") or ADCC activity against an antigen positive cell line is evaluated by a known method [Cancer Immunol. Immunother., 36, 373 (1993)].

4. Method of controlling effector activity of antibody

[0260] As a method for controlling an effector activity of the monoclonal antibody of the present invention, a method for controlling an amount of fucose (hereinafter, referred to also as "core fucose") which is bound in α-1,6 linkage to N-acetylglucosamine (G1cNAc) present in a reducing end of a complex type N-linked sugar chain which is bound to asparagine (Asn) at position 297 of an Fc region of an antibody (W02005/035586, W02002/31140, and WO00/61739), a method for controlling an effector activity of a monoclonal antibody by modifying amino acid group(s) of an Fc region of the antibody, and the like are known. The effector activity of the anti-TIM-3 monoclonal antibody of the present invention can be controlled by using any of the methods.

[0261] The "effector activity" means an antibody-dependent activity which is induced via an Fc region of an antibody. As the effector activity, ADCC activity, CDC activity, an antibody-dependent phagocytosis (ADP activity) by phagocyte such as macrophages or dendritic cells, and the like are known.

[0262] By controlling a content of core fucose of a complex type N-linked sugar chain of Fc of an antibody, an effector activity of the antibody can be increased or decreased. According to a method for lowering a content of fucose which is bound to a complex type N-linked sugar chain bound to Fc of the antibody, an antibody to which fucose is not bound can be obtained by the expression of an antibody using a CHO cell which is deficient in a gene encoding α1,6-fucosyl-transferase. The antibody to which fucose is not bound has a high ADCC activity.

[0263] On the other hand, according to a method for increasing a content of fucose which is bound to a complex type N-linked sugar chain bound to Fc of an antibody, an antibody to which fucose is bound can be obtained by the expression of an antibody using a host cell into which a gene encoding α1,6-fucosyltransferase is introduced. The antibody to which fucose is bound has a lower ADCC activity than the antibody to which fucose is not bound.

[0264] Further, by modifying amino acid residue(s) in an Fc region of an antibody, the ADCC activity or CDC activity can be increased or decreased. For example, the binding activity to an antibody can be increased by using the amino acid sequence of the Fc region described in US2007/0148165. Further, the ADCC activity or CDC activity can be increased or decreased by modifying the amino acid as described in US Patent Nos. 6,737,056, or 7,297,775 or 7,317,091.

[0265] Furthermore, an antibody in which the effector activity is controlled can be obtained by combining the above method within one antibody.

5. Method for treating disease using the anti-TIM-3 monoclonal antibody or antibody fragment of the present invention

[0266] The monoclonal antibody or an antibody fragment thereof of the present invention can be used for treating a disease relating to a TIM-3 positive cell.

[0267] The therapeutic agent comprising the antibody or antibody fragment of the present invention or derivatives thereof may be only the antibody or antibody fragment or derivatives thereof as an active ingredient, and is preferably supplied as a pharmaceutical preparation produced by an appropriate method well known in the technical field of pharmaceutics, by mixing it with one or more pharmaceutically acceptable carriers.

[0268] Examples of a route of administration include oral administration and non-oral administration, such as buccal, tracheal, rectal, subcutaneous, intramuscular or intravenous administration. Examples of the dosage form includes sprays, capsules, tablets, powder, granules, syrups, emulsions, suppositories, injections, ointments, tapes and the like.

[0269] The pharmaceutical preparation suitable for oral administration includes emulsions, syrups, capsules, tablets, powders, granules and the like.

[0270] Liquid preparations such as emulsions and syrups can be produced using, as additives, water; sugars such as sucrose, sorbitol and fructose; glycols such as polyethylene glycol and propylene glycol; oils such as sesame oil, olive oil and soybean oil; antiseptics such as p-hydroxybenzoic acid esters; flavors such as strawberry flavor and peppermint; and the like.

[0271] Capsules, tablets, powders, granules and the like can be produced using, as additives, excipients such as lactose, glucose, sucrose and mannitol; disintegrating agents such as starch and sodium alginate; lubricants such as magnesium stearate and talc; binders such as polyvinyl alcohol, hydroxypropylcellulose and gelatin; surfactants such as fatty acid ester; plasticizers such as glycerin; and the like.

[0272] The pharmaceutical preparation suitable for parenteral administration includes injections, suppositories, sprays and the like.

[0273] Injections can be prepared using a carrier such as a salt solution, a glucose solution or a mixture of both thereof.

Samsung Bioepis Exhibit No. 1002
Page 12096

[0274] Suppositories can be prepared using a carrier such as cacao butter, hydrogenated fat or carboxylic acid.

[0275] Sprays can be prepared using the antibody or antibody fragment as such or using it together with a carrier which does not stimulate the buccal or airway mucous membrane of the patient and can facilitate absorption of the compound by dispersing it as fine particles. The carrier includes lactose, glycerol and the like. It is possible to produce pharmaceutical preparations such as aerosols and dry powders.

[0276] In addition, the components exemplified as additives for oral preparations can also be added to the parenteral preparations.

6. Method for diagnosing disease using the anti-TIM-3 monoclonal antibody or antibody fragment thereof in the present invention

[0277] A disease relating to TIM-3 can be diagnosed by detecting or determining TIM-3 or a cell expressing TIM-3 using the monoclonal antibody or antibody fragment of the present invention.

[0278] A diagnosis of cancer which is one of the diseases relating to TIM-3 can be carried out by, for example, the following detection or measurement of TIM-3.

[0279] The diagnosis of cancer can be carried out by detecting TIM-3 expression on the cell in a patient's body by an immunological method such as a flow cytometry.

[0280] An immunological method is a method in which an antibody amount or an antigen amount is detected or determined using a labeled antigen or antibody. Examples of the immunological method include radioactive substance-labeled immunoantibody method, enzyme immunoassay, fluorescent immunoassay, luminescent immunoassay, Western blotting method, physico-chemical means and the like.

[0281] Examples of the radioactive substance-labeled immunoantibody method include a method, in which the antibody or antibody fragment of the present invention is allowed to react with an antigen, a cell expressing an antigen or the like, then anti-immunoglobulin antibody subjected to a radioactive labeling or a binding fragment thereof is allowed to react therewith, followed by determination using a scintillation counter or the like.

[0282] Examples of the enzyme immunoassay include a method, in which the antibody or antibody fragment of the present invention is allowed to react with an antigen, a cell expressing an antigen or the like, then an anti-immunoglobulin antibody or an binding fragment thereof subjected to antibody labeling is allowed to react therewith and the colored pigment is measured by a spectrophotometer, and, for example, sandwich ELISA may be used.

[0283] As a label used in the enzyme immunoassay, any known enzyme label (Enzyme Immunoassay, published by Igaku Shoin, 1987) can be used as described previously. Examples include alkaline phosphatase labeling, peroxidase labeling, luciferase labeling, biotin labeling and the like.

[0284] Sandwich ELISA is a method in which an antibody is bound to a solid phase, antigen to be detected or measured is trapped and another antibody is allowed to react with the trapped antigen. In the ELISA, two kinds of antibody which recognizes the antigen to be detected or measured or the antibody fragment thereof in which antigen recognizing site is different are prepared and the first antibody or antibody fragments is previously adsorbed on a plate (such as a 96-well plate) and the second antibody or antibody fragment is labeled with a fluorescent substance such as FITC, an enzyme such as peroxidase, or biotin.

[0285] The plate to which the above antibody is adsorbed is allowed to react with the cell separated from living body or disrupted cell suspension thereof, tissue or disintegrated solution thereof, supernatant of cell culture, serum, pleural effusion, ascites, eye solution or the like, then allowed to react with a labeled monoclonal antibody or an antibody fragment and a detection reaction corresponding to the labeled substance is carried out. The antigen concentration in the sample to be tested can be calculated from a calibration curve prepared by a stepwise dilution of antigen of known concentration.

[0286] As antibody used for sandwich ELISA, any of polyclonal antibody and monoclonal antibody may be used or antibody fragments such as Fab, Fab' and $F(ab)_2$ may be used. As a combination of 2 kinds of antibodies used in sandwich ELISA, a combination of monoclonal antibodies or antibody fragments recognizing different epitopes may be used or a combination of polyclonal antibody with monoclonal antibody or antibody fragments may be used.

[0287] A fluorescent immunoassay includes a method described in the literatures [Monoclonal Antibodies - Principles and practice, Third Edition, Academic Press (1996); Manual for Monoclonal Antibody Experiments, Kodansha Scientific (1987)] and the like. As a label for the fluorescent immunoassay, any of known fluorescent labels [Fluorescent Immunoassay, by Akira Kawao, Soft Science, (1983)] may be used. Examples of the label include FITC, RITC and the like.

[0288] The luminescent immunoassay can be carried out using the methods described in the literature [Bioluminescence and Chemical Luminescence, Rinsho Kensa, 42, Hirokawa Shoten (1998)] and the like. As a label used for luminescent immunoassay, any of known luminescent labels can be included. Examples include acridinium ester, lophine or the like may be used.

[0289] Western blotting is a method in which an antigen or a cell expressing an antigen is fractionated by SDS (Sodium dodecyl sulfate)-PAGE [Antibodies-A Laboratory Manual (Cold Spring Harbor Laboratory, 1988)], the gel is blotted onto PVDF membrane or nitrocellulose membrane, the membrane is allowed to react with antigen-recognizing antibody or

Samsung Bioepis Exhibit No. 1002
Page 12097

antibody fragment, further allowed to react with an anti-mouse IgG antibody or antibody fragment which is labeled with a fluorescent substance such as FITC, an enzyme label such as peroxidase, a biotin labeling, or the like, and the label is visualized to confirm the reaction. An example thereof is described below.

[0290] Cells or tissues in which a polypeptide having the amino acid sequence represented by SEQ ID NO: 53 is expressed are dissolved in a solution and, under reducing conditions, 0.1 to 30 μg as a protein amount per lane is electrophoresed by an SDS-PAGE method. The electrophoresed protein is transferred onto a PVDF membrane and allowed to react with PBS containing 1 to 10% of BSA (hereinafter referred to as "BSA-PBS") at room temperature for 30 minutes for blocking.

[0291] Here, the monoclonal antibody of the present invention is allowed to react therewith, washed with PBS containing 0.05 to 0.1% Tween 20 (hereinafter referred to as "Tween-PBS") and allowed to react with goat anti-mouse IgG labeled with peroxidase at room temperature for 2 hours. It is washed with Tween-PBS and a band to which the monoclonal antibody is bound is detected using ECL Western Blotting Detection Reagents (manufactured by Amersham) or the like to thereby detect a polypeptide having the amino acid sequence represented by SEQ ID NO: 1. As an antibody used for the detection in Western blotting, an antibody which can be bound to a polypeptide having no three-dimensional structure of a natural type is used.

[0292] The physicochemical method is specifically carried out by reacting TIM-3 as the antigen with the antibody or antibody fragment of the present invention to form an aggregate, and detecting this aggregate. Other examples of the physicochemical methods include a capillary method, a one-dimensional immunodiffusion method, an immunoturbidimetry, a latex immunoturbidimetry [Handbook of Clinical Test Methods, Kanehara Shuppan, (1988)] and the like.

[0293] For example, in a latex immunodiffusion method, a carrier such as polystyrene latex having a particle size of about of 0.1 to 1 μm sensitized with antibody or antigen may be used and when an antigen-antibody reaction is carried out using the corresponding antigen or antibody, scattered light in the reaction solution increases while transmitted light decreases. When such a change is detected as absorbance or integral sphere turbidity, it is possible to measure antigen concentration, etc. in the sample to be tested.

[0294] In addition, for the detection of the cell expressing TIM-3, known immunological detection methods can be used, and an immunoprecipitation method, an immuno cell staining method, an immune tissue staining method, a fluorescent antibody staining method and the like are preferably used.

[0295] An immunoprecipitation method is a method in which a cell expressing TIM-3 is allowed to react with the monoclonal antibody or antibody fragment of the present invention and then a carrier having specific binding ability to immunoglobulin such as protein G-Sepharose is added so that an antigen-antibody complex is precipitated. Also, the following method can be carried out. The above-described antibody or antibody fragment of the present invention is solid-phased on a 96-well plate for ELISA and then blocked with BSA-PBS.

[0296] When the antibody is in a non-purified state such as a culture supernatant of hybridoma cell, anti-mouse immunoglobulin or rat immunoglobulin or protein A or Protein G or the like is previously adsorbed on a 96-well plate for ELISA and blocked with BSA-PBS and a culture supernatant of hybridoma cell is dispensed thereto for binding. After BSA-PBS is discarded and the residue is sufficiently washed with PBS, reaction is carried out with a dissolved solution of cells or tissues expressing TIM-3. An immune precipitate is extracted from the well-washed plate with a sample buffer for SDS-PAGE and detected by the above-described Western blotting.

[0297] An immune cell staining method or an immune tissue staining method are a method where cells or tissues in which antigen is expressed are treated, if necessary, with a surfactant, methanol or the like to make an antibody easily permeate to the cells or tissues, then the monoclonal antibody of the present invention is allowed to react therewith, then further allowed to react with an anti-immunoglobulin antibody or binding fragment thereof subjected to fluorescent labeling such as FITC, enzyme label such as peroxidase or biotin labeling and the label is visualized and observed under a microscope.

[0298] In addition, cells can be detected by an immunofluorescent staining method where cells are allowed to react with a fluorescence-labeled antibody and analyzed by a flow cytometer [Monoclonal Antibodies - Principles and practice, Third Edition, Academic Press (1996), Manual for Experiments of Monoclonal Antibodies, Kodansha Scientific (1987)] in which cells are allowed to react with a fluorescence-labeled antibody and analyzed by a flow cytometer.

[0299] Particularly, the monoclonal antibody or antibody fragment of the present invention which binds to amino acids sequences of an extracellular region of the TIM-3 or a three-dimensional structure thereof can detect a cell expressing the polypeptide maintaining a natural three-dimensional structure by a fluorescence antibody method.

[0300] In addition, in the case of using FMAT8100HTS system (manufactured by Applied Biosystems) and the like among fluorescent antibody staining methods, the antigen quantity or antibody quantity can be measured without separating the formed antibody-antigen complex and the free antibody or antigen which is not concerned in the formation of the antibody-antigen complex.

The present invention can provide a monoclonal antibody or an antibody fragment of thereof, which binds to amino acids sequences of an extracellular region of TIM-3 or a three-dimensional structure and expresses ADCC activity; a hybridoma which produces the antibody; a DNA which encodes the antibody; a vector which comprises the DNA; a transformant

Samsung Bioepis Exhibit No. 1002
Page 12098

obtained by transforming the vector; a process for producing an antibody or an antibody fragment thereof using the hybridoma or the transformant; and a therapeutic agent or a diagnostic agent comprising the antibody or the antibody fragment thereof as an active ingredient.

[0301] Hereinafter, exemplary embodiments of the present invention will be described specifically. However, the present invention is not limited to the exemplary embodiments described below.

Example

[Example 1]

(Molecular cloning of human TIM-3 cDNA and establishment of stable expression cell)

[0302] Human TIM-3 cDNA was amplified by PCR using ExTaq (manufactured by Takara Bio Inc.) and Human MTC panel (manufactured by Clontech) as a template. For primers, TIM-3 Fw2 (SEQ ID NO: 31) and TIM-3 Re2 (SEQ ID NO: 32) were used. The obtained PCR product was inserted into pGEM-T Easy vector (manufactured by Promega Corp.), and the plasmid was introduced into TOP10 One shot competent cells (manufactured by Invitrogen) to amplify. The plasmid DNA was extracted by the miniprep method.

[0303] By analyzing the sequence of purified DNA using primers TIM-3 Fw and TIM-3 Re2, the clone having the same sequence as the coding region of GenBank accession number NM_032782 was selected. A human TIM-3 retrovirus (hTIM-3/pMCs-IG) was constructed by recombination of the insert of the selected clone into pMCs-IRES-GFP vector (manufactured by Cell Biolabs Inc.) using Retrovirus Constructive System Ampho (manufactured by Takara Bio Inc.).

[0304] The human TIM-3 retrovirus was infected into Jurkat cell (ATCC accession NO: CRL-2063), EoL-1 cell (RIKEN CELL BANK NO: RCB0641) and L929 cell (manufactured by Sigma-Aldrich Co., LLC.) which were confirmed not to endogenously express TIM-3 was confirmed by flow cytometry analysis. After several passages, TIM-3 positive cells were collected by FACSAria (manufactured by BD Biosciences). Human TIM-3 stable expression cell line was established by recollecting the TIM-3 positive cells by FACSAria after several passages.

[Example 2]

(Preparation of expression vector of fusion protein of soluble extracellular human TIM-3-human Fc)

[0305] The cDNA encoding the extracellular region of human TIM-3 was amplified by PCR using ExTaq (manufactured by Takara Bio Inc.) and hTIM-3/pMCs-Ig constructed in Example 1 as a template. For primers, pMCs-Fw (SEQ ID NO: 33) and TIM3ED-FcReXba 2 (SEQ ID NO: 34) were used.

[0306] The amplified PCR product was inserted into pTracer-CMV-FLAG-human Fc vetctor [modified vector in which FLAG and Fc domain of human IgG1 were inserted into pTracer-CMV (manufactured by Invitrogen) vector between *Xba*I site and *Apa*I site]. After the plasmid was introduced into TOP10 One shot competent cells (manufactured by Invitrogen) to amplify, the plasmid DNA (sTIM-3-FLAG-Fc/pTracerCMV) was extracted by miniprep method.

[0307] By the analysis of the DNA sequence using T7 (SEQ ID NO: 35) and hTIM-3 Fw1 (SEQ ID NO: 36) as a primer, the purified sTIM-3-FLAG-Fc/pTracerCMV was confirmed to have the same nucleotide sequence as the corresponding region in GenBank accession number NM_032782. The nucleotide sequence (from *Eco*RI recognition site to *Apa*I recognition site) was identical to the nucleotide sequence represented by SEQ ID NO: 37.

[Example 3]

(Preparation of expression vector of soluble extracellular human TIM-3)

[0308] The cDNA encoding the extracellular region of human TIM-3 was amplified by PCR using ExTaq (manufactured by Takara Bio Inc.) and sTIM-3-FLAG-Fc/pTracerCMV established in Example 2 as a template. As primers, TIM-3 Fw2 (SEQ ID NO: 31) and TIM3ED-FLAG4aa (SEQ ID NO: 39) were used.

[0309] Next, FLAG epitope was ligated by PCR method using ExTaq (manufactured by Takara Bio Inc.), TIM-3 Fw2 (SEQ ID NO: 31) and C-FLAG-NotR2 (SEQ ID NO: 40) as primers and the obtained PCR product as a template. The PCR product was inserted into pGEM-T Easy vector (manufactured by Promega Corp.). After the plasmid was introduced into TOP10 One shot competent cells (manufactured by Invitrogen) to amplify the plasmid DNA (sTIM-3-FLAG/pEF6Myc_HisC) was extracted by the miniprep method.

[0310] By the DNA sequence analysis using T7 (SEQ ID NO: 35) and BGH-R (SEQ ID NO: 41) as a primer, the purified sTIM-3-FLAG-Fc/pEF6 Myc_HisC was confirmed to have the same nucleotide sequence as the corresponding region in GenBank accession number NM_032782.

Samsung Bioepis Exhibit No. 1002
Page 12099

[Example 4]

(Preparation of the fusion protein of soluble extracellular human TIM-3-human Fc and soluble extracellular human TIM-3)

[0311] Each of sTIM-3-FLAG-Fc/pTracerCMV plasmid DNA and sTIM-3-FLAG-Fc/pEF6 Myc_HisC plasmid DNA obtained in Example 2 and Example 3, respectively, was introduced into HEK293F cells (manufactured by Invitrogen) and was transiently expressed. Six days after, each of the cell supernatant was recovered and used for protein purification.

[0312] The culture supernatant containing the fusion protein of soluble extracellular human TIM-3-human Fc or soluble extracellular human TIM-3 was recovered by centrifugation six days after transfection. The fusion proteins were purified by an anti-FLAG column prepared using Anti-FLAG M2 Agarose Affinity gel (manufactured by Sigma-Aldrich Co., LLC.) and by FLAG peptides (manufactured by Sigma-Aldrich Co., LLC.) according to the manufacturer's protocols.

[0313] The eluted samples were fractionated and then each fraction was analyzed by SDS-PAGE under reduced conditions, and then silver staining and Western blotting were carried out. For Western blotting, an anti-FLAG M2 antibody (manufactured by Sigma-Aldrich Co., LLC.) and an alkaline phosphatase labeled rabbit anti-mouse immunoglobulin antibody was used (manufactured by Dako). The fraction containing the target protein was concentrated using Amicon Ultra 4 10K (manufactured by Millipore) and was applied for gel filtration chromatography using Superdex 200 gp column (manufactured by GE Healthcare).

[0314] After fractionation, each fraction was applied to SDS-PAGE under reduced condition, silver stained and then Western blotted. The fraction in which the target protein was found was concentrated and washed with 0.5 ml of PBS. The soluble extracellular human TIM-3-human Fc fusion protein or soluble extracellular human TIM-3 was collected after filtering through the MILLEX-GV sterilizing filter (manufactured by Millipore) having a pore diameter of 0.22 μm. The purity of the protein was measured by Limulus ES-II kit Wako (manufactured by Wako Pure Chemical Industries, Ltd.) which is a kit to detect endotoxin and confirmed that the fraction was sufficiently purified.

[Example 5]

(Preparation of human antibody expressing mouse)

[0315] The mice used for immunization has a genetic background in which both of endogenous Ig heavy chain locus and κ light chain locus were homozygously disrupted and maintained a chromosome 14 fragment (SC20) comprising a human heavy chain transchromosome, and a human Igκ chain transgene (KCo5) at the same time. This mouse strain was established by cross breeding mice strain A which had human Ig heavy chain loci and mice strain B which maintained human Igκ chain transgene.

[0316] Mouse strain A is a homozygote in which both of the endogenous Ig heavy chain locus and κ light chain locus are homozygously disrupted, and maintains a chromosome 14 fragment (SC20) which can be transmitted to the progeny and for example, described in Tomizuka *et al.* (Tomizuka, K. et al., 2000, Proc. Natl. Acad. Sci. U.S.A. 97:722-727).

[0317] Mouse Strain B is a mouse strain (transgenic mouse) in which both of the endogenous Ig heavy chain locus and κ light chain locus are homozygously disrupted, and maintains a human Igκ light chain transgene (KCo5), and is ,for example, described in Fishwild et al. (1996) [Nature Biotechnology 14:845-851].

[0318] The animal individual was obtained by cross-breeding male mouse of strain A and female mouse of strain B, or female mouse of strain A and male mouse of strain B and was a mouse in which human Ig heavy chain and Igκ light chain could be detected at the same time in their serum [Ishida& Lonberg, IBC's 11th Antibody Engineering, Abstract 2000] was further used for immunological experiments. For your information,, the human antibody expressing mouse (hereinafter referred to as "KM mouse") can be obtained from Kyowa Hakko Kirin by establishing a license.

[Example 6]

(Preparation of anti-human TIM-3 monoclonal antibody)

[0319] The preparation of monoclonal antibody in the present Example was carried out according to the general methods, such as published in Monoclonal Antibody Experiment Manual, (Yasuhigashi Tamie et al., Kodansha, 1991). Either TIM-3 expressing L929 cell prepared in Example 1 or the soluble extracellular human TIM-3-human Fc fusion protein prepared in Example 4 was used as a TIM-3 immunogen. The immunized animal was KM mouse described above.

[0320] The TIM-3 expressing L929 cell was intraperitoneally injected into mice at a dose of 1×10^7 cells/animal. After the first immunization, the same cell was further administered for another three times or more thereafter. Three days before obataining the spleen, the soluble extracellular human TIM-3-human Fc fusion protein prepared in Example 4 was administered from caudal vein at 20 μg/mouse. The spleen was surgically removed from the immunized mouse, put into 4 ml of PBS and mashed on a mesh (cell strainer: manufactured by Falcon) using a syringe piston.

Samsung Bioepis Exhibit No. 1002
Page 12100

[0321] The cells were precipitated by centrifuging the cell suspension which was passed through the mesh, and the cells were resupsended in 1 ml of Red Blood Cell Lysis Buffer (manufactured by Sigma-Aldrich Co., LLC.). After incubating for 5 min at room temperature, 10 ml of serum free DMEM medium (manufactured by Invitrogen) (hereinafter referred to as "serum free DMEM medium") containing 50 unit/ml penicillin and 50 μg/ml streptomycin was added, and the cells were precipitated by centrifugation.

[0322] The cell pellets were resuspended in serum free DMEM medium. On the other hand, myeloma cell line SP2/0 (ATCC NO: CRL-1581) was cultured in DMEM medium containing 10% FBS, 50 unit/ml penicillin and 50 μg/ml streptomycin (hereinafter referred to as "DMEM medium containing serum") and incubated at 37°C under 5% CO_2 so as not exceed the cell number of 1×10^6 cells/ml.

[0323] The SP2/0 cells were washed with 10 ml of serum free DMEM medium and suspended in serum free DMEM medium as in the case of the spleen derived cells. These suspension of spleen derived cells and suspension of myeloma cell were mixed at a ratio of 5:1, centrifuged, and the supernatant was completely removed. To fuse the cells, 1 ml of 50% (w/v) of polyethylene glycol (manufactured by Boehringer Mannheim Corp.) was slowly added while stirring the pellet with the pipette tip, and then 1 ml of serum free DMEM medium preheated at 37°C was added. Slowly, 5 ml and 10 ml of serum free DMEM was added followed by 5 min incubation at 37°C under 5% CO_2.

[0324] After the centrifugation and removal of supernatant, the fused cells were resuspended in 50 ml of DMEM medium containing 10% FBS (manufactured by Invitrogen), penicillin-streptomycin-glutamine (manufactured by Invitrogen, 100-fold dilution of Catalog No.10378-016), IL-6 (5 ng/ml), and 2-mercaptoethanol (manufactured by Invitrogen, 1000-fold dilution of Catalog No. 21985-023) (hereinafter referred to as "DMEM medium containing IL-6") and incubated at 37°C under 5% CO_2.

[0325] The next day, cells were harvested by pipetting, centrifuged and the pellet was resuspended in 10 ml of DMEM medium containing IL-6. On the next day, Hypoxanthine-aminopterin-thymidine (hereinafter referred to as "HAT", manufactured by Sigma-Aldrich Co., LLC.) was added. After incubating for about 7 to 10 days, the culture supernatant was collected for hybridoma screening.

[Example 7]

(Preparation of anti-human TIM-3 mouse monoclonal antibody)

[0326] The preparation of monoclonal antibody in the present Example was carried out according to the general methods published in Introduction to Monoclonal Antibody Experiment (Yasuhigashi Tamie et al., Kodansha, 1991). Either TIM-3 expressing L929 cell prepared in Example 1 or soluble extracellular human TIM-3 prepared in Example 4 was used as a TIM-3 immunogen. The immunized animal was Balb/c mouse (purchased from Nihon Charles River).

[0327] First, a Balb/c mouse was immunized by injecting TIM-3 expressing L929 cells intraperitoneallyat a dose of 1×10^7 cells/animal. After the first immunization, the same cell was further administered for another three times or more thereafter. Three days before extracting the spleen, the soluble extracellular human TIM-3 protein prepared in Example 4 was administered from caudal vein at 20 μg/mouse. The spleen was surgically removed from the immunized mouse, put into 4 ml of PBS and mashed on a mesh (cell strainer: manufactured by Falcon) using a syringe piston.

[0328] The cells were precipitated by centrifuging the cell suspension which was passed through the mesh, and the cells were resuspended in 1 ml of Red Blood Cell Lysis Buffer (manufactured by Sigma-Aldrich Co., LLC.). After incubating for 5 min at room temperature, 10 ml of serum free DMEM medium was added, and then cells were precipitated by centrifugation. The pellets were resuspended in serum free DMEM medium. On the other hand, myeloma cell line SP2/0 (ATCC NO: CRL-1581) were cultured in DMEM medium by incubating at 37°C under 5% CO_2 to the cell number of 1×10^6 cells/ml or less.

[0329] Similar to the spleen derived cells, the SP2/0 cells were washed with 10 ml of serum free DMEM medium and suspended in serum free DMEM medium. The suspension of spleen cell and the suspension of myeloma cell were mixed at a ratio of 5:1. After centrifugation, the supernatant was removed. To this pellet, 1 ml of 50% (w/v) of polyethylene glycol (manufactured by Boehringer Mannheim Corp.) was slowly added while stirring the pellet with the pipette tip, and then 1 ml of serum free DMEM medium preheated to 37°C was added.

[0330] To this suspension, 5 ml of DMEM medium was slowly added. After further adding 10 ml of serum free DMEM, the suspension was incubated for 5 min at 37°C under 5% CO_2. After the suspension was centrifuged, the cell pellets were resuspended in 50 ml of DMEM medium containing IL-6 and cultured at 37°C under 5% CO_2. After incubation for one day, cells were collected by pipetting. After centrifugation, the pellet was resuspended in 10 ml of DMEM medium containing IL-6. On the next day, HAT medium (manufactured by Sigma-Aldrich Co., LLC.) was added. After incubation for about 7 to 10 days, the culture supernatant was recovered and used for hybridoma screening.

Samsung Bioepis Exhibit No. 1002
Page 12101

[Example 8]

(Screening of hybridoma producing a human or mouse monoclonal antibody which binds to human TIM-3)

[0331] The hybridoma was screened using the cell supernatant prepared in Example 6 and Example 7. The method to be used was a flow cytometry method using human TIM-3 expressing cell lines. First, the human TIM-3 expressing Jurkat cell or EoL-1 cell prepared in Example 1 were washed with staining medium (PBS containing 2% FBS and 0.05% sodium azide), and then resuspended in 1 ml of staining medium to give a cell density of 1×10^6 cells/ml. The cell suspension was dispensed at 10 μl/well into a 96-well culture plate.

[0332] Then, 50 μl of the hybridoma supernatant was added and incubated for 30 min at 4°C. After the cells were washed twice with the staining medium, 50 μl of labeled antibody which was diluted 200-fold with staining medium was added to each well and incubated for 30 min at 4°C. As for labeled antibodies, Goat $F(ab')_2$ Anti-Human IgG (γ chain specific)-R-PE (manufactured by SouthernBiotech) were used for the human monoclonal antibody and Goat $F(ab')_2$ Anti-Mouse IgG(H+L)R-PE (manufactured by SouthernBiotech) was used for the mouse monoclonal antibody.

[0333] After washing twice with staining medium, the cells were analysed using FACSCalibur (manufactured by BD Biosciences) as a primary screening. After positive clones were picked and expanded, the hybridoma cells were clone-sorted by FACSAria (manufactured by BD Biosciences) and cultured for seven days in DMEM medium containing IL-6 which further contains Hypoxanthine-thymidine (hereinafter referred to as "HT", manufactured by Sigma-Aldrich Co., LLC.).

[0334] Harvested supernatants were screened as the same as in the primary screening method for cloning of hybridomas expressing anti-human TIM-3 human monoclonal antibody and hybridomas expressing anti-human TIM-3 mouse monoclonal antibody and selected hybridoma clone was used for purification of monoclonal antibody.

[Example 9]

(Purification of hybridoma derived monoclonal antibody)

[0335] An anti-TIM-3 human or mouse monoclonal antibody was purified from the anti-human TIM-3 human or mouse monoclonal antibody expressing hybridoma prepared in Example 8. Briefly, hybridoma supernatant containing a high concentration of the anti-TIM-3 antibody was prepared using a CELLine antibody production system (manufactured by BD Biosciences) and the anti-human TIM-3 monoclonal antibody was purified from the supernatant. First, to adapt the cloned hybridoma to the serum free medium, the hybridomas were cultured for several days in a medium mixing DMEM medium containing HT and IL-6 and BD Cell MAb serum free medium (manufactured by BD Biosciences) at a ratio of 1:1, and then cultured for several days in a medium having a mixing ratio of 1:2.

[0336] Next, the hybridomas were cultured in a BD Cell MAb serum free medium (manufactured by BD Biosciences) and adapted hybridomas to the serum free medium. The hybridoma cells adapted to the serum free medium were cultured in CL-1000 flasks according to the manufacturer's instructions and the supernatant of the hybridoma containing high concentration of the anti-TIM-3 antibody was collected from the flasks. The antibody from the supernatant of the hybridoma was purified in accordance with the standard procedures using Protein A.

[0337] Specifically, MabSelect (manufactured by GE Healthcare) were packed in an open column and the supernatant diluted 2-fold by PBS was loaded and then eluted with 0.1 mol/L Glycine-HCl (pH 2.7), followed by concentration with Amicon Ultra (manufactured by Millipore). Next, by using a NAP-5 column (manufactured by GE Healthcare), the obtained solution was equilibrated with PBS buffer, and then sterilized by filtration to obtain 4 clones of the anti-human TIM-3 human monoclonal antibodies (antibody 512, antibody 644, antibody 4545 and antibody 4177) and one clone (antibody 8213) of the anti-human TIM-3 mouse monoclonal antibody.

[Example 10]

(Identification of isotype of anti-TIM-3 human monoclonal antibody)

[0338] Each of the isotype of anti-TIM-3 human monoclonal antibodies which was prepared in Example 9 was determined by a solid-phase ELISA and flow cytometry.

Specifically, as for the solid-phase ELISA, soluble extracellular human TIM-3 obtained by Example 4 was diluted with a Carbonate-Biacarbonate Buffer (manufactured by Sigma-Aldrich Co., LLC.) to give a concentration of 1 μg/ml and dispensed at 50 μl/well into a 96-well culture plate (Maxisorp, manufactured by Nunc). The soluble extracellular human TIM-3 was adsorbed to the microplate by incubating overnight at 4°C.

[0339] After the supernatant was discarded, SuperBlock Blocking Buffer in TBS (manufactured by PIERCE) was added to the plate and then incubated for 10 min at room temperature and 50 μl of the culture supernatant of the hybridoma

Samsung Bioepis Exhibit No. 1002
Page 12102

was added and then incubated for 30 min at room temperature. After washing each well with Tris-buffered saline containing 0.1% Tween20 (TBS-T), 50 μl of each of HRP-labeled mouse anti-human IgG1, anti-human IgG2, anti-human IgG3 or anti-human IgG4 antibodies, each antibody was diluted 2000, 2000, 2000 and 4000-fold with TBS-T containing 10% SuperBlock Blocking Buffer, respectively; manufactured by SouthernBiotech), were added and incubated for 30 minutes at room temperature.

[0340] After washing each well with TBS-T, 50 μl of substrate buffer (TMB, manufactured by DAKO) was added and then incubated for 20 min at room temperature. The reaction was stopped by adding 50 μl of 0.5 mol/L sulfuric acid (manufactured by Wako Pure Chemical Industries, Ltd.). The absorbance at wavelength of 450 nm (reference wavelength: 570 nm) was measured on a microplate reader (VersaMax, manufactured by Molecular Devices, LLC.).

[0341] In addition, in flow cytometry method, the Jurkat cell which expressed human TIM-3 prepared in Example 1 was washed with staining medium, and then 50 μl of the supernatant of the hybridoma was added and incubated for 30 min at 4°C. After washing, 50 μl of each of Mouse anti-Human IgG1-PE, Mouse anti-Human IgG2-PE, Mouse anti-Human IgG3 (Hinge)-PE and Mouse anti-Human IgG4(Fc)-PE (manufactured by SouthernBiotech) which was diluted 100-fold with staining medium was added, allowed to stand still for 30 min at 4°C and then analyzed using FACSCalibur flow cytometer (manufactured by BD Biosciences).

[0342] Based on the result, the isotypes of antibody 512, antibody 644, and antibody 4545 were IgG1, IgG4 and IgG2, respectively.

[Example 11]

(Identification of the isotype of the mouse monoclonal antibody for human TIM-3)

[0343] The isotype of the anti-human TIM-3 mouse monoclonal antibody prepared in Example 9 was determined using Iso Strip Mouse Monoclonal Antibody Isotyping Kit (manufactured by Roche-diagnostics). By using the supernatant of the hybridoma containing the anti-TIM-3 antibody prepared in Example 8, the isotype was determined according to the manufacturer's instructions. As a result, the isotype of antibody 8213 was determined as IgG2b.

[Example 12]

(Isolation of anti-TIM-3 monoclonal antibody gene)

[0344] The gene of anti TIM-3 human or mouse monoclonal antibody which was prepared in Example 9 was isolated from the hybridoma which produced anti-human TIM-3 human or mouse monoclonal antibody prepared in Example 9. Total RNA was extracted from the cloned hybridoma using High Pure RNA Isolation Kit (manufactured by Roche-Diagnostics), according to the manufacturer's instructions. The cloning of the cDNA encoding the variable region was carried out using SMART RACE cDNA amplification Kit (manufactured by Clontech) in accordance with the instructions attached thereto.

[0345] The heavy chain (VH) of the human monoclonal antibody was amplified by PCR using UPM (SMART RACE cDNA amplification Kit; manufactured by Clontech) and primer hh-6 (SEQ ID NO: 44). Using part of the reaction product as a template, PCR was carried out using NUP (SMART RACE cDNA amplification Kit; manufactured by Clontech) and primer hh-3 (SEQ ID NO: 45). The cloning of the PCR product was carried out using Zero Blunt TOPO PCR Cloning Kit (manufactured by Invitrogen). The nucleotide sequence was analyzed by universal primers of the vector (e.g., T7 or M13R primer) and the amino acid sequence was deduced from the nucleotide sequence.

[0346] As a result, the nucleotide sequence and the amino acid sequence of VH of antibody 512 were represented by SEQ ID NO: 54, was and SEQ ID NO: 55, respectively, the nucleotide sequence and the amino acid sequence of VH of antibody 644 were represented by SEQ ID NO: 58 and SEQ ID NO: 59, respectively, the nucleotide sequence and the amino acid sequence of VH of antibody 4545 were represented by SEQ ID NO: 7 and SEQ ID NO: 8, respectively, and the nucleotide sequence and the amino acid sequence of VH of antibody 4177 were represented by SEQ ID NO: 17 and SEQ ID NO: 18, respectively. Each of the obtained variable regions obtained and the constant region of human IgG1 were inserted and ligated into the expression vector, N5KG1 (manufactured by Biogen IDEC Inc.).

[0347] Human monoclonal antibody light chain (VL) was amplified by PCR using UPM (SMART RACE cDNA amplification Kit; manufactured by Clontech) and primer hk-2 (SEQ ID NO: 46). Using part of the reaction product as a template, PCR was carried out using NUP (SMART RACE cDNA amplification Kit; manufactured by Clontech) and primer hk-6 (SEQ ID NO: 47). The PCR product was cloned using Zero Blunt TOPO PCR Cloning Kit (manufactured by Invitrogen). The nucleotide sequence was analyzed by universal primers of the vector (e.g., T7 or M13R) and the amino acid sequence was deduced from the nucleotide sequence.

[0348] As a result, the nucleotide sequence and the amino acid sequence of VL of antibody 512 were represented by SEQ ID NO: 56 and SEQ ID NO: 57, respectively, the nucleotide sequence and the amino acid sequence of VL of

Samsung Bioepis Exhibit No. 1002
Page 12103

antibody 644 were represented by SEQ ID NO: 60 and SEQ ID NO: 61, respectively, the nucleotide sequence and the amino acid sequence of VL of antibody 4545 were represented by SEQ ID NO: 9 and SEQ ID NO: 10, respectively, and the nucleotide sequence and the amino acid sequence of VH of antibody 4177 were represented by SEQ ID NO: 19 and SEQ ID NO: 20, respectively. Each of the obtained variable regions and constant region of κ chain were inserted and ligated into the expression vector, N5KG1 (manufactured by Biogen IDEC Inc.).

[0349] The heavy chain (VH) of mouse monoclonal antibody was amplified by PCR using UPM (SMART RACE cDNA amplification Kit; manufactured by Clontech) and a primer, mH_Rv1 (SEQ ID NO: 48). Using part of the reaction product e as template, PCR was carried out using NUP (SMART RACE cDNA amplification Kit; manufactured by Clontech) and primer mH_Rv2 (SEQ ID NO: 49).

[0350] The cloning of the PCR product was carried out using Zero Blunt TOPO PCR Cloning Kit (manufactured by Invitrogen). The nucleotide sequence was analyzed by universal primers of the vector (e.g., T7 or M13R) and the amino acid sequence was deduced from the nucleotide sequence.

[0351] As a result, the nucleotide sequence and the amino acid sequence of VH of antibody 8213 were represented by SEQ ID NO: 27 and SEQ ID NO: 28, respectively. The obtained variable region and the constant region of mouse IgG2a were ligated and inserted into the expression vector, N5KG1 (manufactured by Biogen IDEC Inc.).

[0352] The light chain (VL) of the mouse monoclonal antibody was amplified by PCR using UPM (SMART RACE cDNA amplification Kit; manufactured by Clontech) and primer mK_Rv1 (SEQ ID NO: 50). Additionally, part of the reaction product was used as a template, and PCR was carried out using NUP (SMART RACE cDNA amplification Kit; manufactured by Clontech) and primer mK_Rv2 (SEQ ID NO: 51). The PCR product was cloned using Zero Blunt TOPO PCR Cloning Kit (manufactured by Invitrogen). Nucleotide sequences were analyzed by universal primers of the vector (e.g., T7 or M13R) and the amino acid sequence was deduced from the nucleotide sequence.

[0353] As a result, the nucleotide sequence and the amino acid sequence of the VL of antibody 8213 were represented by SEQ ID NO: 29 and SEQ ID NO: 30, respectively. The variable region obtained and the constant region of κ chain were ligated and inserted into the above mentioned expression vector encoding VH of antibody 8213.

[0354] In addition, in order to obtain anti-dinitrophenyl (DNP) human IgG1 antibody as a negative control, the nucleotide sequence of the heavy chain (VH) of the antibody (SEQ ID NO: 62), the nucleotide sequence of the light chain of the antibody (SEQ ID NO: 64), and the constant region of human IgG1 and the κ chain were inserted into expression vector N5KG1 (manufactured by Biogen IDEC Inc.).

[Example 13]

(Purification of recombinant anti-TIM-3 human monoclonal defucose antibody)

[0355] A cell expressing a recombinant antibody was produced by introducing the recombinant antibody expression vector prepared in Example 12 into the host cell. As the host cell for expression, FUT8$^{-/-}$CHO cells were used in accordance with a published report *(Clin Cancer Res* 2006; 12(9) Iida *et al.*). Briefly, the expression vectors for each of 512, 644, 4545 and 4177 prepared in Example 12 were introduced into FUT8$^{-/-}$ CHO cell using FreeStyle™ MAX Reagent (manufactured by Invitrogen). The FUT8$^{-/-}$CHO cells were cultured on a shaker at 37°C under 5% CO_2. The culture supernatant was recovered after about five days.

[0356] The recovered supernatant was purified using Protein A (manufactured by GE Healthcare) and further using 0.8×40 cm column (manufactured by BioRad) and the like, depending on the sample amount. Antibodies were affinity purified using PBS as the binding buffer and 0.02 mol/L sodium citrate (pH 2.7, 50 mmol/L NaCl) buffer as the elution buffer. The elution fraction was added with 0.2 mol/L of sodium phosphate buffer (pH 7.0).

[0357] The prepared antibody solution was equilibrated with PBS using NAP-25 column (manufactured by GE Healthcare) and concentrated with Amicon Ultra (10000 cut, manufactured by Millipore). After sterilization by filtration, the recombinant anti-TIM-3 human monoclonal defucose antibodies (antibody 512, antibody 644, antibody 4545 and antibody 4177) were obtained. The purity of the protein was determined by Limulus ES-II kit Wako (manufactured by Wako Pure Chemical Industries, Ltd.) and found that these antibodies were sufficiently purified.

The vector for expressing anti-DNP prepared in Example 12 was introduced into CHO-DG44 cells. The CHO-DG44 cells were cultured on a shaker at 37°C under 5% CO_2. The cultured supernatant was recovered following incubation for 5 days. The collected supernatant was purified using Protein A (manufactured by GE Healthcare) and further using 0.8×40 cm column (manufactured by BioRad) and the like, depending on the sample amount. The affinity purification of the antibodies was carried out using PBS as the binding buffer and 0.02 mol/L of sodium citrate (pH 2.7, 50 mmol/L NaCl) buffer as the elution buffer. The elution fraction was added with 0.2 mol/L of sodium phosphate buffer (pH 7.0). The prepared antibody solution was equilibrated with PBS and concentrated using NAP-25 column (manufactured by GE Healthcare) with Amicon Ultra (10000 cut, manufactured by Millipore) respectively. After sterilization by filtration, the recombinant anti-DNP antibody was obtained. The purity of the protein was determined using a Limulus ES-II kit Wako (manufactured by Wako Pure Chemical Industries, Ltd.) and found that the antibody was sufficiently purified.

Samsung Bioepis Exhibit No. 1002
Page 12104

[Example 14]

(Purification of recombinant anti-TIM-3 mouse monoclonal antibody)

[0358] The vector for expressing antibody 8213 prepared in Example 12 was introduced into HEK293F cells (manufactured by Invitrogen) using 293 fectin (manufactured by Invitrogen). HEK293F cells were incubated on a shaker at 37°C under 5% CO_2. The cultured supernatant was collected after incubation for five days. The collected supernatant was purified using Protein A (manufactured by GE Healthcare) and further using 0.8×40 cm column (manufactured by BioRad) and the like, depending on the sample amount. The affinity purification of the antibody was carried out using PBS as a binding buffer and 0.02 mol/L sodium citrate buffer (pH 2.7, 50 mmol/L NaCl) as an elution buffer.

[0359] To the elution fraction, 0.2 mol/L of sodium phosphate buffer (pH 7.0) was added. The prepared antibody solution was equilibrated with PBS using NAP-25 column (manufactured by GE Healthcare) and concentrated with Amicon Ultra (10000 cut, manufactured by Millipore). After sterilization by filtration, the recombinant anti-TIM-3 mouse monoclonal antibody (8213 antibody) was obtained. The purity of the protein was determined using a Limulus ES-II kit Wako (manufactured by Wako Pure Chemical Industries, Ltd.) and found that the antibody was sufficiently purified.

[Example 15]

(Fluorescent labeling of purified monoclonal antibody)

[0360] The fluorescent labeling of the hybridoma derived monoclonal antibody and recombinant monoclonal antibody was carried out by using Alexa Fluor 647 Monoclonal Antibody Labeling Kit (manufactured by Invitrogen) according to the manufacturer's instructions. After the labeling, each antibody was confirmed to be positively labeled with Alexa Fluor 647 (hereinafter referred to as "Alexa-647") by FACSCalibur (manufactured by BD Biosciences) analysis for TIM-3 expressing cells.

[Example 16]

(Classification of epitopes using competition test-1)

[0361] The relation of epitopes between antibodies prepared in Example 13 and Example 14, and commercially available anti-TIM-3 antibody 344823 (Clone 344823, manufactured by R&D Systems) was analyzed by a competition test. In brief, the test antibody was allowed to interact with the TIM-3 expression cell prepared in Example 1, and then whether another anti-TIM-3 antibody could further bind to TIM-3 expressing cells was evaluated by flow cytometry method.

[0362] In the first step, whether or not the competition between each of the monoclonal antibodies prepared in Example 13 and Example 14 (antibody 512, antibody 644, antibody 4177 and antibody 8213) and antibody 34823 were examined. First, human TIM-3 expressing EoL-1 cells and the parent cell, EoL-1 cells were washed with staining medium and then allowed to react with each of the purified subjective monoclonal antibodies (antibody 512, antibody 644, antibody 4177 and antibody 8213) (4°C, 30 min). The final concentration was 10 μg/ml. Next, the PE labeled antibody 344823 (Clone 344823, manufactured by R&D Systems) was added and allowed to react (4°C, 30 min). After washing with staining medium, 7-ADD (manufactured by BD Biosciences) was added and analyzed using FACSCalibur (manufactured by BD Biosciences).

[0363] As a result, the goat derived anti-human TIM-3 polyclonal antibody (manufactured by R&D Systems) used as a positive control and antibody 644 almost completely blocked the binding of PE-labeled antibody 344823 to TIM-3 expressing cell. However, antibody 512, 4545 and 8213 did not inhibit the binding of PE-labeled antibody 344823 to TIM-3 expressing cell. Antibody 4177 inhibited the binding of PE-labeled antibody 344823 to TIM-3 expressing cells, but this inhibition was weaker than that of antibody 644. Accordingly, antibody 644 competed with antibody 344823, but antibodies 512, 4545 and 8213 did not compete with antibody 344823. It was found that the antibody 4177 and antibody 344823 competed with each other, but they competed partially.

[0364] In the second step, among the anti-TIM-3 monoclonal antibodies tested, antibodies 512, 4545 and 8213 which did not interact with antibody 344823 were examined whether or not they competed. The experiment was carried out in the same manner as the first step except for using Alexa-647 labeled antibody 512 or Alexa-647 labeled antibody 8213 prepared in Example 15 as a labeled antibody. As a result, antibody 4545 and antibody 8213 did not inhibit the binding of Alexa-647 labeled antibody 512 to the TIM-3 expressing cells.

[0365] However, antibody 4545 inhibited the binding of Alexa-647 labeled antibody 8213 to TIM-3 expressing cells. Therefore, it was found that antibody 4545 and antibody 8213 competed with each other, but these two antibodies did not compete with antibody 512. This result suggested that antibody 512 recognized different epitope from antibody 344823 and antibody 8213.

Samsung Bioepis Exhibit No. 1002
Page 12105

[0366] In the third step, a competitive assay with antibody 512 and antibody 8213 was carried out on antibody 4177 which was shown to partially compete with antibody 344823 in the first step. The experiment was performed in the same manner as described in second step. As a result, antibody 4177 did not inhibit the binding of the Alexa-647 labeled antibody 512 to the TIM-3 expressing cells, but inhibited the binding of the Alexa-647 labeled antibody 8213 to the TIM-3 expressing cells. Therefore, it was found that antibody 4177 did not compete with antibody 512, but only with antibody 8213.

[0367] Based on these results, among the 5 antibodies prepared in Example 13 and Example 14, antibody 644 recognized an epitope which was near the epitope to which antibody 344823 recognized; antibody 512 recognized an epitope different from of the epitope to which antibody 344823 and other four antibodies (antibody 644, antibody 4545, antibody 4177 and antibody 8213) recognized.

[0368] It was suggested that antibody 8213 recognized epitope different from of the epitope to which antibodies 344823 or 512 recognized. It was suggested that antibody 4545 recognized an epitope which was near the epitope to which antibody 8213 recognized. However, antibody 4177 recognized the epitope which was near the epitope to which antibody 8213 recognized, and also weakly recognized an epitope which was near the epitope to which antibody 344823 recognized.

[Example 17]

(Antibody dependent cellular cytotoxicity test of recombinant anti-TIM-3 human monoclonal defucose antibody)

[0369] Regarding the cellular cytotoxic activity via antibody, the ADCC activity against the target cell was measured by using human Peripheral Blood Mononuclear Cells (hereinafter referred to as "PBMC") as an effector in the presence of the antibody. First, peripheral blood was collected from the healthy human donor and mixed with anticoagulant. The obtained blood was loaded onto Ficoll-Plaque Plus (manufactured by GE Healthcare), and centrifuged at 2000 rpm for 20 min using a large scale centrifuge (CF9RX, manufactured by Hitachi Koki Co., Ltd.) so as not to disturb the boundary.

[0370] The middle fraction containing cells were collected and washed with PBS, and then centrifuged at 900 rpm for 20 min to remove the platelets. Thus obtained PBMC was used for the measurement. Next, the Daudi cell used as a target cell and the PBMC were mixed at the ratio of effector/target = 50.

[0371] Each of the recombinant anti-human monoclonal defucose antibodies (antibody 512, antibody 644, antibody 4545 and antibody 4177) prepared in Example 13 and Example 14, and anti-DNP antibody as a human IgG1 control was suspended in the medium to give a final concentration of 1 μg/ml and a total volume of 100 μl. After mixing, the solution was incubated at 37°C under 5% CO_2 for 4 hr. The lysis ratio of the target cell was evaluated based on the amount of LDH released into the medium. The LDH activity and lysis ratio were calculated using CytoTox 96 Non-Radioactive Cytotoxicity Assay (manufactured by Promega Corp.) in accordance with the instructions attached thereto. As statistical analysis, standard Student's t-test was used wherein a sample having a risk rate (p) of less than 0.05 was considered as one which was significantly different.

[0372] As the result that the ADCC activity on Daudi cells was measured, it was found that antibody 4545 and antibody 4177 exhibited the significant increase in the lysis ratio of the target cell as compared to anti-DNP antibody. This result suggests that anti-TIM-3 mouse antibody 8213 and anti-TIM-3 antibody which competes with anti-TIM-3 mouse antibody 8213 have high ADCC activity.

[0373] Similarly, the ADCC activity was measured by using recombinant anti-TIM-3 human monoclonal defucose antibodies (antibody 4545 and antibody 4177) prepared in Example 13, commercially available anti-TIM-3 monoclonal antibody 344823, and anti-DNP antibody as a negative control.

[0374] First, peripheral blood was collected from the healthy human donor and mixed with anticoagulant. The obtained blood was then loaded onto Ficoll-Plaque Plus (manufactured by GE Healthcare), and centrifuged at 2000 rpm for 20 min using a large scale centrifuge (CF9RX, manufactured by Hitachi Koki Co., Ltd.) so as not to disturb the boundary. The middle fraction containing cells were collected and washed with PBS, and then centrifuged at 900 rpm for 20 min to remove the platelets. Thus obtained PBMC fraction was used for the measurement of t the ADCC activity.

[0375] Next, the Daudi cell used as a target cell and the PBMC were mixed at the ratio of effector/target = 25. Each of the antibody 4545, antibody 4177, antibody 344823, anti-DNP antibody and PBS were suspended in the medium to give a final concentration of 1 μg/ml and a total volume of 100 μl. After mixing, the solution was incubated at 37°C under 5% CO_2 for 4 hr. The lysis ratio of the target cell was evaluated based on using the amount of LDH released into the medium.

[0376] The LDH activity and the lysis ratio were calculated using CytoTox 96 Non-Radioactive Cytotoxicity Assay (manufactured by Promega Corp.) in accordance with the instructions attached thereto. As statistical analysis, standard Student's t-test was used wherein a sample having a risk rate (p) of less than 0.05 was considered as one which was significantly different. As the result of the ADCC activity on Daudi cells was measured, it was found that antibody 4545 and antibody 4177 exhibited the significant increase in the lysis ratio of the target cell as compared to anti-DNP antibody.

Samsung Bioepis Exhibit No. 1002
Page 12106

On the other hand, antibody 344823 exhibited no significant increase in the lysis ratio of the target cell as compared to anti-DNP antibody and PBS.

[Example 18]

(Calculating the bound/dissociation constant using anti-TIM-3 antibody)

[0377] The bound/dissociation constant was analyzed using surface plasmon resonance based biosensor (Biacore, manufactured by GE Healthcare). In brief, an anti-human antibody or an anti-mouse antibody was immobilized on the CM5 sensor chips. Next, the anti-TIM-3 human or mouse antibody were made to flow to bind the chip, and then soluble extracellular human TIM-3 prepared in Example 4 was made to flow to examine the bound/association constant of TIM-3 to the anti-TIM-3 antibody. Throughout the experimental process, basically the experimental method provided by GE Healthcare for calculating bound/dissociation constant was used.

[0378] Specifically, CM5 was used as the sensor chip (Research grade, manufactured by GE Healthcare). First, CM5 chip was activated by flowing through a mixed solution of equal parts of 400 mmol/L EDC (N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrocholoride) and 100 mmol/L NHS(N-hyderoxysuccinimide). Next, the anti-human antibody attached to the Human Antibody Capture Kit (manufactured by GE Healthcare) was diluted with the solution attached to the kit and the obtained solution was made to flow so that the required amount of the antibody to an antibody for a human antibody was immobilized on the CM5 chip.

[0379] For the mouse antibody, the antibody against mouse antibody was immobilezed on the CM5 surface by diluting in the solution, which was provided in the Mouse Antibody Capture Kit (manufactured by GE Healthcare antibody). The activated chip surface was blocked by the passing through 1 mol/L for ethanolamide hydrochloride and inactivated.

[0380] Next, one kind of the anti-TIM-3 antibodies was diluted with HBS-EP buffer (manufactured by GE Healthcare) per one flow cell and passed through so as to bind the antibody for the human antibody or antibody for the mouse antibody immobilized on the chip surface. Then soluble extracellular human TIM-3 was flown through. To dissociate the bound anti-TIM-3 antibody from the soluble extracellular human TIM-3, either the total volume of 3 mol/L of $MgCl_2$ which was attached to the Human Antibody Capture Kit or Glycine-HCl (pH 1.7) which was attached to the Mouse Antibody Capture Kit were flown through the cell.

[0381] The above described procedures were considered as one step, and the similar procedure was repeated using different concentrations of the soluble extracellular human TIM-3, to collect data (sensorgram) for calculating the bound/association constant. The concentration of soluble extracellular human TIM-3 used as an analyte was calculated by measuring the absorbance at 280 nm and then converting the value of 1.4 OD to 1 mg/mL.

[0382] The molecular weight of the soluble extracellular human TIM-3 was calculated as 42.8 kDa based on the mobility on electrophoresis. The data was analyzed using Biaevaluation soft-ware (manufactured by GE Healthcare) according to the Biaevaluation Software Handbook. Specifically, the simultaneous Kinetics analysis was performed and the association rate constant (Ka) and dissociation rate constant (Kd) was calculated, by basically adopting a 1:1 Langmuir Binding reaction model was used for fitting. Then the value of the dissociation constant (K_D) was calculated from Kd/Ka.

[0383] Most of the anti-human TIM-3 human monoclonal antibody had the K_D value of the order of 10^{-9} mol/L. In this aspect, there was no correlation between ADCC activity and binding affinity targeting for TIM-3.

[0384] When the anti-human TIM-3 monoclonal antibody was monitored (e.g., monitored the dissociation state for 30 min), there was no dissociation detected with the antigen soluble extracellular human TIM-3 as an antigen. As a result, it was found that it was possible to produce a monoclonal antibody having a very high affinity for human TIM-3.

[Example 19]

(Classification of epitopes using competition test-2)

[0385] The epitopes of anti-TIM-3 antibodies, i.e., antibody 512, antibody 644, antibody 4545, antibody 8213, antibody 344823, antibody F38-2E2 and anti-DNP antibody as a control were analyzed by a competitive assay. In brief, the unlabeled target antibody was allowed to interact with the TIM-3 expression cell prepared in Example 1, and whether or not other fluorescence labeled anti-TIM-3 antibody was further bound to TIM-3 expression cells were evaluated by flow cytometry method.

[0386] Human TIM-3 expressing EoL-1 cells were washed with staining medium and allowed to react with purified test monoclonal antibodies [antibody 512, antibody 644, antibody 4545, antibody 8213, antibody 344823 (manufactured by R&D Systems), antibody F38-2E2 (manufactured by Imgenex)] (4°C, 30 min). The final concentration was 10 μg/ml. Next, the Alexa-647 or APC labeled anti-TIM-3 antibodies [antibody 344823 (manufactured by R&D Systems) and antibody F38-2E2 (manufactured by eBiosciences)] were added and were allowed to react (4°C, 30 min). After washing with staining medium, 7-ADD (manufactured by BD Biosciences) was added before analyzing with FACSCalibur (man-

Samsung Bioepis Exhibit No. 1002
Page 12107

ufactured by BD Biosciences).

[0387] The results are shown in Table 1. As shown in Table 1, the case the degree of the binding to the TIM-3 expression cell to which the unlabeled anti-TIM-3 antibody was bound was similar to that of a negative control were indicated as "+", the case where the degree to the binding to the TIM-3 expression cell to which the unlabeled anti-TIM-3 antibody was bound was found but was lower than that of a negative control was indicated as "+/-"and the case where the binding to the TIM-3 expression cell to which the unlabeled anti-TIM-3 antibody was bound was not detected, it was indicated as "-".

[0388]

[Table 1]

		Unlabeled antibody						
		DNP	512	644	4545	8213	344823	F38-2E2
Alexa-647 or APC labeled antibody	DNP	-	-	-	-	-	-	-
	512	+	-	+	+	+	+	+
	644	+	+	+/-	+	+	+/-	+/-
	4545	+	+	+	-	-	+	+
	8213	+	+	+	-	-	+	+
	344823	+	+	-	+	+	-	+/-
	F38-2E2	+	+	-	+	+	-	-

[0389] As shown in Table 1, since Alexa-647 labeled antibody 512 was found to bind to the TIM-3 expressing cell to which the other unlabeled anti-TIM-3 antibodies were bound, this antibody was suggested to recognize an independent epitope with which antibody 644, antibody 4545, antibody 8213, antibody 344823 and antibody F38-2E2 did not compete.

[0390] Since it was found that Alexa-647 labeled antibody 644 did not bind or reduced in binding to the TIM-3 expressing cell to which the unlabeled anti-TIM-3 antibody 344823 or F38-2E2 was bound, it was indicated that this antibody competed with antibody 344823 or F38-E2E in the recognition of the epitope close to each other.

[0391] Since it was found that Alexa-647 labeled antibody 4545 did not bind to the TIM-3 expressing cell to which the unlabeled anti-TIM-3 antibody 8213 was bound, it was indicated that this antibody competed with antibody 8213 in the recognition of the epitope close to each other.

[0392] Since it was found that Alexa-647 labeled antibody 8213 did not bind to the TIM-3 expressing cell to which the unlabeled anti-TIM-3 antibody 4545 was bound, it was indicated that this antibody competed with antibody 4545 in the recognition of the epitope close to each other.

[0393] Since it was found that APC labeled antibody 344823 did not bind to the TIM-3 expressing cell to which the unlabeled anti-TIM-3 antibody 644 or F38-2E2 was bound, it was indicated that this antibody competed with antibody 644 or F38-E2E antibody in the recognition of the epitope close to each other.

[0394] Since it was found that APC labeled Antibody F38-2E2 did not bind to the TIM-3 expressing cell to which the unlabeled anti-TIM-3 antibody 644 or 344823 was bound, it was indicated that this antibody competed with antibody 644 or antibody 344823 in the recognition of the epitope close to each other.

[Example 20]

(Molecular cloning of mouse TIM-3 cDNA)

[0395] The cDNA of mouse TIM-3 was prepared in the same manner as described in Example 1. Total RNA was extracted from Balb/c mouse derived bone marrow cells using High Pure RNA isolation Kit (manufactured by Roche). Template cDNA was synthesized using ThermoScript RT-PCR system (manufactured by Invitrogen). For primers, mTim-3 Fw3 (SEQ ID NO: 70) and mTim-3 Re3 (SEQ ID NO: 71) were used. The cDNA was inserted into pGEM-T Easy Vector (manufactured by Promega Corp.), and the sequence was analyzed. The clone having identical nucleotide sequence with the coding region of GenBank accession number AF450241 was selected.

[0396] PCR was carried out using the selected clone as the template and inserting the DNA into NotI site of the pEF6/Myc-HisC vector (manufactured by Invitrogen) (mTim-3/pEF6 Myc_HisC). For PCR primers, mTim-3 Fw4NotI (SEQ ID NO: 72) and mTim-3 Re4NotI (SEQ ID NO: 73) were used.

Samsung Bioepis Exhibit No. 1002
Page 12108

[Example 21]

(Construction of hTim-3/pEF6 Myc_HisC)

[0397] The plasmid DNA hTIM-3/pMCs-IG prepared in Example 1 and pEF6 Myc_HisC were both digested with NotI to construct human TIM-3 expressing pEF6 Myc_HisC vector (hTim-3/pEF6 Myc_HisC). DNA sequence analysis confirmed that the vector sequence matched the coding region of the GenBank accession number NM_032782.

[Example 22]

(Cross-reactivity of anti-human TIM-3 antibody to anti-mouse TIM-3 antibody)

[0398] Each of the plasmid DNAs, mTim-3/pEF6 Myc_HisC and hTim-3/pEF6 Myc_HisC prepared in Example 20 and Example 21, and an empty vector control was introduced into HEK293F cell in the same manner as Example 4. Two days later, in the same manner as Example 15, the binding activity of Alexa-647 labeled antibodies (antibody 512, antibody 644, antibody 4545 and antibody 8213), commercially available APC labeled anti-human TIM-3 antibodies (antibody 344823 and antibody F38-2E2) and commercially available PE labeled anti-mouse TIM-3 antibody (RMT3-23 antibody, manufactured by BioLegend Inc.) to human TIM-3 and mouse TIM-3 was evaluated using flow cytometry analysis.

[0399] As a result, antibody 512, antibody 644, antibody 4545, antibody 8213, antibody 344823 and antibody F38-2E2 exclusively interacted with human TIM-3 expressing 293F cells. However, RMT3-23 antibody interacted exclusively with mouse TIM-3 expressing 293F cells. Therefore, it was found that antibody 512, antibody 644, antibody 4545, antibody 8213, antibody 344823 and antibody F38-2E2 did not cross-react with mouse TIM-3.

[Example 23]

(Construction of expression system for TIM-3 chimeric protein with IgV domain substituted for mouse TIM-3)

[0400] The objective sequence was amplified by the PCR using hTim-3/pEF6 Myc_HisC plasmid DNA as a template, hTIM3+mIgV_vecR1 primer (SEQ ID NO: 74) and hTIM3+mIgV_vecF1 primer (SEQ ID NO: 75), and PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.). The objective sequence was amplified by PCR using mTim-3/pEF6 Myc_HisC plasmid DNA as a template, hTIM3+mIgV_insF1 primer (SEQ ID NO: 76) and hTIM3+mIgV_insR1 primer (SEQ ID NO: 77), and PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.).

[0401] The two PCR products obtained were ligated using GENEART seamless cloning and assembly kit (manufactured by Invitrogen). The sequence from the transformant was analyzed and it was found that the PCR products had the objective sequences (IgV chimeraTIM-3/pEF6 Myc_HisC, SEQ ID NO: 78).

[Example 24]

(Construction of expression system for TIM-3 chimeric protein with Mucin domain substituted for mouse TIM-3)

[0402] The objective sequence was amplified by PCR using hTim-3/pEF6 Myc_HisC plasmid DNA as a template, hTIM3+mMucin_vecR2 primer (SEQ ID NO: 80) and hTIM3+mMucin_vecF2 primer (SEQ ID NO: 81), and PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.). The objective sequence was amplified by PCR using mTim-3/pEF6 Myc_HisC plasmid DNA as a template, hTIM3+mMuicn_insF2 primer (SEQ ID NO: 82) and hTIM3+mMucin_insR2 primer (SEQ ID NO: 83), and PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.).

[0403] The two PCR products obtained were ligated using GENEART seamless cloning and assembly kit (manufactured by Invitrogen). The sequence from the transformant was analyzed and it was found that the PCR products had the objective sequences(Mucin chimeraTIM-3/pEF6 Myc_HisC, SEQ ID NO: 84).

[Example 25]

(Binding assay of anti-TIM-3 antibody to TIM-3 chimeric protein in which IgV domain was substituted with mouse TIM-3 and TIM-3 chimeric protein in which Mucin domain was substituted with mouse TIM-3)

[0404] Each of the plasmid DNAs prepared in Example 23 and Example 24, IgV chimeraTIM-3/pEF6 Myc_HisC, Mucin chimeraTIM-3/pEF6 Myc_HisC, hTim-3/pEF6 Myc_HisC, mTim-3/pEF6 Myc_HisC, and an empty vector control was introduced into HEK293F cell in the same manner as Example 4. Two days later, in the same manner as Example 22,

Samsung Bioepis Exhibit No. 1002
Page 12109

the binding activity of anti-TIM-3 antibody was evaluated using flow cytometry.

[0405] As a result, antibody 512, antibody 644, antibody 4545, antibody 8213, antibody 4177, antibody 344823 and antibody F38-2E2 bound to the human TIM-3 expressing cells and Mucin chimeraTIM-3 expressing cells only. However, RMT-23 antibody bound to the mouse TIM-3 expressing cells and the IgV chimeraTIM-3 expressing cells only.

[0406] Therefore, as a result, it was found that all of the anti-human TIM-3 antibodies tested (antibody 512, antibody 644, antibody 4545, antibody 8213, antibody 344823 and antibody F38-2E2) and mouse TIM-3 antibody (antibody RMT3-23) recognized the IgV domain.

[Example 26]

(Construction of TIM-3 chimera 22-47/pEF6 Myc_HisC)

[0407] A vector which expressed TIM-3 chimeric protein in which the amino acid of human TIM-3 (SEQ ID NO: 53) at position 22 to position 47 were substituted with the corresponding amino acid of mouse TIM-3 (hereinafter referred to as " TIM-3 chimera 22-47") was constructed. By using hTim-3/pEF6 Myc_HisC plasmid DNA prepared in Example 21 as a template, and hTIM3chimera22-47F1 primer (SEQ ID NO: 86) and hTIM3chimera22-47R1 primer (SEQ ID NO: 87), and PCR was carried out using PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.).

[0408] Using the obtained PCR product as a template, the objective sequence was amplified by PCR using hTIM3chimera22-47F2 primer (SEQ ID NO: 88)and hTIM3chimera22-47R2 primer (SEQ ID NO: 89) and using PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.).

[0409] Using the obtained PCR product as a template, the objective sequence was amplified by PCR using hTIM3chimera22-47F3 primer (SEQ ID NO: 90) and hTIM3chimera22-47R3 primer (SEQ ID NO: 91), and using PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.).

[0410] After the obtained PCR product obtained from the third PCR was digested with *DpnI* (manufactured by New England Biolabs), it was subjected to agarose gel electrophoresis. The DNA was extracted and ligated using GENEART seamless cloning and assembly kit (manufactured by Invitrogen). The sequence of the clone obtained from the transformant was analyzed and confirmed that the clone had the objective sequence (TIM-3 chimera 22-47/pEF6 Myc_HisC, SEQ ID NO: 92).

[Example 27]

(Construction of TIM-3 chimera 57-66/pEF6 Myc_HisC)

[0411] A vector which expressed TIM-3 chimeric protein in which the amino acid of human TIM-3 (SEQ ID NO: 53) at position 57 to position 66 were substituted with the corresponding amino acid of mouse TIM-3 (hereinafter referred to as " TIM-3 chimera 57-66") was constructed. PCR was carried out using hTim-3/pEF6 Myc_HisC plasmid DNA prepared in Example 21 as a template, hTIM3chimera57-66F primer (SEQ ID NO: 94) and hTIM3chimera57-66R primer (SEQ ID NO: 95) phosphorylated by T4 Polynucleotide Kinase (manufactured by New England Biolabs) and PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.) to amplify the objective sequence.

[0412] After the obtained PCR product was digested with *DpnI* (manufactured by New England Biolabs), it was subjected to the agarose gel electrophoresis. The DNA was extracted and ligated with LigaFast™ Rapid DNA Ligation System (manufactured by Promega Corp.). The sequence of the clone obtained from the transformant was analyzed and confirmed that it was the objective sequence (TIM-3 chimera 57-66/pEF6 Myc_HisC, SEQ ID NO: 96).

[Example 28]

(Construction of TIM-3 chimera 67-105/pEF6 Myc_HisC)

[0413] A vector which expressed TIM-3 chimeric protein in which the amino acid of human TIM-3 (SEQ ID NO: 53) at position 67 to position 105 were substituted with the corresponding amino acid of mouse TIM-3 (hereinafter referred to as " TIM-3 chimera 67-105") was constructed. PCR was carried out using hTim-3/pEF6 Myc_HisC plasmid DNA as a template, hTIM3chimera67-105F primer (SEQ ID NO: 98) and hTIM3chimera67-105R primer (SEQ ID NO: 99) and using PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.) to amplify the objective sequence..

[0414] PCR was carried out using mTim-3/pEF6 Myc_HisC plasmid DNA as a template, mTIM3chimera67-105F primer (SEQ ID NO: 100) and mTIM3chimera67-105R primer (SEQ ID NO: 101) and using PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.). The two PCR products were ligated by GENEART seamless cloning and assembly kit (manufactured by Invitorgen). The sequence of the clone obtained from the transformant was analyzed and confirmed that it was the objective sequence (TIM-3 chimera 67-105/pEF6 Myc_HisC, SEQ ID NO: 102).

Samsung Bioepis Exhibit No. 1002
Page 12110

[Example 29]

(Construction of TIM-3 chimera 74-81/pEF6 Myc_HisC)

[0415] A vector which expressed TIM-3 chimeric protein in which the amino acid of human TIM-3 (SEQ ID NO: 53) at position 74 to position 81 were substituted with the corresponding amino acid of mouse TIM-3 (hereinafter referred to as " TIM-3 chimera 74-81") was constructed. PCR was carried out using hTim-3/pEF6 Myc_HisC plasmid DNA prepared in Example 21 as a template, hTIM3 chimera74-8 1 F primer (SEQ ID NO: 104) and hTIM3chimera74-81R primer (SEQ ID NO: 105) and using PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.).

[0416] After the PCR product was digested with *DpnI* (manufactured by New England Biolabs), it was subjected to agarose gel electrophoresis. The DNA was extracted and ligated with GENEART seamless cloning and assembly kit (manufactured by Invitrogen). The sequence of the clone obtained from the transformant was analyzed and confirmed that it was the objective sequence (TIM-3 chimera 74-81/pEF6 Myc_HisC, SEQ ID NO: 106).

[Example 30]

(Construction of TIM-3 chimera 88-96/pEF6 Myc_HisC)

[0417] A vector which expressed TIM-3 chimeric protein in which the amino acid of human TIM-3 (SEQ ID NO: 53) at position 88 to position 96 were substituted with the corresponding amino acid of mouse TIM-3 (hereinafter referred to as " TIM-3 chimera 88-96") was constructed. The PCR was carried out by preparing a reaction solution containing hTim-3/pEF6 Myc_HisC plasmid DNA prepared in Example 21 as a template, hTIM3chimera88-96F primer (SEQ ID NO: 108) and hTIM3chimera88-96R primer (SEQ ID NO: 109) and using PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.).

[0418] After the obtained PCR product was digested with *DpnI* (manufactured by New England Biolabs), it was subjected to agarose gel electrophoresis. The DNA was extracted and ligated with GENEART seamless cloning and assembly kit (manufactured by Invitrogen). The sequence of the clone obtained from the transformant was analyzed and confirmed that it was the objective sequence (TIM-3 chimera 88 -96/pEF6 Myc_HisC, SEQ ID NO: 110).

[Example 31]

(Construction of TIM-3 chimera 96-105/pEF6 Myc_HisC)

[0419] A vector which expressed TIM-3 chimeric protein in which the amino acid of human TIM-3 (SEQ ID NO: 53) at position 96 to position 105 were substituted with the corresponding amino acid of mouse TIM-3 (hereinafter referred to as "TIM-3 chimera 96-105") was constructed. The PCR was carried out by preparing a reaction solution containing hTim-3/pEF6 Myc_HisC plasmid DNA prepared in Example 21 as a template, hTIM3chimera96-105F primer (SEQ ID NO: 112) and hTIM3chimera96-105R primer (SEQ ID NO: 113) and using PrimeSTAR GXL DNA Polymerase (manufactured by Takara Bio Inc.).

[0420] After the obtained PCR product was digested with *DpnI* (manufactured by New England Biolabs), it was subjected to agarose gel electrophoresis. The DNA was extracted and ligated with GENEART seamless cloning and assembly kit (manufactured by Invitrogen). The sequence of the clone obtained from the transformant was analyzed and confirmed that it was the objective sequence (TIM-3 chimera 96 - 105/pEF6 Myc_HisC, SEQ ID NO: 114).

[Example 32]

(Binding assay of anti-TIM-3 antibody to TIM-3 chimeric protein in which part of the IgV domain was substituted with mouse TIM-3)

[0421] Each of various TIM-3 vectors prepared in Examples 26 to 31 and an empty vector as a control were introduced into HEK293F in the same manner as Example 4. The introduced vectors and the expressed TIM-3 chimeric proteins thereof were as follows:

(1) TIM-3 chimera 22-47: TIM-3 chimeric protein in which the amino acid sequence at position 22 to position 47 of human TIM-3 (SEQ ID NO: 53) were substituted with the corresponding amino acids of mouse TIM-3;
(2) TIM-3 chimera 57-66: TIM-3 chimeric protein in which the amino acid sequence at position 57 to position 66 of human TIM-3 (SEQ ID NO: 53) were substituted with the corresponding amino acids of mouse TIM-3;
(3) TIM-3 chimera 67-105: TIM-3 chimeric protein in which the amino acid sequence at position 67 to position 105

Samsung Bioepis Exhibit No. 1002
Page 12111

of human TIM-3 (SEQ ID NO: 53) were substituted with the corresponding amino acids of mouse TIM-3;
(4) TIM-3 chimera 74-81: TIM-3 chimeric protein in which the amino acid sequence at position 74 to position 81 of human TIM-3 (SEQ ID NO: 53) were substituted with the corresponding amino acids of mouse TIM-3;
(5) TIM-3 chimera 88-96: TIM-3 chimeric protein in which the amino acid sequence at position 88 to position 96 of human TIM-3 (SEQ ID NO: 53) were substituted with the corresponding amino acids of mouse TIM-3; and
(6) TIM-3 chimera 96-105: TIM-3 chimeric protein in which the amino acid sequence at position 96 to position 105 of human TIM-3 (SEQ ID NO: 53) were substituted with the corresponding amino acids of mouse TIM-3.

Two days after transfection, in the same manner as Example 22, the binding activity of anti-TIM-3 antibody was evaluated using flow cytometry.

[0422] The results are shown in Table 2. As shown in Table 2, the case where the binding of the antibody to the transfected cell was detected was indicated as "+", the case where the binding of the antibody to the transfected cell was detected but the degree of the binding was reduced was indicated as "+/-"and the case where the binding of the antibody to the trasfected cell was not detected was indicated as "-".

[Table 2]

Vector name	4545	8213	4177	512	644	344823	F38-2E2
TIM-3 chimera 22-47	+	+	+/-	-	+	+	+
TIM-3 chimera 57-66	+	+	+/-	+	-	-	-
TIM-3 chimera 67-105	-	-	+/-	+	+	+	+
TIM-3 chimera 74-81	-	-	+	+	+	+	+
TIM-3 chimera 88-96	+	+	+	+	+	+	+
TIM-3 chimera 96-105	+	+	+	+	+	+	+

[0423] As shown in Table 2, antibody 4545 and antibody 8213 bound to the cells transfected with TIM3-chimera 22-47, TIM3-chimera 57-66, TIM3-chimera 88-96 or TIM3-chimera 96-105 transfected cells. However, these antibodies did not bind to the cell into which TIM-3 chimera 67-105 were introduced.

[0424] The antibody 512 bound to the cells transfected with TIM3-chimera 57-66, TIM3-chimera 88-96, TIM3-chimera 96-105, TIM-3 chimera 67-105 or TIM-3 chimera 74-81. However, antibody 512 did not bind to the cells transfected with TIM-3 chimera 22-47.

[0425] The antibody 644, antibody 344823 and antibody F38-2E2 bound to the cells transfected with TIM3-chimera 22-47, TIM3-chimera 88-96, TIM3-chimera 96-105, TIM-3 chimera 67-105 or TIM-3 chimera 74-81. However, these antibodies did not bind to the cells transfected with to TIM-3 chimera 57-66.

The antibody 4177 bound to the cells transfected with TIM3-chimera 88-96, TIM3-chimera 96-105 or TIM-3 chimera 74-81. Antibody 4177 weakly bound to TIM-3 the cells transfected with chimera 22-47, TIM-3 chimera 57-66 or TIM-3 chimera 67-105.

[0426] Based on the above result and results from Example 16 and Example 19, it was suggested that antibody 4545 and antibody 8213 bound to the amino acid sequence at position 67 to 87 of human TIM-3. Since antibody 4545 and antibody 8213 did not bind to the cells transfected with TIM-3 chimera 74-81, it was suggested that the amino acids required for binding of antibody 4545 and antibody 8213 to human TIM-3 were included in the amino acid at position 74 to 81.

[0427] In addition, it was suggested that antibody 512 bound to the amino acids up to at position 47 of human TIM-3 and that antibody 644, antibody 344823 and antibody F38- 2E2 bound to the amino acid sequence at position 57 to 66 of human TIM-3.

[0428] Furthermore, it was suggested that antibody 4177 bound to the amino acids other than at position 74 to 81 within the amino acids at position 67 to 87 of human TIM-3 to which antibody 4545 and antibody 8213 bind although antibody 512, antibody 644, antibody 344823 and antibody F38-2E2 did not bind.

Samsung Bioepis Exhibit No. 1002
Page 12112

[Example 33]

(Preparation of anti-human TIM-3 antibody 8213 humanized antibody)

(1) Design of amino acid sequences of VH and VL of antibody 8213 humanized antibody

[0429] The amino acid sequence of VH of antibody 8213 humanized antibody was designed in the following manner. The amino acid sequences of FRs in VH of human antibody which is suitable for the grafting of the amino acid sequences (SEQ ID NOs: 21 to 23) of CDRs1 to 3 of antibody 8213 were selected as follows.

[0430] Kabat *et al.,* have classified the VH of conventionally known various human antibodies into three subgroups (HSG I to III) based on the homology of their amino acid sequences and reported the consensus sequences for each of the subgroups [*Sequences of Proteins of Immunological Interest,* US Dept. Health and Human Services (1991)]. Therefore, the homology search of the amino acid consensus sequences of FR of VH subgroups I to III of human antibodies with the amino sequence of FR ofVH of antibody 8213 was conducted.

[0431] As a result of the homology search, the homologies of HSGI, HSGII, and HSGIII were 77.0%, 55.2%, and 58.6%, respectively. Therefore, the amino acid sequence of FR of the VH region of antibody 8213 had the highest homology to the subgroup I.

[0432] Based on the above results, the amino acid sequence of CDR of the VH of antibody 8213 (SEQ ID NOs: 21 to 23) was grafted to an appropriate position of the FR amino acid sequence of the consensus sequence of subgroup I of human antibody VH. In this manner, the 8213 antibody HV0 represented by SEQ ID NO: 67, i.e., the amino acid sequence of VH of an anti-human TIM-3 antibody 8213 humanized antibody was designed.

[0433] Next, the amino acid sequence of VL of antibody 8213 humanized antibody was designed in the following manner. The amino acid sequences of FR in VL of human antibody which were suitable for the grafting of the amino acid sequences (SEQ ID NOs: 24 to 26) of CDRs1 to 3 in VL of antibody 8213 were selected as follows.

[0434] Kabat *et al.,* have classified the VL of various known human antibodies into four subgroups (HSG I to IV) based on the homology of their amino acid sequences and reported the consensus sequences for each of the subgroups [Sequences of Proteins of Immunological Interest, US Dept. Health and Human Services (1991)]. Therefore, the homology search among the FR amino acid consensus sequences of VL subgroup I to IV of human antibodies were searched for sequence homology with FR amino sequence of VL of antibody 8213.

[0435] As a result of the homology search, the homologies of HSGI, HSGII, HSGIII and HSGIV were 76.3%, 61.3%, 61.3%, and 68.8%, respectively. Therefore, the amino acid sequence of FR of the VL region of antibody 8213 had the highest homology to the subgroup I.

[0436] Based on the above results, each of the amino acid sequences of CDRs of the VL of antibody 8213 (SEQ ID NOs: 24 to 26) was grafted into an appropriate position in the amino acid sequence of FR of the consensus sequence of subgroup I of VL of an human antibody. In this manner, the 8213 antibody LV0 represented by SEQ ID NO: 69, i.e., the amino acid sequence of VL of an anti-human TIM-3 antibody 8213 humanized antibody, was designed.

[0437] The amino acid sequence of 8213 antibody HV0 which was VH of antibody 8213 humanized antibody; and the amino acid sequence of 8213 antibody LV0 which was VL of antibody 8213 humanized antibody designed in the above were the sequences in which only the amino acid sequences of CDRs of the mouse monoclonal antibody 8213 were grafted into the amino acid sequence of the selected FR of human antibody.

[0438] However, in general, it is known that a humanized antibody prepared merely by grafting CDRs of a mouse antibody to FRs of a human antibody has a lower binding activity. In order to avoid decreasing of the binding activity, attempts have been made in the preparation of a humanized antibody to raise the lowered binding activity by modifying the amino acid residues which were considered to have influence on the binding activity among the amino acid sequences of FRs of a human antibody which are different from a mouse antibody as well as grafting amino acid sequences of CDRs. Therefore, in Examples, the inventors decided to identify and modify the amino acid residues of FR which were considered to have influence on the binding activity in the following manner.

[0439] First, three-dimensional structure of the above designed antibody V region (hereinafter referred to as " HV0LV0") comprising the amino acid sequence of antibody 8213 HV0 which was VH of the antibody 8213 humanized antibody and the amino acid sequence of antibody 8213 LV0 which was VL of antibody 8213 humanized antibody was constructed using a computer modeling technique. Discovery Studio (manufactured by Accelrys Inc.) was used for preparation of the three-dimensional structure and display of the three-dimensional structure. A computer model of the three-dimensional structure of V region of antibody 8213 was constructed in the same manner.

[0440] Furthermore, amino acid residues which were different from those of antibody 8213 in the amino acid sequence of FRs ofVH and VL of HV0LV0 were selected, prepared an amino acid sequence in which such amino acid residues were substituted with the corresponding amino acid residues of 8213 antibody and then a three-dimensional structure model was constructed in the same manner. The amino acids which were considered to have influence on the binding activity were selected by comparing the three-dimensional structures of the V regions of antibody 8213 and HV0LV0

Samsung Bioepis Exhibit No. 1002
Page 12113

and the modified product.

[0441] As a result, as amino acid residues of FR in HV0LV0 which were considered to change the three-dimensional structure of the antigen binding region and have influence on the binding activity, Lys at position 12, Val at position 20, Arg at position 38, Ala at position 40, Met at position 48, Arg at position 67, Val at position 68, Ile at position 70, Ala at position 72, Thr at position 74, Arg at position 98 and Val at position 113 were selected in antibody 8213 HV0; and Leu at position 11, Ala at position 13, Val at position 15, Tyr at position 36, Ala at position 43, Pro at position 44, Leu at position 46, Phe at position 71 and Thr at position 85 were selected in antibody 8213 LV0.

[0442] Among the selected amino acid residues, at least one or more amino acid residues was substituted with amino acid residues which were present at the corresponding sites of antibody 8213 and VHs and VLs of the humanized antibody comprising various modifications were constructed.

[0443] Specifically, as for VH, at least one modification was introduced among the amino acid modifications for substituting Lys at position 12 with Val, Val at position 20 with Leu, Arg at position 38 with Lys, Ala at position 40 with Arg, Met at position 48 with Ile, Arg at position 67 with Lys, Val at position 68 with Ala, Ile at position 70 with Leu, Ala at position 72 with Val, Thr at position 74 with Lys, Arg at position 98 with Gly, or Val at position 113 with Leu in the amino acid sequence represented by SEQ ID NO: 67.

[0444] As for VL, at least one modification was introduced among the amino acid modifications for substituting Leu at position 11 with Met, Ala at position 13 with Val, Val at position 15 with Leu, Tyr at position 36 with Leu, Ala at position 43with Ser, Pro at position 44 with Phe, Leu at position 46 with Gly, Phe at position 71 with Tyr and Thr at position 85 with Asp in the amino acid sequence represented by SEQ ID NO: 69.

[0445] As the antibody V region of 8213 antibody-humanized antibody in which at least one amino acid existing in FR in HV0LV0 was modified, HV0LV0, HV0LV2, HV0LV4, HV0LV5, HV0LV6, HV0LV7, HV0LV9, HV3LV0, HV3LV2, HV3LV4, HV3LV5, HV3LV6, HV3LV7, HV3LV9, HV4LV0, HV4LV2, HV4LV4, HV4LV5, HV4LV6, HV4LV7, HV4LV9, HV5LV0, HV5LV2, HV5LV4, HV5LV5, HV5LV6, HV5LV7, HV5LV9, HV6LV0, HV6LV2, HV6LV4, HV6LV5, HV6LV6, HV6LV7, HV6LV9, HV7LV0, HV7LV2, HV7LV4, HV7LV5, HV7LV6, HV7LV7, HV7LV9, HV8LV0, HV8LV2, HV8LV4, HV8LV5, HV8LV6, HV8LV7, HV8LV9, HV10LV0, HV10LV2, HV10LV4, HV10LV5, HV10LV6, HV10LV7, HV10LV9, HV12LV0, HV12LV2, HV12LV4, HV12LV5, HV12LV6, HV12LV7, and HV12LV9 were designed.

[0446] The amino acid sequences of each of the H chain variable regions, HV3, HV4, HV5, HV6, HV7, HV8, HV10 and HV12; and the amino acid sequence of the L chain variable region, LV2, LV4, LV5, LV6, LV7 and LV9 were shown in Fig. 1 and Fig. 2, respectively.

(2) Preparation of 8213 antibody-humanized antibody

[0447] DNA encoding the amino acid sequence of the variable region of 8213 antibody-humanized antibody was designed using codons used in the DNAs (SEQ ID NO: 27 and 29) encoding the amino acid sequence of VH of 8213 antibody and VL of 8213 antibody, respectively. When the amino acid modification was introduced, DNA was designed using a codon which was used in a mammal cell with a high frequency.

[0448] Using these DNA sequences, vectors for expressing an antibody were constructed and humanized antibodies were expressed.

[0449] While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skill in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

This application is based on U.S. provisional application No. 61/353,836, filed on June 11, 2010, the entire contents of which are incorporated hereinto by reference. All references cited herein are incorporated in their entirety.

Industrial Applicability

[0450] The persent invention can provide a monoclonal antibody or an antibody fragment thereof which binds to the amino acid sequence or the three-dimensional structure thereof of the extracellular region of human TIM-3 and has ADCC activity; a hybridoma which produces the antibody; a DNA which encods the antibody; a vector which comprises the DNA; a transformant which is obtained by transofrming the vector; a process for producing an antibody or an antibody fragment thereof using the hybridoma or the transformant; and a diagnostic agent or a therapeutic agent using the antibody or the antibody fragment thereof as an active ingredient.

Free text of Sequence Listing

[0451]

SEQ ID NO: 1: The amino acid sequence of Human 4545 H chain CDR1

Samsung Bioepis Exhibit No. 1002
Page 12114

SEQ ID NO: 2: The amino acid sequence of Human 4545 H chain CDR2
SEQ ID NO: 3: The amino acid sequence of Human 4545 H chain CDR3
SEQ ID NO: 4: The amino acid sequence of Human 4545 L chain CDR1
SEQ ID NO: 5: The amino acid sequence of Human 4545 L chain CDR2
SEQ ID NO: 6: The amino acid sequence of Human 4545 L chain CDR3
SEQ ID NO: 11: The amino acid sequence of Human 4177 H chain CDR1
SEQ ID NO: 12: The amino acid sequence of Human 4177 H chain CDR2
SEQ ID NO: 13: The amino acid sequence of Human 4177 H chain CDR3
SEQ ID NO: 14: The amino acid sequence of Human 4177 L chain CDR1
SEQ ID NO: 15: The amino acid sequence of Human 4177 L chain CDR2
SEQ ID NO: 16: The amino acid sequence of Human 4177 L chain CDR3
SEQ ID NO: 21: The amino acid sequence of Mouse 8213 H chain CDR1
SEQ ID NO: 22: The amino acid sequence of Mouse 8213 H chain CDR2
SEQ ID NO: 23: The amino acid sequence of Mouse 8213 H chain CDR3
SEQ ID NO: 24: The amino acid sequence of Mouse 8213 L chain CDR1
SEQ ID NO: 25: The amino acid sequence of Mouse 8213 L chain CDR2
SEQ ID NO: 26: The amino acid sequence of Mouse 8213 L chain CDR3
SEQ ID NO: 31: The nucleotide sequence of primer TIM-3 Fw2
SEQ ID NO: 32: The nucleotide sequence of primer TIM-3 Re2
SEQ ID NO: 33: The nucleotide sequence of primer pMCs-Fw
SEQ ID NO: 34: The nucleotide sequence of primer TIM3ED-FcReXba
SEQ ID NO: 35: The nucleotide sequence of primer T7
SEQ ID NO: 36: The nucleotide sequence of primer hTIM-3 Fw1
SEQ ID NO: 37: The nucleotide sequence of insert hTIM-3 ECD Fc fusion
SEQ ID NO: 38: The amino acid sequence of insert hTIM-3 ECD Fc fusion
SEQ ID NO: 39: The nucleotide sequence of primer TIM3ED-FLAG4aa
SEQ ID NO: 40: The nucleotide sequence of primer C-FLAG-NotR2
SEQ ID NO: 41: The nucleotide sequence of primer BGH-R
SEQ ID NO: 42: The nucleotide sequence of insert hTIM-3 ECD
SEQ ID NO: 43: The amino acid sequence of insert hTIM-3 ECD
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SEQ ID NO: 45: The nucleotide sequence of primer hh-3
SEQ ID NO: 46: The nucleotide sequence of primer hk-2
SEQ ID NO: 47: The nucleotide sequence of primer hk-6
SEQ ID NO: 48: The nucleotide sequence of primer mH_Rv1
SEQ ID NO: 49: The nucleotide sequence of primer mH_Rv2
SEQ ID NO: 50: The nucleotide sequence of primer mK_Rv1
SEQ ID NO: 51: The nucleotide sequence of primer mK_Rv2
SEQ ID NO: 66: The nucleotide sequence of 8213 antibody HV0 variable region
SEQ ID NO: 67: The amino acid sequence of 8213 antibody HV0 variable region
SEQ ID NO: 68: The nucleotide sequence of 8213 antibody LV0 variable region
SEQ ID NO: 69: The amino acid sequence of 8213 antibody LV0 variable region
SEQ ID NO: 70: The nucleotide sequence of primer mTim-3 Fw3
SEQ ID NO: 71: The nucleotide sequence of primer mTim-3 Re3
SEQ ID NO: 72: The nucleotide sequence of primer mTim-3 Fw4NotI
SEQ ID NO: 73: The nucleotide sequence of primer mTim-3 Re4NotI
SEQ ID NO: 74: The nucleotide sequence of primer hTIM3+mIgV_vecR1
SEQ ID NO: 75: The nucleotide sequence of primer hTIM3+mIgV_vecF1
SEQ ID NO: 76: The nucleotide sequence of primer hTIM3+mIgV_insF1
SEQ ID NO: 77: The nucleotide sequence of primer hTIM3+mIgV_insR1
SEQ ID NO: 78: The nucleotide sequence of insert IgV chimeraTIM-3/pEF6 Myc_HisC
SEQ ID NO: 79: The amino acid sequence of insert IgV chimeraTIM-3/pEF6 Myc_HisC
SEQ ID NO: 80: The nucleotide sequence of primer hTIM3+mMucin_vecR2
SEQ ID NO: 81: The nucleotide sequence of primer hTIM3+mMucin_vecF2
SEQ ID NO: 82: The nucleotide sequence of primer hTIM3+mMucin_insF2
SEQ ID NO: 83: The nucleotide sequence of primer hTIM3+mMucin_insR2
SEQ ID NO: 84: The nucleotide sequence of insert Mucin chimeraTIM-3/pEF6 Myc_HisC
SEQ ID NO: 85: The amino acid sequence of insert Mucin chimeraTIM-3/pEF6 Myc_HisC

Samsung Bioepis Exhibit No. 1002
Page 12115

SEQ ID NO: 86: The nucleotide sequence of primer hTIM3chimera22-47F1
SEQ ID NO: 87: The nucleotide sequence of primer hTIM3chimera22-47R1
SEQ ID NO: 88: The nucleotide sequence of primer hTIM3chimera22-47F2
SEQ ID NO: 89: The nucleotide sequence of primer hTIM3chimera22-47R2
SEQ ID NO: 90: The nucleotide sequence of primer hTIM3chimera22-47F3
SEQ ID NO: 91: The nucleotide sequence of primer hTIM3chimera22-47R3SEQ ID NO: 92 : The nucleotide sequence of insert TIM-3 chimera 22-47/pEF6 Myc_HisC
SEQ ID NO: 93: The amino acid sequence of insert TIM-3 chimera 22-47/pEF6 Myc_HisC
SEQ ID NO: 94: The nucleotide sequence of primer hTIM3chimera57-66F
SEQ ID NO: 95: The nucleotide sequence of primer hTIM3chimera57-66R
SEQ ID NO: 96: The nucleotide sequence of insert TIM-3 chimera 57-66/pEF6 Myc_HisC
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SEQ ID NO: 99: The nucleotide sequence of primer hTIM3chimera67-105R
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SEQ ID NO: 101: The nucleotide sequence of primer mTIM3chimera67-105R
SEQ ID NO: 102: The nucleotide sequence of insert TIM-3 chimera 67-105/pEF6 Myc_HisC
SEQ ID NO: 103: The amino acid sequence of insert TIM-3 chimera 67-105/pEF6 Myc_HisC
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SEQ ID NO: 105: The nucleotide sequence of primer hTIM3chimera74-81R
SEQ ID NO: 106: The nucleotide sequence of insert TIM-3 chimera 74-81/pEF6 Myc_HisC
SEQ ID NO: 107: The amino acid sequence of insert TIM-3 chimera 74-81/pEF6 Myc_HisC
SEQ ID NO: 108: The nucleotide sequence of primer hTIM3chimera88-96F
SEQ ID NO: 109: The nucleotide sequence of primer hTIM3chimera88-96R
SEQ ID NO: 110: The nucleotide sequence of insert TIM-3 chimera 88-96/pEF6 Myc_HisC
SEQ ID NO: 111: The amino acid sequence of insert TIM-3 chimera 88-96/pEF6 Myc_HisC
SEQ ID NO: 112: The nucleotide sequence of primer hTIM3chimera96-105F
SEQ ID NO: 113: The nucleotide sequence of primer hTIM3chimera96-105R
SEQ ID NO: 114: The nucleotide sequence of insert TIM-3 chimera 96-105/pEF6 Myc_HisC
SEQ ID NO: 115: The amino acid sequence of insert TIM-3 chimera 96-105/pEF6 Myc_HisC

Samsung Bioepis Exhibit No. 1002
Page 12116

SEQUENCE LISTING

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Kyushu University, National University Corporation

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Samsung Bioepis Exhibit No. 1002
Page 12117

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35 40 45

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50 55 60

Samsung Bioepis Exhibit No. 1002
Page 12118

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65                  70                  75                  80

aac ccc tcc ctc aag agt cga gtc acc atc tca cta gac acg tcc aag      288
Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys
                85                  90                  95

aac cag ttc tcc ctg aag ctg agc tct gtg acc gct gcg gac acg gcc      336
Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

gtg tat tac tgt gcg aga gat cat tat agc agc agc tgg acc ttt gac      384
Val Tyr Tyr Cys Ala Arg Asp His Tyr Ser Ser Ser Trp Thr Phe Asp
        115                 120                 125

tac tgg ggc cag gga acc ctg gtc acc gtc tcc tca                      420
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140
```

<210> 8
<211> 140
<212> PRT
<213> Homo sapiens

<400> 8

```
Met Lys His Leu Trp Phe Phe Leu Leu Leu Ala Ala Ala Pro Arg Trp
1               5                   10                  15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe
        35                  40                  45

Ser Arg Gly Gly Tyr Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys
    50                  55                  60

Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr
65                  70                  75                  80

Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys
                85                  90                  95

Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
            100                 105                 110

Val Tyr Tyr Cys Ala Arg Asp His Tyr Ser Ser Ser Trp Thr Phe Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140
```


Samsung Bioepis Exhibit No. 1002
Page 12119

<210> 9
<211> 381
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(381)

<400> 9

```
atg gaa gcc cca gct cag ctt ctc ttc ctc ctg cta ctc tgg ctc cca       48
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                  10                  15

gat acc acc gga gaa att gtg ttg aca cag tct cca gcc acc ctg tct       96
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
            20                  25                  30

ttg tct cca ggg gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt      144
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

gtt agc agc tac tta gcc tgg tac caa cag aaa cct ggc cag gct ccc      192
Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60

agg ctc ctc atc tat gat gca tcc aac agg gcc act ggc atc cca gcc      240
Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65                  70                  75                  80

agg ttc agt ggc agt ggg tct ggg aca gac ttc act ctc acc atc agc      288
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95

agc cta gag cct gaa gat ttt gca gtt tat tac tgt cag cag cgt agc      336
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser
            100                 105                 110

aac tgg cct ccg acg ttc ggc cag ggg acc aag ctg gag atc aaa          381
Asn Trp Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
        115                 120                 125
```

<210> 10
<211> 127
<212> PRT
<213> Homo sapiens

<400> 10

```
Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                  10                  15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
            20                  25                  30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45
```


Samsung Bioepis Exhibit No. 1002
Page 12120

Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60

Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65 70 75 80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95

Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser
100 105 110

Asn Trp Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120 125

<210> 11
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Human4177 H-chain CDR1

<400> 11

Ser Tyr Tyr Trp Ser
1 5

<210> 12
<211> 16
<212> PRT
<213> Artificial

<220>
<223> Human4177 H-chain CDR2

<400> 12

Tyr Ile Phe His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 13
<211> 13
<212> PRT
<213> Artificial

<220>
<223> Human4177 H-chain CDR3

<400> 13

Asp Gly Glu Tyr Phe Asp Met Leu Thr Gly Phe Asp Tyr
1 5 10

Samsung Bioepis Exhibit No. 1002
Page 12121

<210> 14
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Human4177 L-chain CDR1

<400> 14

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala
1 5 10

<210> 15
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Human4177 L-chain CDR2

<400> 15

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 16
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Human4177 L-chain CDR3

<400> 16

Gln Gln Tyr Asn Ser Tyr Pro Arg Thr
1 5

<210> 17
<211> 420
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(420)

<400> 17

```
atg aaa cat ctg tgg ttc ttc ctt ctc ctg gtg gca gct ccc aga tgg       48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1               5                   10                  15

gtc ctg tcc cag gtg cag ttg cag gag tcg ggc cca gga ctg gtg aag       96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

cct tcg gag acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc      144
```


Samsung Bioepis Exhibit No. 1002
Page 12122

```
Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35                  40                  45

agt agt tac tac tgg agc tgg atc cgg cag ccc cca ggg aag gga ctg      192
Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
    50                  55                  60

gag tgg att ggg tat atc ttt cac agt ggg agc acc aac tac aac ccc      240
Glu Trp Ile Gly Tyr Ile Phe His Ser Gly Ser Thr Asn Tyr Asn Pro
65                  70                  75                  80

tcc ctc aag agt cga gtc acc ata tca gta gac acg tcc aag aac cag      288
Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
                85                  90                  95

ttc tcc ctg aag ctg agc tct gtg acc gct gcg gac acg gcc gtg tat      336
Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110

tac tgt gcg aga gat ggg gag tat ttc gat atg ttg act ggt ttt gac      384
Tyr Cys Ala Arg Asp Gly Glu Tyr Phe Asp Met Leu Thr Gly Phe Asp
        115                 120                 125

tac tgg ggc cag gga acc ctg gtc acc gtc tcc tca                      420
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140
```

<210> 18
<211> 140
<212> PRT
<213> Homo sapiens

<400> 18

```
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1               5                   10                  15

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
        35                  40                  45

Ser Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Ile Gly Tyr Ile Phe His Ser Gly Ser Thr Asn Tyr Asn Pro
65                  70                  75                  80

Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln
                85                  90                  95

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
            100                 105                 110
```


Samsung Bioepis Exhibit No. 1002
Page 12123

```
Tyr Cys Ala Arg Asp Gly Glu Tyr Phe Asp Met Leu Thr Gly Phe Asp
        115                 120                 125

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135                 140


<210>  19
<211>  387
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(387)

<400>  19
atg gac atg agg gtc ctc gct cag ctc ctg ggg ctc ctg ctg ctc tgt       48
Met Asp Met Arg Val Leu Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys
1               5                   10                  15

ttc cca ggt gcc aga tgt gac atc cag atg acc cag tct cca tcc tca       96
Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

ctg tct gca tct gta gga gac aga gtc acc atc act tgt cgg gcg agt      144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

cag ggt att agc agc tgg tta gcc tgg tat cag cag aaa cca gag aaa      192
Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys
    50                  55                  60

gcc cct aag tcc ctg atc tat gct gca tcc agt ttg caa agt ggg gtc      240
Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80

cca tca agg ttc agc ggc agt gga tct ggg aca gat ttc act ctc acc      288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

atc agc agc ctg cag cct gaa gat ttt gca act tat tac tgc caa cag      336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

tat aat agt tac cct cgg acg ttc ggc caa ggg acc aag gtg gaa atc      384
Tyr Asn Ser Tyr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

aaa                                                                  387
Lys


<210>  20
<211>  129
<212>  PRT
<213>  Homo sapiens

<400>  20
```


Samsung Bioepis Exhibit No. 1002
Page 12124

```
Met Asp Met Arg Val Leu Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys
1               5                  10                  15

Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys
    50                  55                  60

Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Tyr Asn Ser Tyr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
        115                 120                 125

Lys
```

<210> 21
<211> 5
<212> PRT
<213> Artificial

<220>
<223> Mouse8213 H-chain CDR1

<400> 21

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Ser Tyr Trp Met His
1               5
```

<210> 22
<211> 17
<212> PRT
<213> Artificial

<220>
<223> Mouse8213 H-chain CDR2

<400> 22

```
Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe Lys
1               5                  10                  15
```


Samsung Bioepis Exhibit No. 1002
Page 12125

Thr

<210> 23
<211> 8
<212> PRT
<213> Artificial

<220>
<223> Mouse8213 H-chain CDR3

<400> 23

Gly Tyr Tyr Leu Tyr Phe Asp Tyr
1 5

<210> 24
<211> 11
<212> PRT
<213> Artificial

<220>
<223> Mouse8213 L-chain CDR1

<400> 24

His Ala Ser Gln Gly Ile Arg Ile Asn Ile Gly
1 5 10

<210> 25
<211> 7
<212> PRT
<213> Artificial

<220>
<223> Mouse8213 L-chain CDR2

<400> 25

His Gly Thr Asn Leu Glu Asp
1 5

<210> 26
<211> 9
<212> PRT
<213> Artificial

<220>
<223> Mouse8213 L-chain CDR3

<400> 26

Val Gln Tyr Gly Gln Phe Pro Trp Thr
1 5

<210> 27
<211> 408

Samsung Bioepis Exhibit No. 1002
Page 12126

<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)..(408)

<400> 27
atg gga tgg agc tat atc atc ctc ttt ttg gta gca aca gcg aca gat 48
Met Gly Trp Ser Tyr Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Asp
1 5 10 15

gtc cac tcc cag gtc caa ctg cag cag cct ggg gct gaa ctg gtg aag 96
Val His Ser Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys
20 25 30

cct ggg gct tca gtg aag ctg tcc tgc aag gct tct ggc tac acc ttc 144
Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

acc agc tac tgg atg cac tgg gtg aag cag agg cct gga caa ggc ctt 192
Thr Ser Tyr Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
50 55 60

gag tgg att gga gag att aat cct agc aac ggt cgt act aac tac aat 240
Glu Trp Ile Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn
65 70 75 80

gag aag ttc aag acc aag gcc aca ctg act gta gac aaa tcc tcc agc 288
Glu Lys Phe Lys Thr Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
85 90 95

aca gcc tac atg caa ctc agc agc ctg aca tct gag gac tct gcg gtc 336
Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
100 105 110

tat tac tgt gcg ggg ggt tac tac ctc tac ttt gac tac tgg ggc caa 384
Tyr Tyr Cys Ala Gly Gly Tyr Tyr Leu Tyr Phe Asp Tyr Trp Gly Gln
115 120 125

ggc acc act ctc aca gtc tcc tca 408
Gly Thr Thr Leu Thr Val Ser Ser
130 135

<210> 28
<211> 136
<212> PRT
<213> Mus musculus

<400> 28

Met Gly Trp Ser Tyr Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Asp
1 5 10 15

Val His Ser Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys
20 25 30

Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Samsung Bioepis Exhibit No. 1002
Page 12127

Thr Ser Tyr Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu
50 55 60

Glu Trp Ile Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn
65 70 75 80

Glu Lys Phe Lys Thr Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser
85 90 95

Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val
100 105 110

Tyr Tyr Cys Ala Gly Gly Tyr Tyr Leu Tyr Phe Asp Tyr Trp Gly Gln
115 120 125

Gly Thr Thr Leu Thr Val Ser Ser
130 135

<210> 29
<211> 387
<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (1)..(387)

<400> 29

```
atg gac atg atg gtc ctt gct cag ttt ctt gca ttc ttg ttg ctt tgg   48
Met Asp Met Met Val Leu Ala Gln Phe Leu Ala Phe Leu Leu Leu Trp
1               5                   10                  15

ttt cca ggt gca aca tgt gac atc ctg atg acc caa tct cca tcc tcc   96
Phe Pro Gly Ala Thr Cys Asp Ile Leu Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

atg tct gta tct ctg gga gac aca gtc aac atc act tgc cat gca agt  144
Met Ser Val Ser Leu Gly Asp Thr Val Asn Ile Thr Cys His Ala Ser
        35                  40                  45

cag ggc att agg att aat ata ggg tgg ttg cag cag aag cca ggg aaa  192
Gln Gly Ile Arg Ile Asn Ile Gly Trp Leu Gln Gln Lys Pro Gly Lys
    50                  55                  60

tca ttt aag ggc ctg atc tat cat gga acc aac ttg gaa gat gga gtt  240
Ser Phe Lys Gly Leu Ile Tyr His Gly Thr Asn Leu Glu Asp Gly Val
65                  70                  75                  80

cca tca agg ttc agt ggc agt gga tct gga cca gat tat tct ctc acc  288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Pro Asp Tyr Ser Leu Thr
                85                  90                  95

atc agc agc ctg gaa tct gaa gat ttt gca gac tat tac tgt gta cag  336
Ile Ser Ser Leu Glu Ser Glu Asp Phe Ala Asp Tyr Tyr Cys Val Gln
```


Samsung Bioepis Exhibit No. 1002
Page 12128

```
            100                 105                 110

tat ggt cag ttt ccg tgg acg ttc ggt gga ggc acc aag ctg gaa atg      384
Tyr Gly Gln Phe Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Met
        115                 120                 125

aaa                                                                  387
Lys
```

<210> 30
<211> 129
<212> PRT
<213> Mus musculus

<400> 30

```
Met Asp Met Met Val Leu Ala Gln Phe Leu Ala Phe Leu Leu Leu Trp
1               5                   10                  15

Phe Pro Gly Ala Thr Cys Asp Ile Leu Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Met Ser Val Ser Leu Gly Asp Thr Val Asn Ile Thr Cys His Ala Ser
        35                  40                  45

Gln Gly Ile Arg Ile Asn Ile Gly Trp Leu Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ser Phe Lys Gly Leu Ile Tyr His Gly Thr Asn Leu Glu Asp Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Pro Asp Tyr Ser Leu Thr
                85                  90                  95

Ile Ser Ser Leu Glu Ser Glu Asp Phe Ala Asp Tyr Tyr Cys Val Gln
            100                 105                 110

Tyr Gly Gln Phe Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Met
        115                 120                 125

Lys
```

<210> 31
<211> 26
<212> DNA
<213> Artificial

<220>
<223> Primer TIM-3 Fw2

<400> 31

Samsung Bioepis Exhibit No. 1002
Page 12129

gccaccatgt tttcacatct tccctt 26

<210> 32
<211> 20
<212> DNA
<213> Artificial

<220>
<223> Primer TIM-3 Re2

<400> 32
ctatggcatt gcaaagcgac 20

<210> 33
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Primer pMCs-Fw

<400> 33
tcaaagtaga cggcatcgca g 21

<210> 34
<211> 27
<212> DNA
<213> Artificial

<220>
<223> Primer TIM3ED-FcReXba

<400> 34
ttttctagat ctgatggttg ctccaga 27

<210> 35
<211> 20
<212> DNA
<213> Artificial

<220>
<223> Primer T7

<400> 35
taatacgact cactataggg 20

<210> 36
<211> 18
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM-3 Fw1

<400> 36
actctggagc aaccatca 18

Samsung Bioepis Exhibit No. 1002
Page 12130

<210> 37
<211> 1333
<212> DNA
<213> Artificial

<220>
<223> Insert hTIM-3 ECD Fc fusion

<220>
<221> CDS
<222> (11)..(1333)

<400> 37

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gattgccacc atg ttt tca cat ctt ccc ttt gac tgt gtc ctg ctg ctg        49
           Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu
           1               5                   10

ctg ctg cta cta ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag       97
Leu Leu Leu Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu
    15                  20                  25

gtc ggt cag aat gcc tat ctg ccc tgc ttc tac acc cca gcc gcc cca      145
Val Gly Gln Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro
30                  35                  40                  45

ggg aac ctc gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt      193
Gly Asn Leu Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe
                50                  55                  60

gaa tgt ggc aac gtg gtg ctc agg act gat gaa agg gat gtg aat tat      241
Glu Cys Gly Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr
            65                  70                  75

tgg aca tcc aga tac tgg cta aat ggg gat ttc cgc aaa gga gat gtg      289
Trp Thr Ser Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val
        80                  85                  90

tcc ctg acc ata gag aat gtg act cta gca gac agt ggg atc tac tgc      337
Ser Leu Thr Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys
    95                  100                 105

tgc cgg atc caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg      385
Cys Arg Ile Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu
110                 115                 120                 125

aag ttg gtc atc aaa cca gcc aag gtc acc cct gca ccg act cgg cag      433
Lys Leu Val Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln
                130                 135                 140

aga gac ttc act gca gcc ttt cca agg atg ctt acc acc agg gga cat      481
Arg Asp Phe Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His
            145                 150                 155

ggc cca gca gag aca cag aca ctg ggg agc ctc cct gat ata aat cta      529
Gly Pro Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu
        160                 165                 170

aca caa ata tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc      577
Thr Gln Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala
    175                 180                 185

aat gac tta cgg gac tct gga gca acc atc aga tct aga gca gac tac      625
```


Samsung Bioepis Exhibit No. 1002
Page 12131

```
Asn Asp Leu Arg Asp Ser Gly Ala Thr Ile Arg Ser Arg Ala Asp Tyr
190                 195                 200                 205

aag gac gac gat gac aag act agt gac aaa act cac aca tgc cca ccg      673
Lys Asp Asp Asp Asp Lys Thr Ser Asp Lys Thr His Thr Cys Pro Pro
                210                 215                 220

tgc cca gca cct gaa ctc ctg ggg gga ccg tca gtc ttc ctc ttc ccc      721
Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
            225                 230                 235

cca aaa ccc aag gac acc ctc atg atc tcc cgg acc cct gag gtc aca      769
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        240                 245                 250

tgc gtg gtg gtg gac gtg agc cac gaa gac cct gag gtc aag ttc aac      817
Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    255                 260                 265

tgg tac gtg gac ggc gtg gag gtg cat aat gcc aag aca aag ccg cgg      865
Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
270                 275                 280                 285

gag gag cag tac aac agc acg tac cgt gtg gtc agc gtc ctc acc gtc      913
Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                290                 295                 300

ctg cac cag gac tgg ctg aat ggc aag gag tac aag tgc aag gtc tcc      961
Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            305                 310                 315

aac aaa gcc ctc cca gcc ccc atc gag aaa acc atc tcc aaa gcc aaa     1009
Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        320                 325                 330

ggg cag ccc cga gaa cca cag gtg tac acc ctg ccc cca tcc cgg gag     1057
Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu
    335                 340                 345

gag atg acc aag aac cag gtc agc ctg acc tgc ctg gtc aaa ggc ttc     1105
Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
350                 355                 360                 365

tat ccc agc gac atc gcc gcg gag tgg gag agc aat ggg cag ccg gag     1153
Tyr Pro Ser Asp Ile Ala Ala Glu Trp Glu Ser Asn Gly Gln Pro Glu
                370                 375                 380

aac aac tac aag acc acg cct ccc gtg ctg gac tcc gac ggc tcc ttc     1201
Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            385                 390                 395

ttc ctc tac agc aag ctc acc gtg gac aag agc agg tgg cag cag ggg     1249
Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        400                 405                 410

aac gtc ttc tca tgc tcc gtg atg cat gag gct ctg cac aac cac tac     1297
Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    415                 420                 425

acg cag aag agc ctc tcc ctg tct ccg ggt aaa tga                    1333
Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
430                 435                 440
```


Samsung Bioepis Exhibit No. 1002
Page 12132

<210> 38
<211> 440
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 38

```
Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                  10                  15

Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45

Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
    50                  55                  60

Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65                  70                  75                  80

Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
                85                  90                  95

Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
            100                 105                 110

Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
        115                 120                 125

Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
    130                 135                 140

Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145                 150                 155                 160

Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
                165                 170                 175

Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
            180                 185                 190

Arg Asp Ser Gly Ala Thr Ile Arg Ser Arg Ala Asp Tyr Lys Asp Asp
        195                 200                 205
```


Samsung Bioepis Exhibit No. 1002
Page 12133

```
Asp Asp Lys Thr Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala
    210                 215                 220

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
225                 230                 235                 240

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
                245                 250                 255

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
            260                 265                 270

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
        275                 280                 285

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
    290                 295                 300

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
305                 310                 315                 320

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
                325                 330                 335

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
            340                 345                 350

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
        355                 360                 365

Asp Ile Ala Ala Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
    370                 375                 380

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
385                 390                 395                 400

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
                405                 410                 415

Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
            420                 425                 430

Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440
```

<210> 39
<211> 30
<212> DNA

Samsung Bioepis Exhibit No. 1002
Page 12134

<213> Artificial

<220>
<223> Primer TIM3ED-FLAG4aa

<400> 39
gtccttgtag tctctgatgg ttgctccaga 30

<210> 40
<211> 39
<212> DNA
<213> Artificial

<220>
<223> Primer C-FLAG-NotR2

<400> 40
aaaagcggcc gctcacttgt cgtcatcgtc cttgtagtc 39

<210> 41
<211> 18
<212> DNA
<213> Artificial

<220>
<223> Primer BGH-R

<400> 41
tagaaggcac agtcgagg 18

<210> 42
<211> 645
<212> DNA
<213> Artificial

<220>
<223> Insert hTIM-3 ECD

<220>
<221> CDS
<222> (19)..(645)

<400> 42
gggaattcga ttgccacc atg ttt tca cat ctt ccc ttt gac tgt gtc ctg 51
Met Phe Ser His Leu Pro Phe Asp Cys Val Leu
1 5 10

ctg ctg ctg ctg cta cta ctt aca agg tcc tca gaa gtg gaa tac aga 99
Leu Leu Leu Leu Leu Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg
15 20 25

gcg gag gtc ggt cag aat gcc tat ctg ccc tgc ttc tac acc cca gcc 147
Ala Glu Val Gly Gln Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala
30 35 40

gcc cca ggg aac ctc gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct 195
Ala Pro Gly Asn Leu Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro
45 50 55

Samsung Bioepis Exhibit No. 1002
Page 12135

```
gtg ttt gaa tgt ggc aac gtg gtg ctc agg act gat gaa agg gat gtg      243
Val Phe Glu Cys Gly Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val
60                  65                  70                  75

aat tat tgg aca tcc aga tac tgg cta aat ggg gat ttc cgc aaa gga      291
Asn Tyr Trp Thr Ser Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly
                80                  85                  90

gat gtg tcc ctg acc ata gag aat gtg act cta gca gac agt ggg atc      339
Asp Val Ser Leu Thr Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile
            95                  100                 105

tac tgc tgc cgg atc caa atc cca ggc ata atg aat gat gaa aaa ttt      387
Tyr Cys Cys Arg Ile Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe
        110                 115                 120

aac ctg aag ttg gtc atc aaa cca gcc aag gtc acc cct gca ccg act      435
Asn Leu Lys Leu Val Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr
    125                 130                 135

cgg cag aga gac ttc act gca gcc ttt cca agg atg ctt acc acc agg      483
Arg Gln Arg Asp Phe Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg
140                 145                 150                 155

gga cat ggc cca gca gag aca cag aca ctg ggg agc ctc cct gat ata      531
Gly His Gly Pro Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile
                160                 165                 170

aat cta aca caa ata tcc aca ttg gcc aat gag tta cgg gac tct aga      579
Asn Leu Thr Gln Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg
            175                 180                 185

ttg gcc aat gac tta cgg gac tct gga gca acc atc aga gac tac aag      627
Leu Ala Asn Asp Leu Arg Asp Ser Gly Ala Thr Ile Arg Asp Tyr Lys
        190                 195                 200

gac gat gac gac aag tga                                             645
Asp Asp Asp Asp Lys
    205
```

<210> 43
<211> 208
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 43

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Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                   10                  15

Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45
```


Samsung Bioepis Exhibit No. 1002
Page 12136

Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
50 55 60

Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65 70 75 80

Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
85 90 95

Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
100 105 110

Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
115 120 125

Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
130 135 140

Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145 150 155 160

Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
165 170 175

Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
180 185 190

Arg Asp Ser Gly Ala Thr Ile Arg Asp Tyr Lys Asp Asp Asp Asp Lys
195 200 205

<210> 44
<211> 27
<212> DNA
<213> Artificial

<220>
<223> Primer hh-6

<400> 44
ggtccgggag atcatgaggg tgtcctt 27

<210> 45
<211> 26
<212> DNA
<213> Artificial

<220>
<223> Primer hh-3

<400> 45
gtgcacgccg ctggtcaggg cgcctg 26

Samsung Bioepis Exhibit No. 1002
Page 12137

<210> 46
<211> 26
<212> DNA
<213> Artificial

<220>
<223> Primer hk-2

<400> 46
gttgaagctc tttgtgacgg gcgagc 26

<210> 47
<211> 26
<212> DNA
<213> Artificial

<220>
<223> Primer hk-6

<400> 47
tggcgggaag atgaagacag atggtg 26

<210> 48
<211> 32
<212> DNA
<213> Artificial

<220>
<223> Primer mH_Rv1

<400> 48
attttgtcga cckyggtsyt gctggcyggg tg 32

<210> 49
<211> 30
<212> DNA
<213> Artificial

<220>
<223> Primer mH_Rv2

<400> 49
gcacacyrct ggacagggat ccagagttcc 30

<210> 50
<211> 30
<212> DNA
<213> Artificial

<220>
<223> Primer mK_Rv1

<400> 50
ttgaagctct tgacaatggg tgaagttgat 30

<210> 51
<211> 30

Samsung Bioepis Exhibit No. 1002
Page 12138

<212> DNA
<213> Artificial

<220>
<223> Primer mK_Rv2

<400> 51
gtaggtgctg tctttgctgt cctgatcagt 30

<210> 52
<211> 906
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(906)

<400> 52
atg ttt tca cat ctt ccc ttt gac tgt gtc ctg ctg ctg ctg ctg cta 48
Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1 5 10 15

cta ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag gtc ggt cag 96
Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
20 25 30

aat gcc tat ctg ccc tgc ttc tac acc cca gcc gcc cca ggg aac ctc 144
Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
35 40 45

gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt gaa tgt ggc 192
Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
50 55 60

aac gtg gtg ctc agg act gat gaa agg gat gtg aat tat tgg aca tcc 240
Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65 70 75 80

aga tac tgg cta aat ggg gat ttc cgc aaa gga gat gtg tcc ctg acc 288
Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
85 90 95

ata gag aat gtg act cta gca gac agt ggg atc tac tgc tgc cgg atc 336
Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
100 105 110

caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg gtc 384
Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
115 120 125

atc aaa cca gcc aag gtc acc cct gca ccg act cgg cag aga gac ttc 432
Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
130 135 140

act gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca gca 480
Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145 150 155 160

gag aca cag aca ctg ggg agc ctc cct gat ata aat cta aca caa ata 528
Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile

Samsung Bioepis Exhibit No. 1002
Page 12139

```
                  165                 170                 175

tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc aat gac tta      576
Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
            180                 185                 190

cgg gac tct gga gca acc atc aga ata ggc atc tac atc gga gca ggg      624
Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
        195                 200                 205

atc tgt gct ggg ctg gct ctg gct ctt atc ttc ggc gct tta att ttc      672
Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
    210                 215                 220

aaa tgg tat tct cat agc aaa gag aag ata cag aat tta agc ctc atc      720
Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225                 230                 235                 240

tct ttg gcc aac ctc cct ccc tca gga ttg gca aat gca gta gca gag      768
Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
                245                 250                 255

gga att cgc tca gaa gaa aac atc tat acc att gaa gag aac gta tat      816
Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
            260                 265                 270

gaa gtg gag gag ccc aat gag tat tat tgc tat gtc agc agc agg cag      864
Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
        275                 280                 285

caa ccc tca caa cct ttg ggt tgt cgc ttt gca atg cca tag              906
Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
    290                 295                 300


<210>  53
<211>  301
<212>  PRT
<213>  Homo sapiens

<400>  53

Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                   10                  15

Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45

Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
    50                  55                  60

Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65                  70                  75                  80

Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
```


Samsung Bioepis Exhibit No. 1002
Page 12140

85 90 95

Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
100 105 110

Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
115 120 125

Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
130 135 140

Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145 150 155 160

Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
165 170 175

Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
180 185 190

Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
195 200 205

Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
210 215 220

Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225 230 235 240

Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
245 250 255

Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
260 265 270

Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
275 280 285

Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
290 295 300

<210> 54
<211> 426
<212> DNA
<213> Homo sapiens

<220>
<221> CDS

Samsung Bioepis Exhibit No. 1002
Page 12141

<222> (1)..(426)

<400> 54

```
atg gag ttt ggg ctg agc tgg gtt ttc ctc gtt gct ctt tta aga ggt       48
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                   10                  15

gtc cag tgt cag gtg cag ctg gtg gag tct ggg gga ggc gtg gtc cag       96
Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

cct ggg agg tcc ctg aga ctc tcc tgt gca gcg tct gga ttc acc ttc      144
Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

aat agc tat ggc atg cac tgg gtc cgc cag gct cca ggc aag ggg ctg      192
Asn Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

gag tgg gtg gca gtt ata tgg tat gat gga agt aat aaa tac tat gga      240
Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly
65                  70                  75                  80

gac tcc gtg aag ggc cga ttc acc atc tcc aga gac aat tcc aag aac      288
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

acg ctg tat ctg caa atg aac agc ctg aga gcc gag gac acg gct gtg      336
Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

tat tac tgt gcg ata tgg ttc ggg gag atg ttt tcc gaa tac ttc cag      384
Tyr Tyr Cys Ala Ile Trp Phe Gly Glu Met Phe Ser Glu Tyr Phe Gln
        115                 120                 125

cac tgg ggc cag ggc acc ctg gtc acc gtc tcc tca gct agc              426
His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
    130                 135                 140
```

<210> 55
<211> 142
<212> PRT
<213> Homo sapiens

<400> 55

```
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Asn Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60
```


Samsung Bioepis Exhibit No. 1002
Page 12142

```
Glu Trp Val Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Gly
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Ile Trp Phe Gly Glu Met Phe Ser Glu Tyr Phe Gln
        115                 120                 125

His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser
    130                 135                 140
```

<210> 56
<211> 393
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(393)

<400> 56

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atg gac atg agg gtc ccc gct cag ctc ctg ggg ctt ctg ctg ctc tgg       48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1               5                   10                  15

ctc cca ggt gcc aga tgt gcc atc cag ttg acc cag tct cca tcc tcc       96
Leu Pro Gly Ala Arg Cys Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser
            20                  25                  30

ctg tct gca tct gta gga gac aga gtc acc atc act tgc cgg gca agt      144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

cag ggc att agc agt gct tta gcc tgg tat cag cag aaa cca ggg aaa      192
Gln Gly Ile Ser Ser Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

gct cct aag ctc ctg atc tat gat gcc tcc agt ttg gaa agt ggg gtc      240
Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65                  70                  75                  80

cca tca agg ttc agc ggc agt gga tct ggg aca gat ttc act ctc acc      288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

atc agc agc ctg cag cct gaa gat ttt gca act tat tac tgt caa cag      336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

ttt aat agt tac cct ctc act ttc ggc gga ggg acc aag gtg gag atc      384
Phe Asn Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
        115                 120                 125
```


Samsung Bioepis Exhibit No. 1002
Page 12143

aaa cgt acg 393
Lys Arg Thr
130

<210> 57
<211> 131
<212> PRT
<213> Homo sapiens

<400> 57

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Ser Ala Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Phe Asn Ser Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
115 120 125

Lys Arg Thr
130

<210> 58
<211> 432
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(432)

<400> 58
atg gag ttt ggg ctg agc tgg gtt ttc ctt gtt gct att ata aaa ggt 48
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1 5 10 15

Samsung Bioepis Exhibit No. 1002
Page 12144

```
gtc cag tgt cag gtg cag ctg gtg gag tct ggg gga ggc ttg gtc aag       96
Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
            20                  25                  30

cct gga ggg tcc ctg aga ctc tcc tgt gca gcc tct gga ttc acc ttc      144
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

agt gac tac tac atg agc tgg atc cgc cag gct cca ggg aag ggg ctg      192
Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

gag tgg gtt tca ttc att agt agt agt ggt agt atc ata tac tac gca      240
Glu Trp Val Ser Phe Ile Ser Ser Ser Gly Ser Ile Ile Tyr Tyr Ala
65                  70                  75                  80

gac tct gtg aag ggc cga ttc acc atc tcc agg gac aac gcc aag aac      288
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95

tca ctg tat ctg caa atg aac agc ctg aga gcc gag gac acg gct gtg      336
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

tat tac tgt gcg aga gat ggg tat agc agc agt tgg tat tac tac ggt      384
Tyr Tyr Cys Ala Arg Asp Gly Tyr Ser Ser Ser Trp Tyr Tyr Tyr Gly
        115                 120                 125

atg gac gtc tgg ggc caa ggg acc acg gtc acc gtc tcc tca gct agc      432
Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140
```

<210> 59
<211> 144
<212> PRT
<213> Homo sapiens

<400> 59

```
Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Ile Lys Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Asp Tyr Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ser Phe Ile Ser Ser Ser Gly Ser Ile Ile Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95
```


Samsung Bioepis Exhibit No. 1002
Page 12145

```
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Asp Gly Tyr Ser Ser Ser Trp Tyr Tyr Tyr Gly
        115                 120                 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140
```

<210> 60
<211> 390
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(390)

<400> 60

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atg gaa acc cca gcg cag ctt ctc ttc ctc ctg cta ctc tgg ctc cca       48
Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1               5                   10                  15

gat acc acc gga gaa att gtg ttg acg cag tct cca ggc acc ctg tct       96
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
            20                  25                  30

ttg tct cca ggg gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt      144
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45

gtt agc agc agc tac tta gcc tgg tac cag cag aaa cct ggc cag gct      192
Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
    50                  55                  60

ccc agg ctc ctc atc tat ggt gca tcc agc agg gcc act ggc atc cca      240
Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65                  70                  75                  80

gac agg ttc agt ggc agt ggg tct ggg aca gac ttc act ctc acc atc      288
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
                85                  90                  95

agc aga ctg gag cct gaa gat ttt gca gtg tat tac tgt cag cag tat      336
Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
            100                 105                 110

ggt agc tca ccg ctc act ttc ggc gga ggg acc aag gtg gag atc aaa      384
Gly Ser Ser Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
        115                 120                 125

cgt acg                                                             390
Arg Thr
    130
```

<210> 61
<211> 130

Samsung Bioepis Exhibit No. 1002
Page 12146

<212> PRT
<213> Homo sapiens

<400> 61

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
20 25 30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Val Ser Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65 70 75 80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
85 90 95

Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr
100 105 110

Gly Ser Ser Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
115 120 125

Arg Thr
130

<210> 62
<211> 414
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(414)

<400> 62
atg gac tgg acc tgg agc atc ctt ttc ttg gtg gca gca gca aca ggt 48
Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1 5 10 15

gcc cac tcc cag gtt cag ctg gtg cag tct gga gct gag gtg aag aag 96
Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

cct ggg gcc tca gtg aag gtc tcc tgc aag gct tct ggt tac acc ttt 144
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Samsung Bioepis Exhibit No. 1002
Page 12147

```
acc agc tat ggt atc agc tgg gtg cga cag gcc cct gga caa ggg ctt      192
Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

gag tgg atg gga tgg atc agc gct tac aat ggt aac aca aac tat gca      240
Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala
65                  70                  75                  80

cag aag ctc cag ggc aga gtc acc atg acc aca gac aca tcc acg agc      288
Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95

aca gcc tac atg gag ctg agg agc ctg aga tct gac gac acg gcc gtg      336
Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

tat tac tgt gcg aga tgg gat agc agc agc tgg tcc ttt gac tac tgg      384
Tyr Tyr Cys Ala Arg Trp Asp Ser Ser Ser Trp Ser Phe Asp Tyr Trp
        115                 120                 125

ggc cag gga acc ctg gtc acc gtc tcc tca                              414
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135


<210>  63
<211>  138
<212>  PRT
<213>  Homo sapiens

<400>  63

Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15


Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30


Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45


Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60


Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala
65                  70                  75                  80


Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95


Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110


Tyr Tyr Cys Ala Arg Trp Asp Ser Ser Ser Trp Ser Phe Asp Tyr Trp
        115                 120                 125
```


Samsung Bioepis Exhibit No. 1002
Page 12148

```
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
    130                 135


<210>  64
<211>  390
<212>  DNA
<213>  Homo sapiens


<220>
<221>  CDS
<222>  (1)..(390)

<400>  64
atg gac atg agg gtc ctc gct cag ctc ctg ggg ctc ctg ctg ctc tgt       48
Met Asp Met Arg Val Leu Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys
1               5                   10                  15

ttc cca ggt gcc aga tgt gac atc cag atg acc cag tct cca tcc tca       96
Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

ctg tct gca tct gta gga gac aga gtc acc atc act tgt cgg gcg agt      144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

cag ggt att agc agc tgg tta gcc tgg tat cag cag aaa cca gag aaa      192
Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys
    50                  55                  60

gcc cct aag tcc ctg atc tat gct gca tcc agt ttg caa agt ggg gtc      240
Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80

cca tca agg ttc agc ggc agt gga tct ggg aca gat ttc act ctc acc      288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

atc agc agc ctg cag cct gaa gat ttt gca act tat tac tgc caa cag      336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

tat aat agt tac ccg tac act ttt ggc cag ggg acc aag ctg gag atc      384
Tyr Asn Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
        115                 120                 125

aaa cgt                                                             390
Lys Arg
    130


<210>  65
<211>  130
<212>  PRT
<213>  Homo sapiens

<400>  65

Met Asp Met Arg Val Leu Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys
1               5                   10                  15
```


Samsung Bioepis Exhibit No. 1002
Page 12149

```
Phe Pro Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
            20                  25                  30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
        35                  40                  45

Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys
    50                  55                  60

Ala Pro Lys Ser Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65                  70                  75                  80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            100                 105                 110

Tyr Asn Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
        115                 120                 125

Lys Arg
    130
```

<210> 66
<211> 351
<212> DNA
<213> Artificial

<220>
<223> HV0 Mouse8213 VH

<220>
<221> CDS
<222> (1)..(351)

<400> 66

```
cag gtc caa ctg gtg cag tct ggg gct gaa gtg aag aag cct ggg gct       48
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

tca gtg aag gtg tcc tgc aag gct tct ggc tac acc ttc acc agc tac       96
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

tgg atg cac tgg gtg cgg cag gcg cct gga caa ggc ctt gag tgg atg      144
Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

gga gag att aat cct agc aac ggt cgt act aac tac aat gag aag ttc      192
Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60
```


Samsung Bioepis Exhibit No. 1002
Page 12150

```
aag acc cgg gtc aca atc act gca gac aca tcc acc agc aca gcc tac      240
Lys Thr Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

atg gaa ctc agc agc ctg cga tct gag gac act gcg gtc tat tac tgt      288
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

gcg cgg ggt tac tac ctc tac ttt gac tac tgg ggc caa ggc acc ctg      336
Ala Arg Gly Tyr Tyr Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

gtc aca gtc tcc tca                                                  351
Val Thr Val Ser Ser
        115
```

<210> 67
<211> 117
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 67

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Trp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Thr Asn Tyr Asn Glu Lys Phe
    50                  55                  60

Lys Thr Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Tyr Tyr Leu Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> 68
<211> 321
<212> DNA

Samsung Bioepis Exhibit No. 1002
Page 12151

<213> Artificial

<220>
<223> LV0 Mouse8213 VL

<220>
<221> CDS
<222> (1)..(321)

<400> 68

```
gac atc cag atg acc caa tct cca tcc tcc ttg tct gca tct gtg gga       48
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

gac cga gtc acc atc act tgc cat gca agt cag ggc att agg att aat       96
Asp Arg Val Thr Ile Thr Cys His Ala Ser Gln Gly Ile Arg Ile Asn
            20                  25                  30

ata ggg tgg tat cag cag aag cca ggg aaa gca cct aag ctc ctg atc      144
Ile Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

tat cat gga acc aac ttg gaa gat gga gtt cca tca agg ttc agt ggc      192
Tyr His Gly Thr Asn Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

agt gga tct gga aca gat ttc act ctc acc atc agc agc ctg caa cct      240
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

gaa gat ttt gca acc tat tac tgt gta cag tat ggt cag ttt ccg tgg      288
Glu Asp Phe Ala Thr Tyr Tyr Cys Val Gln Tyr Gly Gln Phe Pro Trp
                85                  90                  95

acg ttc ggt cag ggc acc aag ctg gaa atc aaa                         321
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 69
<211> 107
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 69

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys His Ala Ser Gln Gly Ile Arg Ile Asn
            20                  25                  30

Ile Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr His Gly Thr Asn Leu Glu Asp Gly Val Pro Ser Arg Phe Ser Gly
```


Samsung Bioepis Exhibit No. 1002
Page 12152

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Val Gln Tyr Gly Gln Phe Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 70
<211> 22
<212> DNA
<213> Artificial

<220>
<223> Primer mTim-3 Fw3

<400> 70
ctacacagag ctgtccttgg at 22

<210> 71
<211> 20
<212> DNA
<213> Artificial

<220>
<223> Primer mTim-3 Re3

<400> 71
tttctcagtg gctgtggtca 20

<210> 72
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Primer mTim-3 Fw4NotI

<400> 72
aattgcggcc gccaccatgt tttcaggtct tac 33

<210> 73
<211> 30
<212> DNA
<213> Artificial

<220>
<223> Primer mTim-3 Re4NotI

<400> 73
aattgcggcc gctcaggatg gctgctggct 30

Samsung Bioepis Exhibit No. 1002
Page 12153

<210> 74
<211> 20
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3+mIgV_vecR1

<400> 74
ggaccttgta agtagtagca 20

<210> 75
<211> 22
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3+mIgV_vecF1

<400> 75
gccaaggtca cccctgcacc ga 22

<210> 76
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3+mIgV_insF1

<400> 76
ctacttacaa ggtccttgga agatggttat aaggt 35

<210> 77
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3+mIgV_insR1

<400> 77
aggggtgacc ttggctgctt tgatgtctaa tttca 35

<210> 78
<211> 909
<212> DNA
<213> Artificial

<220>
<223> IgV chimeraTIM-3/pEF6 Myc_HisC

<220>
<221> CDS
<222> (1)..(909)

<400> 78
atg ttt tca cat ctt ccc ttt gac tgt gtc ctg ctg ctg ctg ctg cta 48

Samsung Bioepis Exhibit No. 1002
Page 12154

```
Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                  10                  15

cta ctt aca agg tcc ttg gaa gat ggt tat aag gtt gag gtt ggt aaa  96
Leu Leu Thr Arg Ser Leu Glu Asp Gly Tyr Lys Val Glu Val Gly Lys
            20                  25                  30

aat gcc tat ctg ccc tgc agt tac act cta cct aca tct ggg aca ctt 144
Asn Ala Tyr Leu Pro Cys Ser Tyr Thr Leu Pro Thr Ser Gly Thr Leu
        35                  40                  45

gtg cct atg tgc tgg ggc aag gga ttc tgt cct tgg tca cag tgt acc 192
Val Pro Met Cys Trp Gly Lys Gly Phe Cys Pro Trp Ser Gln Cys Thr
    50                  55                  60

aat gag ttg ctc aga act gat gaa aga aat gtg aca tat cag aaa tcc 240
Asn Glu Leu Leu Arg Thr Asp Glu Arg Asn Val Thr Tyr Gln Lys Ser
65                  70                  75                  80

agc aga tac cag cta aag ggc gat ctc aac aaa gga gat gtg tct ctg 288
Ser Arg Tyr Gln Leu Lys Gly Asp Leu Asn Lys Gly Asp Val Ser Leu
                85                  90                  95

atc ata aag aat gtg act ctg gat gac cat ggg acc tac tgc tgc agg 336
Ile Ile Lys Asn Val Thr Leu Asp Asp His Gly Thr Tyr Cys Cys Arg
            100                 105                 110

ata cag ttc cct ggt ctt atg aat gat aaa aaa tta gaa ctg aaa tta 384
Ile Gln Phe Pro Gly Leu Met Asn Asp Lys Lys Leu Glu Leu Lys Leu
        115                 120                 125

gac atc aaa gca gcc aag gtc acc cct gca ccg act cgg cag aga gac 432
Asp Ile Lys Ala Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp
    130                 135                 140

ttc act gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca 480
Phe Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro
145                 150                 155                 160

gca gag aca cag aca ctg ggg agc ctc cct gat ata aat cta aca caa 528
Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln
                165                 170                 175

ata tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc aat gac 576
Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp
            180                 185                 190

tta cgg gac tct gga gca acc atc aga ata ggc atc tac atc gga gca 624
Leu Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala
        195                 200                 205

ggg atc tgt gct ggg ctg gct ctg gct ctt atc ttc ggc gct tta att 672
Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile
    210                 215                 220

ttc aaa tgg tat tct cat agc aaa gag aag ata cag aat tta agc ctc 720
Phe Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu
225                 230                 235                 240

atc tct ttg gcc aac ctc cct ccc tca gga ttg gca aat gca gta gca 768
Ile Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala
                245                 250                 255
```


Samsung Bioepis Exhibit No. 1002
Page 12155

gag gga att cgc tca gaa gaa aac atc tat acc att gaa gag aac gta 816
Glu Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val
260 265 270

tat gaa gtg gag gag ccc aat gag tat tat tgc tat gtc agc agc agg 864
Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg
275 280 285

cag caa ccc tca caa cct ttg ggt tgt cgc ttt gca atg cca tag 909
Gln Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
290 295 300

<210> 79
<211> 302
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 79

Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1 5 10 15

Leu Leu Thr Arg Ser Leu Glu Asp Gly Tyr Lys Val Glu Val Gly Lys
20 25 30

Asn Ala Tyr Leu Pro Cys Ser Tyr Thr Leu Pro Thr Ser Gly Thr Leu
35 40 45

Val Pro Met Cys Trp Gly Lys Gly Phe Cys Pro Trp Ser Gln Cys Thr
50 55 60

Asn Glu Leu Leu Arg Thr Asp Glu Arg Asn Val Thr Tyr Gln Lys Ser
65 70 75 80

Ser Arg Tyr Gln Leu Lys Gly Asp Leu Asn Lys Gly Asp Val Ser Leu
85 90 95

Ile Ile Lys Asn Val Thr Leu Asp Asp His Gly Thr Tyr Cys Cys Arg
100 105 110

Ile Gln Phe Pro Gly Leu Met Asn Asp Lys Lys Leu Glu Leu Lys Leu
115 120 125

Asp Ile Lys Ala Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp
130 135 140

Phe Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro
145 150 155 160

Samsung Bioepis Exhibit No. 1002
Page 12156

Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln
165 170 175

Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp
180 185 190

Leu Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala
195 200 205

Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile
210 215 220

Phe Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu
225 230 235 240

Ile Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala
245 250 255

Glu Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val
260 265 270

Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg
275 280 285

Gln Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
290 295 300

<210> 80
<211> 21
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3+mMucin_vecR2

<400> 80
tggtttgatg accaacttca g 21

<210> 81
<211> 23
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3+mMucin_vecF2

<400> 81
ataggcatct acatcggagc agg 23

<210> 82
<211> 35
<212> DNA

Samsung Bioepis Exhibit No. 1002
Page 12157

<213> Artificial

<220>
<223> Primer hTIM3+mMucin_insF2

<400> 82
ttggtcatca aaccagccaa ggtcactcca gctca 35

<210> 83
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3+mMucin_insR2

<400> 83
gatgtagatg cctattctga tcgtttctcc agagt 35

<210> 84
<211> 876
<212> DNA
<213> Artificial

<220>
<223> Mucin chimeraTIM-3/pEF6 Myc_HisC

<220>
<221> CDS
<222> (1)..(876)

<400> 84
atg ttt tca cat ctt ccc ttt gac tgt gtc ctg ctg ctg ctg ctg cta 48
Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1 5 10 15

cta ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag gtc ggt cag 96
Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
20 25 30

aat gcc tat ctg ccc tgc ttc tac acc cca gcc gcc cca ggg aac ctc 144
Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
35 40 45

gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt gaa tgt ggc 192
Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
50 55 60

aac gtg gtg ctc agg act gat gaa agg gat gtg aat tat tgg aca tcc 240
Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65 70 75 80

aga tac tgg cta aat ggg gat ttc cgc aaa gga gat gtg tcc ctg acc 288
Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
85 90 95

ata gag aat gtg act cta gca gac agt ggg atc tac tgc tgc cgg atc 336
Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
100 105 110

Samsung Bioepis Exhibit No. 1002
Page 12158

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caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg gtc      384
Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
        115                 120                 125

atc aaa cca gcc aag gtc act cca gct cag act gcc cat ggg gac tct      432
Ile Lys Pro Ala Lys Val Thr Pro Ala Gln Thr Ala His Gly Asp Ser
    130                 135                 140

act aca gct tct cca aga acc cta acc acg gag aga aat ggt tca gag      480
Thr Thr Ala Ser Pro Arg Thr Leu Thr Thr Glu Arg Asn Gly Ser Glu
145                 150                 155                 160

aca cag aca ctg gtg acc ctc cat aat aac aat gga aca aaa att tcc      528
Thr Gln Thr Leu Val Thr Leu His Asn Asn Asn Gly Thr Lys Ile Ser
                165                 170                 175

aca tgg gct gat gaa att aag gac tct gga gaa acg atc aga ata ggc      576
Thr Trp Ala Asp Glu Ile Lys Asp Ser Gly Glu Thr Ile Arg Ile Gly
            180                 185                 190

atc tac atc gga gca ggg atc tgt gct ggg ctg gct ctg gct ctt atc      624
Ile Tyr Ile Gly Ala Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile
        195                 200                 205

ttc ggc gct tta att ttc aaa tgg tat tct cat agc aaa gag aag ata      672
Phe Gly Ala Leu Ile Phe Lys Trp Tyr Ser His Ser Lys Glu Lys Ile
    210                 215                 220

cag aat tta agc ctc atc tct ttg gcc aac ctc cct ccc tca gga ttg      720
Gln Asn Leu Ser Leu Ile Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu
225                 230                 235                 240

gca aat gca gta gca gag gga att cgc tca gaa gaa aac atc tat acc      768
Ala Asn Ala Val Ala Glu Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr
                245                 250                 255

att gaa gag aac gta tat gaa gtg gag gag ccc aat gag tat tat tgc      816
Ile Glu Glu Asn Val Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys
            260                 265                 270

tat gtc agc agc agg cag caa ccc tca caa cct ttg ggt tgt cgc ttt      864
Tyr Val Ser Ser Arg Gln Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe
        275                 280                 285

gca atg cca tag                                                      876
Ala Met Pro
    290
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<210> 85
<211> 291
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 85

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Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                   10                  15
```


Samsung Bioepis Exhibit No. 1002
Page 12159

```
Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45

Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
    50                  55                  60

Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65                  70                  75                  80

Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
                85                  90                  95

Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
            100                 105                 110

Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
        115                 120                 125

Ile Lys Pro Ala Lys Val Thr Pro Ala Gln Thr Ala His Gly Asp Ser
    130                 135                 140

Thr Thr Ala Ser Pro Arg Thr Leu Thr Thr Glu Arg Asn Gly Ser Glu
145                 150                 155                 160

Thr Gln Thr Leu Val Thr Leu His Asn Asn Asn Gly Thr Lys Ile Ser
                165                 170                 175

Thr Trp Ala Asp Glu Ile Lys Asp Ser Gly Glu Thr Ile Arg Ile Gly
            180                 185                 190

Ile Tyr Ile Gly Ala Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile
        195                 200                 205

Phe Gly Ala Leu Ile Phe Lys Trp Tyr Ser His Ser Lys Glu Lys Ile
    210                 215                 220

Gln Asn Leu Ser Leu Ile Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu
225                 230                 235                 240

Ala Asn Ala Val Ala Glu Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr
                245                 250                 255

Ile Glu Glu Asn Val Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys
            260                 265                 270
```


Samsung Bioepis Exhibit No. 1002
Page 12160

Tyr Val Ser Ser Arg Gln Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe
275 280 285

Ala Met Pro
290

<210> 86
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera22-47F1

<400> 86
acatctggga cacttgtgcc cgtctgctgg ggcaa 35

<210> 87
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera22-47R1

<400> 87
ataaccatct tccaaggacc ttgtaagtag tagca 35

<210> 88
<211> 35
<212> DNA
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<220>
<223> Primer hTIM3chimera22-47F2

<400> 88
ctgcagttac actctaccta catctgggac acttg 35

<210> 89
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera22-47R2

<400> 89
ttaccaacct caaccttata accatcttcc aagga 35

<210> 90
<211> 35
<212> DNA
<213> Artificial

<220>

Samsung Bioepis Exhibit No. 1002
Page 12161

<223> Primer hTIM3chimera22-47F3

<400> 90
aaatgcctat ctgccctgca gttacactct accta 35

<210> 91
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera22-47R3

<400> 91
ggcagatagg catttttacc aacctcaacc tta 33

<210> 92
<211> 906
<212> DNA
<213> Artificial

<220>
<223> TIM-3 chimera 22-47/pEF6 Myc_HisC

<220>
<221> CDS
<222> (1)..(906)

<400> 92
atg ttt tca cat ctt ccc ttt gac tgt gtc ctg ctg ctg ctg ctg cta 48
Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1 5 10 15

cta ctt aca agg tcc ttg gaa gat ggt tat aag gtt gag gtt ggt aaa 96
Leu Leu Thr Arg Ser Leu Glu Asp Gly Tyr Lys Val Glu Val Gly Lys
20 25 30

aat gcc tat ctg ccc tgc agt tac act cta cct aca tct ggg aca ctt 144
Asn Ala Tyr Leu Pro Cys Ser Tyr Thr Leu Pro Thr Ser Gly Thr Leu
35 40 45

gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt gaa tgt ggc 192
Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
50 55 60

aac gtg gtg ctc agg act gat gaa agg gat gtg aat tat tgg aca tcc 240
Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65 70 75 80

aga tac tgg cta aat ggg gat ttc cgc aaa gga gat gtg tcc ctg acc 288
Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
85 90 95

ata gag aat gtg act cta gca gac agt ggg atc tac tgc tgc cgg atc 336
Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
100 105 110

caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg gtc 384
Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
115 120 125

Samsung Bioepis Exhibit No. 1002
Page 12162

```
atc aaa cca gcc aag gtc acc cct gca ccg act cgg cag aga gac ttc      432
Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
    130                 135                 140

act gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca gca      480
Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145                 150                 155                 160

gag aca cag aca ctg ggg agc ctc cct gat ata aat cta aca caa ata      528
Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
                165                 170                 175

tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc aat gac tta      576
Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
            180                 185                 190

cgg gac tct gga gca acc atc aga ata ggc atc tac atc gga gca ggg      624
Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
        195                 200                 205

atc tgt gct ggg ctg gct ctg gct ctt atc ttc ggc gct tta att ttc      672
Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
    210                 215                 220

aaa tgg tat tct cat agc aaa gag aag ata cag aat tta agc ctc atc      720
Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225                 230                 235                 240

tct ttg gcc aac ctc cct ccc tca gga ttg gca aat gca gta gca gag      768
Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
                245                 250                 255

gga att cgc tca gaa gaa aac atc tat acc att gaa gag aac gta tat      816
Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
            260                 265                 270

gaa gtg gag gag ccc aat gag tat tat tgc tat gtc agc agc agg cag      864
Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
        275                 280                 285

caa ccc tca caa cct ttg ggt tgt cgc ttt gca atg cca tag              906
Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
    290                 295                 300
```

<210> 93
<211> 301
<212> PRT
<213> Artificial

<220>
<223> Synthetic Construct

<400> 93

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Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                   10                  15

Leu Leu Thr Arg Ser Leu Glu Asp Gly Tyr Lys Val Glu Val Gly Lys
            20                  25                  30
```


Samsung Bioepis Exhibit No. 1002
Page 12163

```
Asn Ala Tyr Leu Pro Cys Ser Tyr Thr Leu Pro Thr Ser Gly Thr Leu
        35                  40                  45

Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
    50                  55                  60

Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65                  70                  75                  80

Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
                85                  90                  95

Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
            100                 105                 110

Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
        115                 120                 125

Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
    130                 135                 140

Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145                 150                 155                 160

Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
                165                 170                 175

Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
            180                 185                 190

Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
        195                 200                 205

Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
    210                 215                 220

Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225                 230                 235                 240

Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
                245                 250                 255

Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
            260                 265                 270

Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
        275                 280                 285
```


Samsung Bioepis Exhibit No. 1002
Page 12164

```
Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
    290                 295                 300
```

<210> 94
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera57-66F

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<210> 95
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera57-66R

<400> 95
gaccaaggac agaatccttt gccccagcag acg 33

<210> 96
<211> 906
<212> DNA
<213> Artificial

<220>
<223> TIM-3 chimera 57-66/pEF6 Myc_HisC

<220>
<221> CDS
<222> (1)..(906)

<400> 96

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atg ttt tca cat ctt ccc ttt gac tgt gtc ctg ctg ctg ctg ctg cta       48
Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                   10                  15

cta ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag gtc ggt cag       96
Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

aat gcc tat ctg ccc tgc ttc tac acc cca gcc gcc cca ggg aac ctc      144
Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45

gtg ccc gtc tgc tgg ggc aaa gga ttc tgt cct tgg tca cag tgt acc      192
Val Pro Val Cys Trp Gly Lys Gly Phe Cys Pro Trp Ser Gln Cys Thr
    50                  55                  60

aat gag gtg ctc agg act gat gaa agg gat gtg aat tat tgg aca tcc      240
Asn Glu Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65                  70                  75                  80
```


Samsung Bioepis Exhibit No. 1002
Page 12165

```
aga tac tgg cta aat ggg gat ttc cgc aaa gga gat gtg tcc ctg acc      288
Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
                85                  90                  95

ata gag aat gtg act cta gca gac agt ggg atc tac tgc tgc cgg atc      336
Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
            100                 105                 110

caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg gtc      384
Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
        115                 120                 125

atc aaa cca gcc aag gtc acc cct gca ccg act cgg cag aga gac ttc      432
Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
    130                 135                 140

act gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca gca      480
Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145                 150                 155                 160

gag aca cag aca ctg ggg agc ctc cct gat ata aat cta aca caa ata      528
Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
                165                 170                 175

tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc aat gac tta      576
Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
            180                 185                 190

cgg gac tct gga gca acc atc aga ata ggc atc tac atc gga gca ggg      624
Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
        195                 200                 205

atc tgt gct ggg ctg gct ctg gct ctt atc ttc ggc gct tta att ttc      672
Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
    210                 215                 220

aaa tgg tat tct cat agc aaa gag aag ata cag aat tta agc ctc atc      720
Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225                 230                 235                 240

tct ttg gcc aac ctc cct ccc tca gga ttg gca aat gca gta gca gag      768
Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
                245                 250                 255

gga att cgc tca gaa gaa aac atc tat acc att gaa gag aac gta tat      816
Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
            260                 265                 270

gaa gtg gag gag ccc aat gag tat tat tgc tat gtc agc agc agg cag      864
Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
        275                 280                 285

caa ccc tca caa cct ttg ggt tgt cgc ttt gca atg cca tag              906
Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
    290                 295                 300
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<210> 97
<211> 301
<212> PRT
<213> Artificial

Samsung Bioepis Exhibit No. 1002
Page 12166

<220>
<223> Synthetic Construct

<400> 97

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Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                  10                  15

Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45

Val Pro Val Cys Trp Gly Lys Gly Phe Cys Pro Trp Ser Gln Cys Thr
    50                  55                  60

Asn Glu Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65                  70                  75                  80

Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
                85                  90                  95

Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
            100                 105                 110

Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
        115                 120                 125

Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
    130                 135                 140

Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145                 150                 155                 160

Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
                165                 170                 175

Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
            180                 185                 190

Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
        195                 200                 205

Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
    210                 215                 220

Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225                 230                 235                 240
```


Samsung Bioepis Exhibit No. 1002
Page 12167

Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
245 250 255

Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
260 265 270

Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
275 280 285

Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
290 295 300

<210> 98
<211> 34
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera67-105F

<400> 98
ctggatgacc atgggatcta ctgctgccgg atcc 34

<210> 99
<211> 33
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera67-105R

<400> 99
atcagttctg agcaacacgt tgccacattc aaa 33

<210> 100
<211> 20
<212> DNA
<213> Artificial

<220>
<223> Primer mTIM3chimera67-105F

<400> 100
ttgctcagaa ctgatgaaag 20

<210> 101
<211> 20
<212> DNA
<213> Artificial

<220>
<223> Primer mTIM3chimera67-105R

<400> 101

Samsung Bioepis Exhibit No. 1002
Page 12168

cccatggtca tccagagtca 20

<210> 102
<211> 909
<212> DNA
<213> Artificial

<220>
<223> TIM-3 chimera 67-105/pEF6 Myc_HisC

<220>
<221> CDS
<222> (1)..(909)

<400> 102

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Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                  10                  15

cta ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag gtc ggt cag       96
Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

aat gcc tat ctg ccc tgc ttc tac acc cca gcc gcc cca ggg aac ctc      144
Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45

gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt gaa tgt ggc      192
Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
    50                  55                  60

aac gtg ttg ctc aga act gat gaa aga aat gtg aca tat cag aaa tcc      240
Asn Val Leu Leu Arg Thr Asp Glu Arg Asn Val Thr Tyr Gln Lys Ser
65                  70                  75                  80

agc aga tac cag cta aag ggc gat ctc aac aaa gga gat gtg tct ctg      288
Ser Arg Tyr Gln Leu Lys Gly Asp Leu Asn Lys Gly Asp Val Ser Leu
                85                  90                  95

atc ata aag aat gtg act ctg gat gac cat ggg atc tac tgc tgc cgg      336
Ile Ile Lys Asn Val Thr Leu Asp Asp His Gly Ile Tyr Cys Cys Arg
            100                 105                 110

atc caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg      384
Ile Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu
        115                 120                 125

gtc atc aaa cca gcc aag gtc acc cct gca ccg act cgg cag aga gac      432
Val Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp
    130                 135                 140

ttc act gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca      480
Phe Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro
145                 150                 155                 160

gca gag aca cag aca ctg ggg agc ctc cct gat ata aat cta aca caa      528
Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln
                165                 170                 175

ata tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc aat gac      576
Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp
```


Samsung Bioepis Exhibit No. 1002
Page 12169

```
                180                 185                 190

tta cgg gac tct gga gca acc atc aga ata ggc atc tac atc gga gca      624
Leu Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala
        195                 200                 205

ggg atc tgt gct ggg ctg gct ctg gct ctt atc ttc ggc gct tta att      672
Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile
    210                 215                 220

ttc aaa tgg tat tct cat agc aaa gag aag ata cag aat tta agc ctc      720
Phe Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu
225                 230                 235                 240

atc tct ttg gcc aac ctc cct ccc tca gga ttg gca aat gca gta gca      768
Ile Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala
                245                 250                 255

gag gga att cgc tca gaa gaa aac atc tat acc att gaa gag aac gta      816
Glu Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val
            260                 265                 270

tat gaa gtg gag gag ccc aat gag tat tat tgc tat gtc agc agc agg      864
Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg
        275                 280                 285

cag caa ccc tca caa cct ttg ggt tgt cgc ttt gca atg cca tag          909
Gln Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
    290                 295                 300


<210>  103
<211>  302
<212>  PRT
<213>  Artificial

<220>
<223>  Synthetic Construct

<400>  103

Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                   10                  15

Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45

Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
    50                  55                  60

Asn Val Leu Leu Arg Thr Asp Glu Arg Asn Val Thr Tyr Gln Lys Ser
65                  70                  75                  80

Ser Arg Tyr Gln Leu Lys Gly Asp Leu Asn Lys Gly Asp Val Ser Leu
                85                  90                  95
```


Samsung Bioepis Exhibit No. 1002
Page 12170

Ile Ile Lys Asn Val Thr Leu Asp Asp His Gly Ile Tyr Cys Cys Arg
100 105 110

Ile Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu
115 120 125

Val Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp
130 135 140

Phe Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro
145 150 155 160

Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln
165 170 175

Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp
180 185 190

Leu Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala
195 200 205

Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile
210 215 220

Phe Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu
225 230 235 240

Ile Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala
245 250 255

Glu Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val
260 265 270

Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg
275 280 285

Gln Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
290 295 300

<210> 104
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera74-81F

<400> 104

Samsung Bioepis Exhibit No. 1002
Page 12171

gtgacatatc agaaatcctc cagatactgg ctaaa 35

<210> 105
<211> 35
<212> DNA
<213> Artificial

<220>
<223> Primer hTIM3chimera74-81R

<400> 105
tttctgatat gtcacattcc tttcatcagt cctga 35

<210> 106
<211> 909
<212> DNA
<213> Artificial

<220>
<223> TIM-3 chimera 74-81/pEF6 Myc_HisC

<220>
<221> CDS
<222> (1)..(909)

<400> 106

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Met Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu
1               5                  10                  15

cta ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag gtc ggt cag       96
Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
            20                  25                  30

aat gcc tat ctg ccc tgc ttc tac acc cca gcc gcc cca ggg aac ctc      144
Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45

gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt gaa tgt ggc      192
Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
    50                  55                  60

aac gtg gtg ctc agg act gat gaa agg aat gtg aca tat cag aaa tcc      240
Asn Val Val Leu Arg Thr Asp Glu Arg Asn Val Thr Tyr Gln Lys Ser
65                  70                  75                  80

tcc aga tac tgg cta aat ggg gat ttc cgc aaa gga gat gtg tcc ctg      288
Ser Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu
                85                  90                  95

acc ata gag aat gtg act cta gca gac agt ggg atc tac tgc tgc cgg      336
Thr Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg
            100                 105                 110

atc caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg      384
Ile Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu
        115                 120                 125

gtc atc aaa cca gcc aag gtc acc cct gca ccg act cgg cag aga gac      432
Val Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp
```


Samsung Bioepis Exhibit No. 1002
Page 12172

```
    130                 135                 140

ttc act gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca      480
Phe Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro
145                 150                 155                 160

gca gag aca cag aca ctg ggg agc ctc cct gat ata aat cta aca caa      528
Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln
                165                 170                 175

ata tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc aat gac      576
Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp
            180                 185                 190

tta cgg gac tct gga gca acc atc aga ata ggc atc tac atc gga gca      624
Leu Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala
        195                 200                 205

ggg atc tgt gct ggg ctg gct ctg gct ctt atc ttc ggc gct tta att      672
Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile
    210                 215                 220

ttc aaa tgg tat tct cat agc aaa gag aag ata cag aat tta agc ctc      720
Phe Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu
225                 230                 235                 240

atc tct ttg gcc aac ctc cct ccc tca gga ttg gca aat gca gta gca      768
Ile Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala
                245                 250                 255

gag gga att cgc tca gaa gaa aac atc tat acc att gaa gag aac gta      816
Glu Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val
            260                 265                 270

tat gaa gtg gag gag ccc aat gag tat tat tgc tat gtc agc agc agg      864
Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg
        275                 280                 285

cag caa ccc tca caa cct ttg ggt tgt cgc ttt gca atg cca tag          909
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            20                  25                  30

Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
        35                  40                  45
```


Samsung Bioepis Exhibit No. 1002
Page 12173

```
Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
    50                  55                  60

Asn Val Val Leu Arg Thr Asp Glu Arg Asn Val Thr Tyr Gln Lys Ser
65                  70                  75                  80

Ser Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu
                85                  90                  95

Thr Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg
            100                 105                 110

Ile Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu
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Val Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp
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Phe Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro
145                 150                 155                 160

Ala Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln
                165                 170                 175

Ile Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp
            180                 185                 190

Leu Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala
        195                 200                 205

Gly Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile
    210                 215                 220

Phe Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu
225                 230                 235                 240

Ile Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala
                245                 250                 255

Glu Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val
            260                 265                 270

Tyr Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg
        275                 280                 285

Gln Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
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Samsung Bioepis Exhibit No. 1002
Page 12174

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cta ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag gtc ggt cag 96
Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
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Asn Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu
35 40 45

gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt gaa tgt ggc 192
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50 55 60

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aga tac tgg cta aat ggg gat ctc aac aaa gga gat gtg tct ctg atc 288
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Samsung Bioepis Exhibit No. 1002
Page 12175

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                    85                  90                  95

ata gag aat gtg act cta gca gac agt ggg atc tac tgc tgc cgg atc      336
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             100                 105                 110

caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg gtc      384
Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
         115                 120                 125

atc aaa cca gcc aag gtc acc cct gca ccg act cgg cag aga gac ttc      432
Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
     130                 135                 140

act gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca gca      480
Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145                 150                 155                 160

gag aca cag aca ctg ggg agc ctc cct gat ata aat cta aca caa ata      528
Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
                165                 170                 175

tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc aat gac tta      576
Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
             180                 185                 190

cgg gac tct gga gca acc atc aga ata ggc atc tac atc gga gca ggg      624
Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
         195                 200                 205

atc tgt gct ggg ctg gct ctg gct ctt atc ttc ggc gct tta att ttc      672
Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
     210                 215                 220

aaa tgg tat tct cat agc aaa gag aag ata cag aat tta agc ctc atc      720
Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225                 230                 235                 240

tct ttg gcc aac ctc cct ccc tca gga ttg gca aat gca gta gca gag      768
Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
                245                 250                 255

gga att cgc tca gaa gaa aac atc tat acc att gaa gag aac gta tat      816
Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
             260                 265                 270

gaa gtg gag gag ccc aat gag tat tat tgc tat gtc agc agc agg cag      864
Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
         275                 280                 285

caa ccc tca caa cct ttg ggt tgt cgc ttt gca atg cca tag              906
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Samsung Bioepis Exhibit No. 1002
Page 12176

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Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
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Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
100 105 110

Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
115 120 125

Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
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165 170 175

Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
180 185 190

Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
195 200 205

Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
210 215 220

Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225 230 235 240

Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu

Samsung Bioepis Exhibit No. 1002
Page 12177

245 250 255

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cta ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag gtc ggt cag 96
Leu Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln
20 25 30

aat gcc tat ctg ccc tgc ttc tac acc cca gcc gcc cca ggg aac ctc 144
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Samsung Bioepis Exhibit No. 1002
Page 12178

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          35                  40                  45

gtg ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt gaa tgt ggc      192
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    50                  55                  60

aac gtg gtg ctc agg act gat gaa agg gat gtg aat tat tgg aca tcc      240
Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65                  70                  75                  80

aga tac tgg cta aat ggg gat ttc cgc aaa gga gat gtg tcc ctg atc      288
Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Ile
                85                  90                  95

ata aag aat gtg act ctg gat gac cat ggg atc tac tgc tgc cgg atc      336
Ile Lys Asn Val Thr Leu Asp Asp His Gly Ile Tyr Cys Cys Arg Ile
            100                 105                 110

caa atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg gtc      384
Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
        115                 120                 125

atc aaa cca gcc aag gtc acc cct gca ccg act cgg cag aga gac ttc      432
Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
    130                 135                 140

act gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca gca      480
Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145                 150                 155                 160

gag aca cag aca ctg ggg agc ctc cct gat ata aat cta aca caa ata      528
Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
                165                 170                 175

tcc aca ttg gcc aat gag tta cgg gac tct aga ttg gcc aat gac tta      576
Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
            180                 185                 190

cgg gac tct gga gca acc atc aga ata ggc atc tac atc gga gca ggg      624
Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly
        195                 200                 205

atc tgt gct ggg ctg gct ctg gct ctt atc ttc ggc gct tta att ttc      672
Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
    210                 215                 220

aaa tgg tat tct cat agc aaa gag aag ata cag aat tta agc ctc atc      720
Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225                 230                 235                 240

tct ttg gcc aac ctc cct ccc tca gga ttg gca aat gca gta gca gag      768
Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
                245                 250                 255

gga att cgc tca gaa gaa aac atc tat acc att gaa gag aac gta tat      816
Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
            260                 265                 270

gaa gtg gag gag ccc aat gag tat tat tgc tat gtc agc agc agg cag      864
Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
        275                 280                 285

caa ccc tca caa cct ttg ggt tgt cgc ttt gca atg cca tag              906
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Samsung Bioepis Exhibit No. 1002
Page 12179

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<212> PRT
<213> Artificial

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20 25 30

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35 40 45

Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
50 55 60

Asn Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser
65 70 75 80

Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Ile
85 90 95

Ile Lys Asn Val Thr Leu Asp Asp His Gly Ile Tyr Cys Cys Arg Ile
100 105 110

Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
115 120 125

Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Arg Gln Arg Asp Phe
130 135 140

Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala
145 150 155 160

Glu Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gln Ile
165 170 175

Ser Thr Leu Ala Asn Glu Leu Arg Asp Ser Arg Leu Ala Asn Asp Leu
180 185 190

Arg Asp Ser Gly Ala Thr Ile Arg Ile Gly Ile Tyr Ile Gly Ala Gly

Samsung Bioepis Exhibit No. 1002
Page 12180

```
          195                 200                 205

Ile Cys Ala Gly Leu Ala Leu Ala Leu Ile Phe Gly Ala Leu Ile Phe
    210                 215                 220

Lys Trp Tyr Ser His Ser Lys Glu Lys Ile Gln Asn Leu Ser Leu Ile
225                 230                 235                 240

Ser Leu Ala Asn Leu Pro Pro Ser Gly Leu Ala Asn Ala Val Ala Glu
                245                 250                 255

Gly Ile Arg Ser Glu Glu Asn Ile Tyr Thr Ile Glu Glu Asn Val Tyr
            260                 265                 270

Glu Val Glu Glu Pro Asn Glu Tyr Tyr Cys Tyr Val Ser Ser Arg Gln
        275                 280                 285

Gln Pro Ser Gln Pro Leu Gly Cys Arg Phe Ala Met Pro
    290                 295                 300
```

Claims

1. A monoclonal antibody or an antibody fragment thereof, which binds to an extracellular region of human TIM-3 while competing with one antibody selected from the following (i) to (iii):

   (i) an antibody which comprises an H chain of an antibody which comprises complementary determining regions CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 1 to 3, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 4 to 6, respectively,
   (ii) an antibody which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 11 to 13, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 14 to 16, respectively,
   (iii) an antibody which comprises an H chain of an antibody which comprises CDRs1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 21 to 23, respectively, and comprises an L chain of an antibody which comprises CDRs1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 24 to 26, respectively.

2. The monoclonal antibody or the antibody fragment thereof according to claim 1, wherein the monoclonal antibody binds to the same epitope to which one antibody selected from the above (i) to (iii) binds.

3. A monoclonal antibody or an antibody fragment thereof, which binds to an extracellular region of human TIM-3 while competing with one antibody selected from the following (a) and (b):

   (a) an antibody which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 8 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 10,
   (b) an antibody which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 18 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 20.

4. The monoclonal antibody or the antibody fragment thereof according to claim 3, which binds to the same epitope to which one antibody selected from the above (a) or (b) binds.

Samsung Bioepis Exhibit No. 1002
Page 12181

5. The monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 4, which is a recombinant antibody.

6. The monoclonal antibody or the antibody fragment thereof according to claim 5, which is a recombinant antibody selected from a human chimeric antibody, a humanized antibody and a human antibody.

7. A monoclonal antibody or an antibody fragment thereof, which is one selected from the following (i) to (iii):

(i) a monoclonal antibody and an antibody fragment thereof which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 1 to 3, respectively, and comprises an L chain of an antibody which comprises CDRs1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 4 to 6, respectively,
(ii) a monoclonal antibody and an antibody fragment thereof which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 11 to 13, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 14 to 16, respectively,
(iii) a monoclonal antibody and an antibody fragment thereof which comprises an H chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 21 to 23, respectively, and comprises an L chain of an antibody which comprises CDRs 1 to 3 comprising the amino acid sequences represented by SEQ ID NOs: 24 to 26, respectively.

8. A monoclonal antibody and an antibody fragment thereof, which is one selected from the following (a) and (b):

(a) a monoclonal antibody and an antibody fragment thereof which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 8 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 10,
(b) a monoclonal antibody and an antibody fragment thereof which comprises VH of an antibody comprising the amino acid sequence represented by SEQ ID NO: 18 and comprises VL of an antibody comprising the amino acid sequence represented by SEQ ID NO: 20.

9. A monoclonal antibody and an antibody fragment thereof which binds to the amino acid sequences at positions 67 to 105, the amino acid sequences at positions 67 to 96 or the amino acid sequences at positions 67 to 87 in the amino acid sequence of IgV domain of human TIM-3 represented by SEQ ID NO: 53.

10. The antibody fragment according to any one of claims 1 to 9, wherein the antibody fragment is an antibody fragment selected from Fab, Fab', $F(ab')_2$, a single chain antibody (scFv), a dimerized V region (diabody), a disulfide stabilized V region (dsFv) and a peptide comprising CDR.

11. A DNA which encodes the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10.

12. A recombinant vector which comprises the DNA according to claim 11.

13. A transformant obtainable by introducing the recombinant vector according to claim 12 into a host cell.

14. A process for producing the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10, which comprises culturing the transformant according to claim 13 in culture to form and accumulate the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10, and recovering the monoclonal antibody or the antibody fragment thereof from the culture.

15. A method for immunologically detecting or measuring a human TIM-3 which comprises using the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10.

16. A reagent for detecting or measuring a human TIM-3 which comprises the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10.

17. A diagnostic agent for a disease relating to a human TIM-3 positive cell which comprises the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10.

Samsung Bioepis Exhibit No. 1002
Page 12182

18. A method for diagnosing a disease relating to a human TIM-3 positive cell which comprises detect or measure a human TIM-3 positive cell using the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10.

19. A method for diagnosing a disease relating to a human TIM-3 positive cell, which comprises ditecting or measuring a human TIM-3 using the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10.

20. Use of the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10 for the manufacture of a diagnostic agent for a disease relating to a human TIM-3 positive cell.

21. A therapeutic agent for a disease relating to a human TIM-3 positive cell, which comprises the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10.

22. A therapeutic method for a disease relating to a human TIM-3 positive cell, which comprises inducing cell death of a human TIM-3 positive cell using the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10.

23. Use of the monoclonal antibody or the antibody fragment thereof according to any one of claims 1 to 10 for the manufacture of a therapeutic agent for a disease relating to a human TIM-3 positive cell.

Samsung Bioepis Exhibit No. 1002
Page 12183

Fig. 1

	1	2	3	4	5	6
	1234567890	1234567890	1234567890	1234567890	1234567890	1234567890
8213 antibody HV0	QVQLVQSGAE	VKKPGASVKV	SCKASGYTFT	SYWMHWVRQA	PGQGLEWMGE	INPSNGRTNY
8213 antibody HV3				K	I	
8213 antibody HV4				K	I	
8213 antibody HV5				K R	I	
8213 antibody HV6		V				
8213 antibody HV7				K R	I	
8213 antibody HV8		L		K	I	
8213 antibody HV10		V		K R	I	
8213 antibody HV12		V L		K R	I	

	7	8	9	10	11	
	1234567890	1234567890	1234567890	1234567890	1234567890	1234567
8213 antibody HV0	NEKFKTRVTI	TADTSTSTAY	MELSSLRSED	TAVYYCARGY	YLYFDYWGQG	TLVTVSS
8213 antibody HV3				G		
8213 antibody HV4	K	K				
8213 antibody HV5	K			G		
8213 antibody HV6	KA	V K		G		
8213 antibody HV7	K	V K		G		
8213 antibody HV8	A L	V		G	L	
8213 antibody HV10	KA L	V K		G		
8213 antibody HV12	KA L	V K		G		

Samsung Bioepis Exhibit No. 1002
Page 12184

Fig. 2

	1	2	3	4	5	6
	1234567890	1234567890	1234567890	1234567890	1234567890	1234567890
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8213 antibody LV2				L	F	
8213 antibody LV4		L		L	G	
8213 antibody LV5				L	SF G	
8213 antibody LV6		L		L	F G	
8213 antibody LV7		M L		L	F G	
8213 antibody LV9		M V L		L	SF G	

	7	8	9	10	
	1234567890	1234567890	1234567890	1234567890	1234567
8213 antibody LV0	RFSGSGSGTD	FTLTISSLQP	EDFATYYCVQ	YGQFPWTFGQ	GTKLEIK
8213 antibody LV2					
8213 antibody LV4		Y			
8213 antibody LV5			D		
8213 antibody LV6		Y	D		
8213 antibody LV7		Y	D		
8213 antibody LV9		Y	D		

Samsung Bioepis Exhibit No. 1002
Page 12185

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/053396

A. CLASSIFICATION OF SUBJECT MATTER
A61P7/00(2006.01)i, *A61K39/00*(2006.01)i, *C07K16/28*(2006.01)i, *C12N1/15*(2006.01)i, *C12N1/19*(2006.01)i, *C12N1/21*(2006.01)i, *C12N5/10*(2006.01)i, *C12N15/09*(2006.01)i, *C12P21/08*(2006.01)i
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61P7/00, A61K39/00, C07K16/28, C12N1/15, C12N1/19, C12N1/21, C12N5/10, C12N15/09, C12P21/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Jitsuyo Shinan Koho 1922-1996 Jitsuyo Shinan Toroku Koho 1996-2011
Kokai Jitsuyo Shinan Koho 1971-2011 Toroku Jitsuyo Shinan Koho 1994-2011

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubMed, JSTPlus/JMEDPlus/JST7580(JDreamII)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 2010-510223 A (THE BRIGHAM AND WOMEN'S HOSPITAL, INC.), 02 April 2010 (02.04.2010), & US 2010/0061992 A1 & EP 2081961 A2 & WO 2008/060617 A2 & CA 2668693 A1	1-17,20,21, 23
Y	JP 2005-526018 A (THE BRIGHAM AND WOMEN'S HOSPITAL, INC., DANA-FARBER CANCER INSTITUTE, INC.), 02 September 2005 (02.09.2005), & US 2004/0005322 A1 & EP 1467759 A2 & WO 2003/063792 A2	1-17,20,21, 23
Y	JP 2007-530560 A (TELOS PHARMACEUTICALS, INC.), 01 November 2007 (01.11.2007), & US 2005/0276756 A1 & EP 1740224 A2 & WO 2005/097211 A2 & KR 10-2007-0037570 A	1-17,20,21, 23

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 September, 2011 (06.09.11)	13 September, 2011 (13.09.11)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 2009)

Samsung Bioepis Exhibit No. 1002
Page 12186

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/063396

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	IIDA S., et al., Nonfucosylated Therapeutic IgG1 Antibody Can Evade the Inhibitory Effect of Serum Immunoglobulin G on Antibody-Dependent Cellular Cytotoxicity through its High Binding to FcγRIIIa., Clin. Cancer Res., 2006, Vol.12, No.9, p.2879-2887	1-17,20,21, 23
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Y	WO 2000/061739 A1 (KYOWA HAKKO KOGYO CO., LTD.), 19 October 2000 (19.10.2000), & US 2005/0272916 A1 & EP 1176195 A1 & WO 2000/061739 A1	1-17,20,21, 23
P,Y	WO 2010/117057 A1 (KYOWA HAKKO KIRIN CO., LTD.), 14 October 2010 (14.10.2010), (Family: none)	1-17,20,21, 23
A	ANDERSON, A.C. et al., Promotion of tissue inflammation by the immune receptor Tim-3 expressed on innate immune cells., Science, 2007, Vol.318, No.5853, p.1141-1143	1-17,20,21, 23
A	FUKUSHIMA, A. et al., Antibodies to T-cell Ig and mucin domain-containing proteins(Tim)-1 and -3 suppress the induction and progression of murine allergic conjunctivitis., Biochem. Biophys. Res. Commun., 2007, Vol.353 No.1, p.211-216	1-17,20,21, 23
A	JU, Y. et al., T cell immunoglobulin- and mucin-domain-containing molecule-3 (Tim-3) mediates natural killer cell suppression in chronic hepatitis B., J. Heapatol., Vol.52, No.3, 2010.01.06, p.322-329	1-17,20,21, 23
A	HASTINGS W.D., TIM-3 is expressed on activated human CD4+ T cells and regulates Th1 and Th17 cytokines., Eur. J. Immunol., 2009, Vol.39, No.9, p.2492-2501	1-17,20,21, 23

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Samsung Bioepis Exhibit No. 1002
Page 12187

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2011/063396

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18,19,22
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 18, 19 and 22 pertain to diagnostic methods to be practiced on the human body or methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under the provisions of PCT Rule 39.1(iv), to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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Samsung Bioepis Exhibit No. 1002
Page 12188

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HUMAN MONOCLONAL ANTIBODIES AGAINST CD20

(57) Abstract: Isolated human monoclonal antibodies which bind to and inhibit human CD20, and related antibody-based compositions and molecules, are disclosed. The human antibodies can be produced by a transfectoma or in a non-human transgenic animal, *e.g.*, a transgenic mouse, capable of producing multiple isotypes of human monoclonal antibodies by undergoing V-D-J recombination and isotype switching. Also disclosed are pharmaceutical compositions comprising the human antibodies, non-human transgenic animals and hybridomas which produce the human antibodies, and therapeutic and diagnostic methods for using the human antibodies.

WO 2004/035607 A2

HUMAN MONOCLONAL ANTIBODIES AGAINST CD20

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No.: 60/419163, filed on October 17, 2002, and U.S. Provisional Application No.: 60/460028, filed on April 2, 2003, both entitled HUMAN MONOCLONAL ANTIBODIES AGAINST CD20, and both of which are incorporated herein in their entirety by this reference.

BACKGROUND OF THE INVENTION

The CD20 molecule (also called human B-lymphocyte-restricted differentiation antigen or Bp35) is a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes (Valentine *et al.* (1989) *J. Biol. Chem.* 264(19):11282-11287; and Einfield *et al.* (1988) *EMBO J.* 7(3):711-717). CD20 is found on the surface of greater than 90% of B cells from peripheral blood or lymphoid organs and is expressed during early pre-B cell development and remains until plasma cell differentiation. CD20 is present on both normal B cells as well as malignant B cells. In particular, CD20 is expressed on greater than 90% of B cell non-Hodgkin's lymphomas (NHL) (Anderson *et al.* (1984) *Blood* 63(6):1424-1433), but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissues (Tedder *et al.* (1985) *J. Immunol.* 135(2):973-979).

The 85 amino acid carboxyl-terminal region of the CD20 protein is located within the cytoplasm. The length of this region contrasts with that of other B cell-specific surface structures such as IgM, IgD, and IgG heavy chains or histocompatibility antigens class II α or β chains, which have relatively short intracytoplasmic regions of 3, 3, 28, 15, and 16 amino acids, respectively (Komaromy *et al.* (1983) NAR 11:6775-6785). Of the last 61 carboxyl-terminal amino acids, 21 are acidic residues, whereas only 2 are basic, indicating that this region has a strong net negative charge. The GenBank Accession No. is NP_690605.

It is thought that CD20 might be involved in regulating an early step(s) in the activation and differentiation process of B cells (Tedder *et al.* (1986) *Eur.J. Immunol.* 16:881-887) and could function as a calcium ion channel (Tedder *et al.* (1990) *J. Cell. Biochem.* 14D:195).

Despite uncertainty about the actual function of CD20 in promoting proliferation and/or differentiation of B cells, it provides an important target for antibody mediated therapy to control or kill B cells involved in cancers and autoimmune disorders. In particular, the expression of CD20 on tumor cells, *e.g.*, NHL, makes it an important target for antibody mediated therapy to specifically target therapeutic agents

Samsung Bioepis Exhibit No. 1002
Page 12192

against CD20-positive neoplastic cells. However, while the results obtained to date clearly establish CD20 as a useful target for immunotherapy, they also show that currently available murine and chimeric antibodies do not constitute ideal therapeutic agents.

Accordingly, the need exists for improved therapeutic antibodies against CD20 which are effective in preventing and/or treating a range of diseases involving cells expressing CD20.

SUMMARY OF THE INVENTION

The present invention provides improved antibody therapeutics for treating and/or preventing diseases associated with cells expressing CD20, including tumor-related diseases, and immune diseases, including autoimmune diseases. The antibodies encompassed by the invention are improved in that they are fully human and, thus, are potentially less immunogenic in patients.

As exemplified herein, the human antibodies of the invention mediate killing of B cells expressing CD20 by a variety of mechanisms. In one embodiment, human antibodies of the invention induce complement dependent cytotoxicity (CDC), *e.g.*, at least about 20% CDC mediated lysis, preferably about 30% CDC mediated lysis, and more preferably 40-50% mediated lysis in cells, such as chronic B-lymphocytic leukaemia (B-CLL) cells. In another embodiment, human antibodies of the invention induce apoptosis of cells expressing CD20. In another embodiment, human antibodies of the invention induce homotypic adhesion of cells expressing CD20. Furthermore, the human antibodies of the invention may induce antibody dependent cellular cytotoxicity (ADCC) of cells expressing CD20 in the presence of human effector cells (*e.g.*, monocytes, mononuclear cells, NK cells and PMNs). Furthermore, human antibodies of the invention may induce phagocytosis of cells expressing CD20 in the presence of macrophages. The human monoclonal antibodies of the invention may work by one or more of these mechanisms. Examples of cells which can be killed by human antibodies of the present invention include, but are not limited to, B cells expressing CD20, such as tumorigenic B cells and B cells involved in immune diseases. In a particular embodiment, the human antibodies are used to mediate killing of B lymphocytes in the treatment of lymphoma, *e.g.*, B cell non-Hodgkin's lymphoma.

Human antibodies of the invention include IgG1 (*e.g.*, IgG1,κ), IgG3 (*e.g.*, IgG3,κ) and IgG4 (*e.g.*, IgG4,κ) antibodies. However, other antibody isotypes are also encompassed by the invention, including IgG2, IgM, IgA1, IgA2, secretory IgA, IgD, and IgE. The antibodies can be whole antibodies or antigen-binding fragments thereof including, for example, Fab, $F(ab')_2$, Fv, single chain Fv fragments or bispecific antibodies. Furthermore, the antigen-binding fragments include binding-domain

Samsung Bioepis Exhibit No. 1002
Page 12193

immunoglobulin fusion proteins comprising (i) a binding domain polypeptide (such as a heavy chain variable region or a light chain variable region) that is fused to an immunoglobulin hinge region polypeptide, (ii) an immunoglobulin heavy chain CH2 constant region fused to the hinge region, and (iii) an immunoglobulin heavy chain CH3 constant region fused to the CH2 constant region. Such binding-domain immunoglobulin fusion proteins are further disclosed in US 2003/0118592 and US 2003/0133939.

Particular human antibodies of the present invention include those referred to as 11B8, 2F2, and 7D8, encoded by human heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NOs:1, 5, or 9 and SEQ ID NOs:3, 7, or 11, respectively, and conservative sequence modifications thereof. In another embodiment, the human antibodies are characterized by having human heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set forth in SEQ ID NOs:2, 6, or 10 and SEQ ID NOs:4, 8, or 12, respectively, and conservative sequence modifications thereof.

In yet another embodiment, the human antibodies are characterized by having human heavy chain and human kappa light chain variable regions which are at least 90% homologous, preferably at least 95% homologous, and more preferably at least 98%, or at least 99% homologous to the amino acid sequences as set forth in SEQ ID NO:2 and SEQ ID NO:4, respectively; SEQ ID NO:6 and SEQ ID NO:8, respectively; or SEQ ID NO:10 and SEQ ID NO:12, respectively.

Other particular human antibodies of the invention include those which comprise a CDR domain having a human heavy and light chain CDR1 region, a human heavy and light chain CDR2 region, and a human heavy and light chain CDR3 region, wherein

(a) the CDR1, CDR2, and CDR3 human heavy chain regions comprise an amino acid sequence selected from the group consisting of the amino acid sequences CDR1, CDR2, and CDR3 shown in Figures 53, 55, or 57 (SEQ ID NOs:13-15, 19-21, and 25-27), and conservative sequence modifications thereof, and

(b) the CDR1, CDR2, and CDR3 human light chain regions comprise an amino acid sequence selected from the group consisting of the amino acid sequences CDR1, CDR2, and CDR3 shown in Figures 53, 55, or 57 (SEQ ID NOs: 16-18, 22-24, and 28-30), and conservative sequence modifications thereof.

Also included within the present invention are antibodies which dissociate from CD20 with a dissociation equilibrium constant (K_D) of approximately 1-10 nM or less. Such antibodies also include those which do not cross-react with related cell-surface antigens and thus do not inhibit their function.

Samsung Bioepis Exhibit No. 1002
Page 12194

In another embodiment, human anti-CD20 antibodies of the present invention can be characterized by one or more of the following properties:

a) specificity for human CD20;

b) a binding affinity to CD20 (K_D) of about 10 nM or less, preferably, about 5 nM or less and, more preferably, about 1-3 nM or less as determined by the binding experiment disclosed in Example 5 (Figure 9) herein;

c) a dissociation rate constant (k_d) from CD20 of about 10^{-4} sec^{-1} or less, preferably, about 10^{-5} sec^{-1} or less and, more preferably, about 10^{-6} sec^{-1} or less, as determined by the dissociation rate experiment disclosed in Example 5 (Figure 9) herein;

d) the ability to mediate a high level of CDC on either CD55/59 negative or CD55/59 positive cells;

e) the ability to translocate into lipid rafts upon binding to CD20;

f) the ability to inhibit the growth of cells which express CD20;

g) the ability to induce apoptosis of cells which express CD20;

h) the ability to induce homotypic adhesion of cells which express CD20;

i) the ability to induce ADCC of cells which express CD20 in the presence of effector cells;

j) the ability to prolong survival of a subject having tumor cells which express CD20;

k) the ability to deplete cells which express CD20; and/or

l) the ability to deplete cells which express low levels of CD20 ($CD20^{low}$ cells).

The human anti-CD20 antibodies of the present invention can be derivatized, linked to or co-expressed to other binding specificities. In a particular embodiment, the invention provides a bispecific or multispecific molecule comprising at least one first binding specificity for CD20 (*e.g.*, a human anti-CD20 antibody or mimetic thereof), and a second binding specificity for a human effector cell, such as a binding specificity for an Fc receptor (*e.g.*, a human Fcγ receptor, such as FcγRI, or a human Fcα receptor) or a T cell receptor, *e.g.*, CD3.

Accordingly, the present invention includes bispecific and multispecific molecules that bind to both human CD20 and to an Fc receptor or a T cell receptor, *e.g.*, CD3. Examples of Fc receptors are, *e.g.*, a human IgG receptor, *e.g.*, an Fc-gamma receptor (FcγR), such as FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16). Other Fc receptors, such as human IgA receptors (*e.g.*, FcαRI), also can be targeted. The Fc receptor is preferably located on the surface of an effector cell, *e.g.*, a monocyte, macrophage or an activated mononuclear cell. In a preferred embodiment, the bispecific and multispecific molecules bind to an Fc receptor at a site which is distinct from the immunoglobulin Fc (*e.g.*, IgG or IgA) binding site of the receptor. Therefore, the

Samsung Bioepis Exhibit No. 1002
Page 12195

binding of the bispecific and multispecific molecules is not blocked by physiological levels of immunoglobulins.

In yet another aspect, human anti-CD20 antibodies of the invention are derivatized, linked to or co-expressed with another functional molecule, *e.g.*, another peptide or protein (*e.g.*, a Fab' fragment). For example, an antibody of the invention can be functionally linked (*e.g.*, by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (*e.g.*, to produce a bispecific or a multispecific antibody), a cytotoxin, cellular ligand or antigen (*e.g.*, to produce an immunoconjugate, such as an immunotoxin). An antibody of the present invention can be linked to other therapeutic moieties, *e.g.*, a radioisotope, a small molecule anti-cancer drug, an anti-inflammatory agent, or an immunosuppressive agent. Accordingly, the present invention encompasses a large variety of antibody conjugates, bispecific and multispecific molecules, and fusion proteins, all of which bind to CD20 expressing cells and which can be used to target other molecules to such cells.

In still another aspect, the invention provides compositions, *e.g.*, pharmaceutical and diagnostic compositions/kits, comprising a pharmaceutically acceptable carrier formulated along with one or a combination of human monoclonal antibodies of the invention. In a particular embodiment, the composition includes a combination of antibodies which bind to distinct epitopes or which possess distinct functional characteristics, such as inducing CDC and inducing apoptosis.

Human antibodies, immunoconjugates, bispecific and multispecific molecules and compositions of the present invention can be used in a variety of methods for inhibiting growth of cells expressing CD20 and/or killing cells expressing CD20 by contacting the cells with an effective amount of the antibody, immunconjugate, bispecific/multispecific molecule or composition, such that the growth of the cell is inhibited and/or the cell is killed. In one embodiment, the method includes killing of the cell expressing CD20 in the presence of effector cells, for example, by CDC, apoptosis, ADCC, phagocytosis, or by a combination of two or more of these mechanisms. The cells are preferably killed or inhibited without killing or inhibiting the activity of cells which do not express CD20 but which may, for example, express a structurally related cell-surface antigen (*i.e.*, without cross-reactivity to related but functionally distinct cell surface antigens). Cells expressing CD20 which can be inhibited or killed using the human antibodies of the invention include, for example, tumorigenic B cells.

Accordingly, human antibodies of the present invention can be used to treat and/or prevent a variety of diseases involving cells expressing CD20 by administering the antibodies to patients suffering from such diseases. Exemplary diseases that can be treated (*e.g.*, ameliorated) or prevented include, but are not limited

Samsung Bioepis Exhibit No. 1002
Page 12196

to, tumorigenic diseases and immune diseases, *e.g.*, autoimmune diseases. Examples of tumorigenic diseases which can be treated and/or prevented include B cell lymphoma, *e.g.*, NHL, including precursor B cell lymphoblastic leukemia/lymphoma and mature B cell neoplasms, such as B cell chronic lymhocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), including low-grade, intermediate-grade and high-grade FL, cutaneous follicle center lymphoma, marginal zone B cell lymphoma (MALT type, nodal and splenic type), hairy cell leukemia, diffuse large B cell lymphoma, Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant lymphoproliferative disorder, Waldenström's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL). Examples of immune disorders in which CD20 expressing B cells are involved which can be treated and/or prevented include psoriasis, psoriatic arthritis, dermatitis, systemic scleroderma and sclerosis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis, glomerulonephritis, eczema, asthma, atherosclerosis, leukocyte adhesion deficiency, multiple sclerosis, Raynaud's syndrome, Sjögren's syndrome, juvenile onset diabetes, Reiter's disease, Behçet's disease, immune complex nephritis, IgA nephropathy, IgM polyneuropathies, immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, hemolytic anemia, myasthenia gravis, lupus nephritis, systemic lupus erythematosus, rheumatoid arthritis (RA), atopic dermatitis, pemphigus, Graves' disease, Hashimoto's thyroiditis, Wegener's granulomatosis, Omenn's syndrome, chronic renal failure, acute infectious mononucleosis, HIV, and herpes virus associated diseases. Further examples are severe acute respiratory distress syndrome and choreoretinitis. Yet further examples are diseases and disorders caused by infection of B-cells with virus, such as Epstein-Barr virus (EBV).

In a particular embodiment of the invention, the subject being administered the antibody is additionally treated with a chemotherapeutic agent, radiation, or an agent that modulates, *e.g.*, enhances or inhibits, the expression or activity of an Fc receptor, *e.g.*, an Fcα receptor or an Fcγ receptor, such as a cytokine. Typical cytokines for administration during treatment include granulocyte colony-stimulating factor (G-CSF), granulocyte- macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ), and tumor necrosis factor (TNF). Typical therapeutic agents include, among others, anti-neoplastic agents such as doxorubicin, cisplatin, bleomycin, carmustine, chlorambucil, and cyclophosphamide.

Samsung Bioepis Exhibit No. 1002
Page 12197

In yet another aspect, the present invention provides a method for detecting *in vitro* or *in vivo* the presence of CD20 in a sample or individual, *e.g.*, for diagnosing a CD20-related disease, preferably at an early stage. This can also be useful for monitoring the disease and effect of treatment and for determining and adjusting the dose of the antibody to be administered. The *in vivo* method can be performed using imaging technique such as PET (positron emission tomography) or SPECT (single photon emission computed tomography). In one embodiment, this is achieved by contacting a sample to be tested, optionally along with a control sample, with a human monoclonal antibody of the invention under conditions that allow for formation of a complex between the antibody and CD20. Complex formation is then detected (*e.g.*, using an FACS analysis or Western blotting). When using a control sample along with the test sample, complex is detected in both samples and any statistically significant difference in the formation of complexes between the samples is indicative of the presence of CD20 in the test sample.

In yet another aspect, the invention provides a transgenic non-human animal, such as a transgenic mouse, which express human monoclonal antibodies that bind to CD20. In a particular embodiment, the transgenic non-human animal is a transgenic mouse having a genome comprising a human heavy chain transgene and a human light chain transgene encoding all or a portion of an antibody of the invention. The transgenic non-human animal can be immunized with a purified or enriched preparation of CD20 antigen and/or cells expressing CD20. Preferably, the transgenic non-human animal, *e.g.*, the transgenic mouse, is capable of producing multiple isotypes of human monoclonal antibodies to CD20 (*e.g.*, IgG, IgA and/or IgM) by undergoing V-D-J recombination and isotype switching. Isotype switching may occur by, *e.g.*, classical or non-classical isotype switching.

Accordingly, in yet another aspect, the invention provides isolated B cells from a transgenic non-human animal as described above, *e.g.*, a transgenic mouse, which expresses human anti-CD20 antibodies. The isolated B cells can then be immortalized by fusion to an immortalized cell to provide a source (*e.g.*, a hybridoma) of human anti-CD20 antibodies. Such hybridomas (*i.e.*, which produce human anti-CD20 antibodies) are also included within the scope of the invention.

As exemplified herein, human antibodies of the invention can be obtained directly from hybridomas which express the antibody, or can be cloned and recombinantly expressed in a host cell (*e.g.*, a CHO cell, a NS/0 cell or a lymphocytic cell). Further examples of host cells are microorganisms, such as *E. coli*, and fungi, such as yeast. Alternatively, they can be produced recombinantly in a transgenic non-human animal or plant. Accordingly, in another aspect, the present invention provides methods for producing human monoclonal antibodies which bind to human CD20. In

Samsung Bioepis Exhibit No. 1002
Page 12198

one embodiment, the method includes immunizing a transgenic non-human animal, *e.g.*, a transgenic mouse, as previously described (*e.g.*, having a genome comprising a human heavy chain transgene and a human light chain transgene encoding all or a portion of an anti-CD20 antibody), with a purified or enriched preparation of human CD20 antigen and/or cells expressing human CD20. B cells (*e.g.*, splenic B cells) of the animal are then obtained and fused with myeloma cells to form immortal, hybridoma cells that secrete human monoclonal antibodies against CD20.

In yet another aspect, the invention provides nucleic acid molecules encoding human anti-CD20 antibodies (*e.g.*, variable regions thereof), as well as recombinant expression vectors which include the nucleic acids of the invention, and host cells transfected with such vectors. Methods of producing the antibodies by culturing these host cells are also encompassed by the invention. Particular nucleic acids provided by the invention comprise the nucleotide sequences shown in SEQ ID NOs:1, 5, or 9 and SEQ ID NOs:3, 7, or 11, encoding the heavy and light chains, respectively, of human anti-CD20 antibodies 2F2, 7D8, and 11B8.

Other features and advantages of the instant invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the pCONγ1f/variable-heavy vector used for recombinant production of the human monoclonal antibodies 2F2 and 11B8.

Figure 2 shows the pCONκ/variable-light vector used for recombinant production of 2F2 and 11B8.

Figure 3 shows the double-gene cloning vector (pCONγ1f/κ2F2) used for recombinant production of 2F2 and 11B8.

Figure 4 is a graph comparing the binding of human monoclonal antibodies 2F2, 7D8, and 11B8 to Raji, Daudi, and CD20 transfected NS/0 cells and parental NS/0 cells using flow cytometry.

Figures 5A and 5B show the binding of 2F2 to PBMCs from three human donors using flow cytometry.

Figure 6 is a graph comparing the binding affinity of ^{125}I-labeled 2F2 and ^{125}I-labeled 11B8 to Ramos-EHRB cells.

Figures 7A and 7B show the binding of ^{125}I-labeled 2F2 and ^{125}I-labeled 11B8 compared to ^{125}I-labeled rituximab (chimeric anti-CD20 antibody, IDEC) and ^{125}I-labeled B1 (the term B1 corresponds to the unlabeled form of Bexxar™, which is a ^{131}I-labeled murine anti-human CD20 antibody, Coulter) to Ramos-EHRB cells (A) and Daudi cells (B).

Samsung Bioepis Exhibit No. 1002
Page 12199

Figure 8 is a graph comparing the dissociation rates of ^{125}I-labeled 11B8T, ^{125}I-labeled 2F2, ^{125}I-labeled rituximab (RIT), and ^{125}I-labeled B1.

Figure 9 shows the dissociation rates of the F(ab')$_2$ fragments of 2F2, 11B8T, and rituximab in Ramos-EHRB cells.

Figures 10A and 10B show the CDC by 2F2T, 11B8T, 7D8, rituximab, and an isotype control antibody (HuMab-KLH) of Daudi cells (A) and SU-DHL-4 cells (B) at different time points (functional off-rate) using flow cytometry.

Figures 11A-E show the kinetics of CDC induced by 2F2 and rituximab in different cell lines using flow cytometry.

Figures 12A-D show CDC induced by 2F2 and rituximab in different cell lines as a function of the concentration of complement (normal human serum (NHS)) at two different antibody concentrations using flow cytometry.

Figures 13A-D show concentration-dependent induction of CDC by 2F2 and rituximab in different cell lines using flow cytometry.

Figures 14A and 14B show concentration-dependent induction of CDC by 2F2, 2F2T, 11B8T, B1, and rituximab in Daudi cells (A) and Raji cells (B).

Figures 15A and 15B are graphs comparing CDC of Daudi cells (cells expressing low levels of CD55/59) by human monoclonal antibodies 2F2, 7D8, and 11B8 and rituximab; (A) shows percent lysis of unwashed cells and (B) shows percent lysis of cells which were washed before the addition of serum.

Figures 16A and 16B are graphs comparing CDC of Raji cells (cells expressing high levels of CD55/59) by human monoclonal antibodies 2F2, 7D8, and 11B8 and rituximab; (A) shows percent lysis of cells not blocked with anti-CD55 and anti-CD59 antibodies, and (B) shows percent lysis of cells blocked with anti-CD55 and anti-CD59 antibodies.

Figures 17A-C show the role of CD55 and CD59 in CDC induced by 2F2 and rituximab in Raji cells. (A) shows the percentage of lysed cells upon addition of anti-CD55 antibody, (B) shows the percentage of lysed cells upon addition of anti-CD59 antibody, and (C) shows the percentage of lysed cells upon addition of both anti-CD55 antibody and anti-CD59 antibody.

Figures 18A-D show the binding of complement factor C1q by 2F2 and rituximab in different cell lines as determined by flow cytometry.

Figures 19A-D show the deposition of complement factor fragment C4c by 2F2 and rituximab in different cell lines as determined by flow cytometry.

Figure 20 shows lysis of ARH-77 cells by 2F2, rituximab, and 11B8T in the presence of PMNs, MNCs, plasma or whole blood.

Figure 21 shows lysis of B-CLL cells by 2F2, rituximab, and 11B8T in the presence of PMNs, MNCs, plasma or whole blood.

Samsung Bioepis Exhibit No. 1002
Page 12200

Figure 22 shows lysis of HCL (hairy cell leukemia) cells by 2F2, rituximab, and 11B8T in the presence of PMNs, MNCs, plasma or whole blood.

Figure 23 shows lysis of B-ALL cells by 2F2, and rituximab, in the presence of PMNs, MNCs, plasma or whole blood.

Figure 24 shows lysis of follicular lymphoma (FL) cells by 2F2, rituximab, and 11B8T in the presence of PMNs, MNCs, plasma or whole blood.

Figure 25 shows lysis of mantle cell lymphoma cells by 2F2, rituximab, and 11B8T in the presence of PMNs, MNCs, plasma or whole blood.

Figure 26 shows concentration dependent lysis of ARH-77 cells by 2F2 and rituximab in the presence of whole blood.

Figure 27 shows MNC-mediated lysis of ARH-77 cells by 2F2T, 11B8T, and rituximab.

Figure 28 shows MNC-mediated lysis of Raji cells by 2F2T, 11B8T, and rituximab.

Figures 29A, B, and C are graphs showing clustering of CD20 in the lipid rafts upon incubation with 2F2, 7D8, or 11B8 using FRET analysis and Triton-X insolubility assay.

Figure 30 shows clustering of CD20 in the lipid rafts upon incubation with 2F2, rituximab, or 11B8T using FRET analysis.

Figure 31 shows the proportion of CD20 remaining in the insoluble raft fraction after treatment with Triton X-100 (TX) and incubation with 2F2, rituximab, or 11B8T.

Figure 32 shows the distribution of CD20 between the raft and non-raft membrane fractions upon stimulating Daudi cells with 2F2, rituximab, or 11B8T.

Figures 33A-G show apoptosis of Daudi cells by 2F2, 7D8, and 11B8 using flow cytometry.

Figure 34 shows induction of apoptosis of Raji cells by 2F2, 11B8T, rituximab, or B1 using flow cytometry.

Figure 35A shows induction of apoptosis of Daudi cells by 2F2T, 11B8T, rituximab, or B1 using flow cytometry.

Figure 35B shows early stage and late stage apoptosis of Daudi cells by human monoclonal antibodies 2F2T, 11B8T, rituximab, and B1 using flow cytometry.

Figures 36A-E show homotypic adhesion of Ramos-EHRB cells by 2F2, 7D8, and 11B8 using light microscopy.

Figure 37 show homotypic adhesion of Daudi cells by 2F2, rituximab, and B1 using light microscopy.

Figure 38 is a graph showing the percent survival of SCID mice injected with Daudi cells and treated with 2F2 or 7D8.

Samsung Bioepis Exhibit No. 1002
Page 12201

Figure 39 shows the percent survival of SCID mice injected with Tanoue cells and treated with 2F2, rituximab, or B1.

Figure 40 shows the percent survival of SCID mice injected with Daudi cells and treated with different concentrations of 2F2 or rituximab.

Figure 41 shows the percent survival of SCID mice injected with Daudi cells and treated with 11B8T or B1.

Figure 42 shows bioluminescence imaging of tumor cells in SCID mice on day 39 (31 days after treatment with 10 μg of B1, rituximab, 11B8T, 2F2T, or huIgG1). The bioluminescence is represented in red color (the dark areas in the mice) (light intensity > 50 photons per 5 min) as overlay on the black and white body image of the mice.

Figure 43 shows the tumor mass in each mouse quantified on day 25, 32, 39, and 46 following administration, on day 8, of 10 μg of B1, rituximab, 11B8T, 2F2T, or huIgG1 by integrating the light signals over the body surface.

Figures 44A-C show flow cytometric analysis of $CD20^+$ cells in peripheral blood of cynomolgus monkeys following intravenous administration of 2F2 or rituximab at different dosages, 4 x 1.25 mk/kg (A), 4 x 6.25 mg/kg (B), or 4 x 12.50 mg/kg (C).

Figures 45A-C show flow cytometric analysis of $CD21^+$ cells in peripheral blood of cynomolgus monkeys following intravenous administration of 2F2 or rituximab at different dosages, 4 x 1.25 mk/kg (A), 4 x 6.25 mg/kg (B), or 4 x 12.50 mg/kg (C).

Figures 46A-C show flow cytometric analysis of $CD20^+$ cells in lymph node of cynomolgus monkeys following intravenous administration of 2F2 or rituximab at different dosages, 4 x 1.25 mk/kg (A), 4 x 6.25 mg/kg (B), or 4 x 12.50 mg/kg (C).

Figures 47A-C show flow cytometric analysis of $CD20^{low}CD23^+CD40^{high}$ expressing cells in peripheral blood of cynomolgus monkeys following intravenous administration of 2F2 or rituximab at different dosages, 4 x 1.25 mk/kg (A), 4 x 6.25 mg/kg (B), or 4 x 12.50 mg/kg (C).

Figures 48A-E show binding of rituximab (A), 2F2 (B), 11B8 (C), B1 (D), or an isotype control antibody (E) to CHO cells expressing wild type (WT) CD20, mutant CD20 (AxP), or both WT CD20 and mutant CD20 (AxP) as determined by flow cytometry.

Figures 49A-F show percentage binding of 2F2, 11B8T, B1 or rituximab to mutant P172S vs. WT CD20 (A), percentage binding of 2F2T, 11B8T, B1, CAT (CAT 13.6E12, a mouse monoclonal IgG2A anti-CD20 antibody, Diatec.Com), a control isotype antibody (KLH) or rituximab to mutant CD20 (AxP) vs.

Samsung Bioepis Exhibit No. 1002
Page 12202

WT CD20 (B), percentage binding of 2F2, 11B8T, B1 or rituximab to mutant N166D vs. WT CD20 (C), percentage binding of 2F2T, CAT or rituximab to mutant N166D vs. WT CD20 (D) , percentage binding of 2F2T, 2F2, 11B8T, B1 or rituximab to mutant N163D vs. WT CD20 (E), and percentage binding of 2F2T, CAT or rituximab to mutant N163D vs. WT CD20 (F).

Figure 50 shows binding of 2F2T, 7D8, and isotype control antibody, as determined by ELISA, to three anti-idiotypic antibodies, anti-2F2 sab 1.1, anti-2F2 sab 1.2, and anti-2F2 sab 1.3, raised against 2F2.

Figure 51 shows binding of 11B8T, as determined by ELISA, to anti-idiotypic antibodies, anti-11B8T sab 2.2, anti-11B8T sab 2.3, anti-11B8T sab 2.4, anti-11B8T sab 2.5, and anti-11B8T sab 2.6, raised against 11B8T, but no binding to the anti-idiotypic anti-2F2 antibodies.

Figures 52A-C show dose-dependent binding of 2F2T, as determined by ELISA, to three anti-idiotypic antibodies, anti-2F2 sab 1.1 (A), anti-2F2 sab 1.2 (B), and anti-2F2 sab 1.3 (C), raised against 2F2.

Figure 53 shows the amino acid sequence (SEQ ID NO:2) of the heavy chain V region and the amino acid sequence (SEQ ID NO:4) of the light (kappa) chain V region of human monoclonal antibody 2F2 with CDR regions designated.

Figure 54 shows the nucleotide sequence (SEQ ID NO:1) of the heavy chain V region and the nucleotide sequence (SEQ ID NO:3) of the light (kappa) chain V region of human monoclonal antibody 2F2.

Figure 55 shows the amino acid sequence (SEQ ID NO:6) of the heavy chain V region and the amino acid sequence (SEQ ID NO:8) of the light (kappa) chain V region of human monoclonal antibody 7D8 with CDR regions designated.

Figure 56 shows the nucleotide sequence (SEQ ID NO:5) of the heavy chain V region and the nucleotide sequence (SEQ ID NO:7) of the light (kappa) chain V region of human monoclonal antibody 7D8.

Figure 57 shows the amino acid sequence (SEQ ID NO:10) of the heavy chain V region and the amino acid sequence (SEQ ID NO:12) of the light (kappa) chain V region of human monoclonal antibody 11B8 with CDR regions designated.

Figure 58 shows the nucleotide sequence (SEQ ID NO:9) of the heavy chain V region and the nucleotide sequence (SEQ ID NO:11) of the light (kappa) chain V region of human monoclonal antibody 11B8.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides improved antibody-based therapies for treating and diagnosing a variety of disorders involving cells expressing CD20. Therapies of the invention employ isolated human monoclonal antibodies which

Samsung Bioepis Exhibit No. 1002
Page 12203

specifically bind to an epitope present on CD20. Isolated human monoclonal antibodies encompassed by the present invention include IgA, IgG1-4, IgE, IgM, and IgD antibodies.

In one embodiment the antibody is an IgG1 antibody, more particularly an IgG1,κ or IgG1,λ isotype. In another embodiment the antibody is an IgG3 antibody, more particularly an IgG3,κ or IgG3,λ isotype. In yet another embodiment the antibody is an IgG4 antibody, more particularly an IgG4,κ or IgG4,λ isotype. In still another embodiment the antibody is an IgA1 or IgA2 antibody.

In still another embodiment the antibody is an IgM antibody.

In one embodiment, the human antibodies are produced in a non-human transgenic animal, *e.g.*, a transgenic mouse, capable of producing multiple isotypes of human monoclonal antibodies to CD20 by undergoing V-D-J recombination and isotype switching. Accordingly, aspects of the invention include not only antibodies, antibody fragments, and pharmaceutical compositions thereof, but also non-human transgenic animals, B cells, host cell transfectomas, and hybridomas which produce monoclonal antibodies. Such transgenic animal can also be a transgenic rabbit for producing polyclonal antibodies such as disclosed in US 2003/0017534. Accordingly, the invention also encompasses human polyclonal antibodies which specifically bind to CD20. In one embodiment the invention relates to polyclonal antibodies which bind to an epitope on CD20 (i) which does not comprise or require the amino acid residue proline at position 172; (ii) which does not comprise or require the amino acid residues alanine at position 170 or proline at position 172; (iii) which comprises or requires the amino acid residues asparagine at position 163 and asparagine at position 166; (iv) which does not comprise or require the amino acid residue proline at position 172, but which comprises or requires the amino acid residues asparagine at position 163 and asparagine at position 166; or (v) which does not comprise or require the amino acid residues alanine at position 170 or proline at position 172, but which comprises or requires the amino acid residues asparagine at position 163 and asparagine at position 166.

In another embodiment the invention relates to human polyclonal antibodies which have one or more of the following characteristics: (i) bind to mutant P172S CD20 (proline at position 172 mutated to serine) with at least the same affinity as to human CD20; (ii) bind to mutant AxP (alanine at position 170 mutated to serine, and proline at position 172 mutated to serine) with at least the same affinity as to human CD20; (iii) show a reduced binding of 50% or more to mutant N166D (asparagine at position 166 mutated to aspartic acid) to human CD20 at an antibody concentration of 10 μg/ml; and/or (iv) show a reduced binding of 50% or more to mutant N163D (asparagine at position 163 mutated to aspartic acid) compared to human CD20 at an antibody concentration of 10 μg/ml.

Samsung Bioepis Exhibit No. 1002
Page 12204

In yet another embodiment the invention the invention relates to human polyclonal antibodies which bind to an epitope in the small first extracellular loop of human CD20. In still another embodiment the invention also encompasses human polyclonal antibodies which bind to a discontinuous epitope on CD20. In a further embodiment the invention relates to human polyclonal antibodies which bind a discontinuous epitope on CD20, which has part of the first small extracellular loop and part of the second extracellular loop. In still a further embodiment the invention relates to human polyclonal antibodies which bind to a discontinuous epitope on CD20, which has residues AGIYAP of the small first extracellular loop and residues MESLNFIRAHTPYI of the second extracellular loop.

Methods of using the antibodies of the invention to detect a cell expressing CD20 are encompassed by the invention. Methods of using the antibodies of the invention to block or inhibit CD20 induced activities, *e.g.*, proliferative and/or differentiation activities, are also provided and are useful in the treatment of disorders associated with CD20, such as tumorigenic diseases (*e.g.*, B cell lymphoma) and autoimmune diseases (*e.g.*, RA, Chrohn's disease and Wegener's granulomatosis).

In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

The terms "CD20" and "CD20 antigen" are used interchangeably herein, and include any variants, isoforms and species homologs of human CD20 which are naturally expressed by cells or are expressed on cells transfected with the CD20 gene. Binding of an antibody of the invention to the CD20 antigen mediate the killing of cells expressing CD20 (*e.g.*, a tumor cell) by inactivating CD20. The killing of the cells expressing CD20 may occur by one or more of the following mechanisms:

complement dependent cytotoxity (CDC) of cells expressing CD20;
apoptosis of cells expressing CD20;
effector cell phagocytosis of cells expressing CD20; or
effector cell antibody dependent cellular cytotoxicity (ADCC) of cells expressing CD20.

Synonyms of CD20, as recognized in the art, include B-lymphocyte antigen CD20, B-lymphocyte surface antigen B1, Leu-16, Bp35, BM5, and LF5.

As used herein, the term "inhibits growth" (*e.g.*, referring to cells) is intended to include any measurable decrease in the cell growth when contacted with an anti-CD20 antibody as compared to the growth of the same cells not in contact with an anti-CD20 antibody, *e.g.*, the inhibition of growth of a cell culture by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 99%, or 100%. Such a decrease in cell

Samsung Bioepis Exhibit No. 1002
Page 12205

growth can occur by a variety of mechanisms, *e.g.*, effector cell phagocytosis, ADCC, CDC, and/or apoptosis.

The term "raft" refers to the sphingolipid- and cholesterol-rich membrane microdomains located in the outer leaflet area of the plasma membrane of a cell. The ability of certain proteins to associate within such domains can effect the protein's function. For example, the translocation of CD20 molecules into lipid rafts, after being bound by human antibodies of the present invention, creates a high density of CD20 antigen-antibody complexes in the plasma membranes. Such a high density of CD20 antigen-antibody complexes can enable efficient activation of the complement system during CDC.

The term "antibody" as referred to herein includes whole antibodies and any antigen binding fragment (*i.e.*, "antigen-binding portion") or single chain thereof. An "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (Clq) of the classical complement system.

The term "antigen-binding portion" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, CD20). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) *Nature* 341:544-546), which consists of a V_H domain; (vi) an isolated complementarity determining region (CDR), and (vii) a combination of two or more

Samsung Bioepis Exhibit No. 1002
Page 12206

isolated CDRs which may optionally be joined by a synthetic linker. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); *see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883).* Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. A further example is binding-domain immunoglobulin fusion proteins comprising (i) a binding domain polypeptide that is fused to an immunoglobulin hinge region polypeptide, (ii) an immunoglobulin heavy chain CH2 constant region fused to the hinge region, and (iii) an immunoglobulin heavy chain CH3 constant region fused to the CH2 constant region. The binding domain polypeptide can be a heavy chain variable region or a light chain variable region. The binding-domain immunoglobulin fusion proteins are further disclosed in US 2003/0118592 and US 2003/0133939. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

The term "epitope" means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and nonconformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

The term "discontinuous epitope," as used herein, means a conformational epitope on a protein antigen which is formed from at least two separate regions in the primary sequence of the protein.

The term "bispecific molecule" is intended to include any agent, *e.g.*, a protein, peptide, or protein or peptide complex, which has two different binding specificities. For example, the molecule may bind to, or interact with, (a) a cell surface antigen and (b) an Fc receptor on the surface of an effector cell. The term "multispecific molecule" or "heterospecific molecule" is intended to include any agent, *e.g.*, a protein, peptide, or protein or peptide complex, which has more than two different binding specificities. For example, the molecule may bind to, or interact with, (a) a cell surface antigen, (b) an Fc receptor on the surface of an effector cell, and (c) at least one other component. Accordingly, the invention includes, but is not limited to, bispecific, trispecific, tetraspecific, and other multispecific molecules which are directed to cell

Samsung Bioepis Exhibit No. 1002
Page 12207

surface antigens, such as CD20, and to other targets, such as Fc receptors on effector cells.

The term "bispecific antibodies" also includes diabodies. Diabodies are bivalent, bispecific antibodies in which the V_H and V_L domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see *e.g.*, Holliger, P., *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Poljak, R.J., *et al.* (1994) *Structure* 2:1121-1123).

The term "human antibody derivatives" refers to any modified form of the antibody, *e.g.*, a conjugate of the antibody and another agent or antibody.

As used herein, a human antibody is "derived from" a particular germline sequence if the antibody is obtained from a system using human immunoglobulin sequences, *e.g.*, by immunizing a transgenic mouse carrying human immunoglobulin genes or by screening a human immunoglobulin gene library, and wherein the selected human antibody is at least 90%, more preferably at least 95%, even more preferably at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a human antibody derived from a particular human germline sequence will display no more than 10 amino acid differences, more preferably, no more than 5, or even more preferably, no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

As used herein, the term "heteroantibodies" refers to two or more antibodies, derivatives therefrom, or antigen binding regions linked together, at least two of which have different specificities. These different specificities include a binding specificity for an Fc receptor on an effector cell, and a binding specificity for an antigen or epitope on a target cell, *e.g.*, a tumor cell.

The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

Samsung Bioepis Exhibit No. 1002
Page 12208

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Accordingly, the term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable and constant regions derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic or transchromosomal non-human animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further in Section I, below), (b) antibodies isolated from a host cell transformed to express the antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

The term "transfectoma", as used herein, includes recombinant eukaryotic host cell expressing the antibody, such as CHO cells, NS/0 cells, HEK293 cells, plant cells, or fungi, including yeast cells .

As used herein, a "heterologous antibody" is defined in relation to the transgenic non-human organism producing such an antibody. This term refers to an antibody having an amino acid sequence or an encoding nucleic acid sequence corresponding to that found in an organism not consisting of the transgenic non-human animal, and generally from a species other than that of the transgenic non-human animal.

As used herein, a "heterohybrid antibody" refers to an antibody having a light and heavy chains of different organismal origins. For example, an antibody having a human heavy chain associated with a murine light chain is a heterohybrid antibody.

Samsung Bioepis Exhibit No. 1002
Page 12209

Examples of heterohybrid antibodies include chimeric and humanized antibodies, discussed supra.

An "isolated antibody," as used herein, is intended to refer to an antibody which is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds to CD20 is substantially free of antibodies that specifically bind antigens other than CD20). An isolated antibody that specifically binds to an epitope, isoform or variant of human CD20 may, however, have cross-reactivity to other related antigens, *e.g.*, from other species (*e.g.*, CD20 species homologs). Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals. In one embodiment of the invention, a combination of "isolated" monoclonal antibodies having different specificities are combined in a well defined composition.

As used herein, "specific binding" refers to antibody binding to a predetermined antigen. Typically, the antibody binds with an affinity corresponding to a K_D of about 1 x 10^{-7} M or less, and binds to the predetermined antigen with an affinity corresponding to a K_D that is at least two orders of magnitude lower than its affinity for binding to a non-specific antigen (*e.g.*, BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "an antibody recognizing an antigen" and " an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen".

As used herein, the term "k_d" (sec^{-1}), as used herein, is intended to refer to the dissociation rate constant of a particular antibody-antigen interaction. Said value is also referred to as the k_{off} value.

The term "k_a" (M^{-1} x sec^{-1}), as used herein, is intended to refer to the association rate constant of a particular antibody-antigen interaction.

The term "K_D" (M), as used herein, is intended to refer to the dissociation equilibrium constant of a particular antibody-antigen interaction.

The term "K_A" (M^{-1}), as used herein, is intended to refer to the association equilibrium constant of a particular antibody-antigen interaction and is obtained by dividing the k_a by the k_d.

As used herein, "isotype" refers to the antibody class (*e.g.*, IgM or IgGl) that is encoded by heavy chain constant region genes.

As used herein, "isotype switching" refers to the phenomenon by which the class, or isotype, of an antibody changes from one Ig class to one of the other Ig classes.

As used herein, "nonswitched isotype" refers to the isotypic class of heavy chain that is produced when no isotype switching has taken place; the CH gene encoding the nonswitched isotype is typically the first CH gene immediately

Samsung Bioepis Exhibit No. 1002
Page 12210

downstream from the functionally rearranged VDJ gene. Isotype switching has been classified as classical or non-classical isotype switching. Classical isotype switching occurs by recombination events which involve at least one switch sequence region in the transgene. Non-classical isotype switching may occur by, for example, homologous recombination between human σ_μ and human $\sum_\mu$ (δ-associated deletion). Alternative non-classical switching mechanisms, such as intertransgene and/or interchromosomal recombination, among others, may occur and effectuate isotype switching.

As used herein, the term "switch sequence" refers to those DNA sequences responsible for switch recombination. A "switch donor" sequence, typically a μ switch region, will be 5' (*i.e.*, upstream) of the construct region to be deleted during the switch recombination. The "switch acceptor" region will be between the construct region to be deleted and the replacement constant region (*e.g.*, γ, ε, etc.). As there is no specific site where recombination always occurs, the final gene sequence will typically not be predictable from the construct.

As used herein, "glycosylation pattern" is defined as the pattern of carbohydrate units that are covalently attached to a protein, more specifically to an immunoglobulin (antibody) protein. A glycosylation pattern of a heterologous antibody can be characterized as being substantially similar to glycosylation patterns which occur naturally on antibodies produced by the species of the non-human transgenic animal, when one of ordinary skill in the art would recognize the glycosylation pattern of the heterologous antibody as being more similar to said pattern of glycosylation in the species of the non-human transgenic animal than to the species from which the CH genes of the transgene were derived.

The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally-occurring.

The term "rearranged" as used herein refers to a configuration of a heavy chain or light chain immunoglobulin locus wherein a V segment is positioned immediately adjacent to a D-J or J segment in a conformation encoding essentially a complete V_H or V_L domain, respectively. A rearranged immunoglobulin (antibody) gene locus can be identified by comparison to germline DNA; a rearranged locus will have at least one recombined heptamer/nonamer homology element.

The term "unrearranged" or "germline configuration" as used herein in reference to a V segment refers to the configuration wherein the V segment is not recombined so as to be immediately adjacent to a D or J segment.

Samsung Bioepis Exhibit No. 1002
Page 12211

The term "nucleic acid molecule", as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

The term "isolated nucleic acid molecule," as used herein in reference to nucleic acids encoding whole antibodies or antibody portions (*e.g.*, V_H, V_L, CDR3) that bind to CD20, is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the intact antibody or antibody portion are free of other nucleotide sequences encoding whole antibodies or antibody portions that bind antigens other than CD20, which other sequences may naturally flank the nucleic acid in human genomic DNA. In one embodiment, the human anti-CD20 antibody includes the nucleotide or amino acid sequence of 2F2, 7D8, or 11B8, as well as heavy chain (V_H) and light chain (V_L) variable regions having the sequences shown in SEQ ID NOs: 1, 5, or 9, and SEQ ID NOs: 3, 7, or 11, respectively.

As disclosed and claimed herein, the sequences set forth in SEQ ID NOs: 1-30 include "conservative sequence modifications," *i.e.*, nucleotide and amino acid sequence modifications which do not significantly affect or alter the binding characteristics of the antibody encoded by the nucleotide sequence or containing the amino acid sequence. Such conservative sequence modifications include nucleotide and amino acid substitutions, additions and deletions. Modifications can be introduced into SEQ ID NOs:1-30 by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions include ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a human anti-CD20 antibody is preferably replaced with another amino acid residue from the same side chain family.

The present invention also encompasses "derivatives" of the amino acid sequences as set forth in SEQ ID NOs: 1-30 and conservative sequence modifications thereof, wherein one or more of the amino acid residues have been derivatised, *e.g.*, by acylation or glycosylation, without significantly affecting or altering the binding characteristics of the antibody containing the amino acid sequences.

Samsung Bioepis Exhibit No. 1002
Page 12212

Furthermore, the present invention comprises antibodies in which alterations have been made in the Fc region in order to change the functional or pharmacokinetic properties of the antibodies. Such alterations may result in a decrease or increase of C1q binding and CDC or of FcγR binding and ADCC. Substitutions can, for example, be made in one or more of the amino acid residues at positions 234, 235, 236, 237, 297, 318, 320 and 322 of the heavy chain constant region, thereby causing an alteration in an effector function while retaining the ability to bind to the antigen as compared with the unmodified antibody, cf. US 5,624,821 and US 5,648,260.

The *in vivo* half-life of the antibodies can also be improved by modifying the salvage receptor epitope of the Ig constant domain or an Ig-like constant domain such that the molecule does not comprise an intact CH2 domain or an intact Ig Fc region, cf. US 6,121,022 and US 6,194,551. The *in vivo* half-life can furthermore be increased by making mutations in the Fc region, *e.g.*, by substituting threonine for leucine at position 252, by substituting threonine for serine at position 254, or by substituting threonine for phenylalanine at position 256, cf. US 6,277,375.

Furthermore, the glycosylation pattern of the antibodies can be modified in order to change the effector function of the antibodies. For example, the antibodies can be expressed in a transfectoma which does not add the fucose unit normally attached to Asn at position 297 of the Fc region in order to enhance the affinity of the Fc region for FcγRIII which, in turn, will result in an increased ADCC of the antibodies in the presence of NK cells, cf. Shield *et al.* (2002) *JBC*, 277:26733. Furthermore, modification of galactosylation can be made in order to modify CDC.

Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a anti-CD20 antibody coding sequence, such as by saturation mutagenesis, and the resulting modified anti-CD20 antibodies can be screened for binding activity.

Accordingly, antibodies encoded by the (heavy and light chain variable region) nucleotide sequences disclosed herein and/or containing the (heavy and light chain variable region) amino acid sequences disclosed herein (*i.e.*, SEQ ID NOs: 1-30) include substantially similar antibodies encoded by or containing similar sequences which have been conservatively modified. Further discussion as to how such substantially similar antibodies can be generated based on the partial (*i.e.*, heavy and light chain variable regions) sequences disclosed herein as SEQ ID Nos:1-30 is provided below.

For nucleic acids, the term "substantial homology" indicates that two nucleic acids, or designated sequences thereof, when optimally aligned and compared, are identical, with appropriate nucleotide insertions or deletions, in at least about 80% of the nucleotides, usually at least about 90% to 95%, and more preferably at least about

Samsung Bioepis Exhibit No. 1002
Page 12213

98% to 99.5% of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to the complement of the strand.

For nucleotide and amino acid sequences, the term "homology" indicates the degree of identity between two nucleic acid or amino acid sequences when optimally aligned and compared with appropriate insertions or deletions. Alternatively, substantial homology exists when the DNA segments will hybridize under selective hybridization conditions, to the complement of the strand.

The percent identity between two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % homology = # of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between two nucleotide or amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (*Comput. Appl. Biosci.*, 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (*J. Mol. Biol.* 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*,

Samsung Bioepis Exhibit No. 1002
Page 12214

(1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov.

The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form. A nucleic acid is "isolated" or "rendered substantially pure" when purified away from other cellular components or other contaminants, *e.g.*, other cellular nucleic acids or proteins, by standard techniques, including alkaline/SDS treatment, CsCl banding, column chromatography, agarose gel electrophoresis and others well known in the art. *See*, F. Ausubel, *et al.*, ed. Current Protocols in Molecular Biology, Greene Publishing and Wiley Interscience, New York (1987).

The nucleic acid compositions of the present invention, while often in a native sequence (except for modified restriction sites and the like), from either cDNA, genomic or mixtures thereof, may be mutated in accordance with standard techniques to provide gene sequences. For coding sequences, these mutations, may affect amino acid sequence as desired. In particular, DNA sequences substantially homologous to or derived from native V, D, J, constant, switches and other such sequences described herein are contemplated (where "derived" indicates that a sequence is identical or modified from another sequence).

A nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For instance, a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. With respect to transcription of regulatory sequences, operably linked means that the DNA sequences being linked are contiguous and, where necessary to join two protein coding regions, contiguous and in reading frame. For switch sequences, operably linked indicates that the sequences are capable of effecting switch recombination.

The term "vector," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors").

Samsung Bioepis Exhibit No. 1002
Page 12215

In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein. Recombinant host cells include, for example, transfectomas, such as CHO cells, NS/0 cells, and lymphocytic cells.

As used herein, the term "subject" includes any human or non-human animal. The term "non-human animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, etc.

The terms "transgenic, non-human animal" refers to a non-human animal having a genome comprising one or more human heavy and/or light chain transgenes or transchromosomes (either integrated or non-integrated into the animal's natural genomic DNA) and which is capable of expressing fully human antibodies. For example, a transgenic mouse can have a human light chain transgene and either a human heavy chain transgene or human heavy chain transchromosome, such that the mouse produces human anti-CD20 antibodies when immunized with CD20 antigen and/or cells expressing CD20. The human heavy chain transgene can be integrated into the chromosomal DNA of the mouse, as is the case for transgenic, *e.g.*, HuMAb mice, such as HCo7 or HCo12 mice, or the human heavy chain transgene can be maintained extrachromosomally, as is the case for transchromosomal (*e.g.*, KM) mice as described in WO 02/43478. Such transgenic and transchromosomal mice are capable of producing multiple isotypes of human monoclonal antibodies to CD20 (*e.g.*, IgG, IgA and/or IgE) by undergoing V-D-J recombination and isotype switching.

Various aspects of the invention are described in further detail in the following subsections.

Samsung Bioepis Exhibit No. 1002
Page 12216

I. Production of Human Antibodies to CD20

Human monoclonal antibodies of the invention can be produced by a variety of techniques, including conventional monoclonal antibody methodology, *e.g.*, the standard somatic cell hybridization technique of Kohler and Milstein, *Nature* 256: 495 (1975). Although somatic cell hybridization procedures are preferred, in principle, other techniques for producing monoclonal antibody can be employed, *e.g.*, viral or oncogenic transformation of B-lymphocytes or phage display techniques using libraries of human antibody genes.

The preferred animal system for preparing hybridomas that secrete human monoclonal antibodies is the murine system. Hybridoma production in the mouse is a very well established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. Fusion partners (*e.g.*, murine myeloma cells) and fusion procedures are also known.

In a preferred embodiment, human monoclonal antibodies directed against CD20 can be generated using transgenic or transchromosomal mice carrying parts of the human immune system rather than the mouse system. These transgenic and transchromosomic mice include mice referred to herein as HuMAb mice and KM mice, respectively, and are collectively referred to herein as "transgenic mice."

The HuMAb mouse contains a human immunoglobulin gene miniloci that encodes unrearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous μ and κ chain loci (Lonberg, N. *et al.* (1994) *Nature* 368 (6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ and in response to immunization, the introduced human heavy and light chain transgenes, undergo class switching and somatic mutation to generate high affinity human IgG κ monoclonal antibodies (Lonberg, N. *et al.* (1994), supra; reviewed in Lonberg, N. (1994) *Handbook of Experimental Pharmacology* 113:49-101; Lonberg, N. and Huszar, D. (1995) *Intern. Rev. Immunol.* Vol. 13: 65-93, and Harding, F. and Lonberg, N. (1995) *Ann. N.Y. Acad. Sci* 764: 536-546). The preparation of HuMAb mice is described in detail in Taylor, L. *et al.* (1992) *Nucleic Acids Research* 20:6287-6295; Chen, J. et al (1993) *International Immunology* 5: 647-656; Tuaillon *et al.* (1994) *J. Immunol.* 152:2912-2920; Lonberg *et al.*, (1994) *Nature* 368(6474): 856-859; Lonberg, N. (1994) *Handbook of Experimental Pharmacology* 113:49-101; Taylor, L. *et al.* (1994) *International Immunology* 6: 579-591; Lonberg, N. and Huszar, D. (1995) *Intern. Rev. Immunol.* Vol. 13:65-93; Harding, F. and Lonberg, N. (1995) *Ann. N.Y. Acad. Sci* 764:536-546; Fishwild, D. *et al.* (1996) *Nature Biotechnology* 14:845-851. See further, US Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; all to Lonberg and Kay, as well as US 5,545,807 to Surani *et al.*; WO

Samsung Bioepis Exhibit No. 1002
Page 12217

98/24884, WO 94/25585, WO 93/1227, WO 92/22645, WO 92/03918 and WO 01/09187.

The KM mouse contains a human heavy chain transchromosome and a human kappa light chain transgene. The endogenous mouse heavy and light chain genes also have been disrupted in the KM mice such that immunization of the mice leads to production of human immunoglobulins rather than mouse immunoglobulins. Construction of KM mice and their use to raise human immunoglobulins is described in detail in WO 02/43478.

Immunizations

To generate fully human monoclonal antibodies to CD20, transgenic or transchromosomal mice containing human immunoglobulin genes (*e.g.*, HCo12, HCo7 or KM mice) can be immunized with an enriched preparation of CD20 antigen and/or cells expressing CD20, as described, for example, by Lonberg *et al.* (1994), supra; Fishwild *et al.* (1996), *supra*, and WO 98/24884. Alternatively, mice can be immunized with DNA encoding human CD20. Preferably, the mice will be 6-16 weeks of age upon the first infusion. For example, an enriched preparation (5-50 μg) of the CD20 antigen can be used to immunize the HuMAb mice intraperitoneally. In the event that immunizations using a purified or enriched preparation of the CD20 antigen do not result in antibodies, mice can also be immunized with cells expressing CD20, *e.g.*, a cell line, to promote immune responses.

Cumulative experience with various antigens has shown that the HuMAb transgenic mice respond best when initially immunized intraperitoneally (IP) or subcutaneously (SC) with CD20 expressing cells in complete Freund's adjuvant, followed by every other week IP immunizations (up to a total of 10) with CD20 expressing cells in PBS. The immune response can be monitored over the course of the immunization protocol with plasma samples being obtained by retroorbital bleeds. The plasma can be screened by FACS analysis (as described below), and mice with sufficient titers of anti-CD20 human immunoglobulin can be used for fusions. Mice can be boosted intravenously with CD20 expressing cells 3 days before sacrifice and removal of the spleen.

Generation of Hybridomas Producing Human Monoclonal Antibodies to CD20

To generate hybridomas producing human monoclonal antibodies to human CD20, splenocytes and lymph node cells from immunized mice can be isolated and fused to an appropriate immortalized cell line, such as a mouse myeloma cell line. The resulting hybridomas can then be screened for the production of antigen-specific antibodies. For example, single cell suspensions of splenic lymphocytes from

Samsung Bioepis Exhibit No. 1002
Page 12218

immunized mice can be fused to SP2/0-Ag8.653 nonsecreting mouse myeloma cells (ATCC, CRL 1580) with 50% PEG (w/v). Cells can be plated at approximately 1 x 10^5 per well in flat bottom microtiter plate, followed by a two week incubation in selective medium containing besides usual reagents 10% fetal Clone Serum, 5-10% origen hybridoma cloning factor (IGEN) and 1X HAT (Sigma). After approximately two weeks, cells can be cultured in medium in which the HAT is replaced with HT. Individual wells can then be screened by ELISA for human kappa-light chain containing antibodies and by FACS analysis using CD20 expressing cells for CD20 specificity. Once extensive hybridoma growth occurs, medium can be observed usually after 10-14 days. The antibody secreting hybridomas can be replated, screened again, and if still positive for human IgG, anti-CD20 monoclonal antibodies can be subcloned at least twice by limiting dilution. The stable subclones can then be cultured *in vitro* to generate antibody in tissue culture medium for characterization.

Generation of Transfectomas Producing Human Monoclonal Antibodies to CD20

Human antibodies of the invention also can be produced in a host cell transfectoma using, for example, a combination of recombinant DNA techniques and gene transfection methods as is well known in the art (Morrison, S. (1985) Science 229:1202).

For example, in one embodiment, the gene(s) of interest, *e.g.*, human antibody genes, can be ligated into an expression vector such as a eukaryotic expression plasmid such as used by the GS gene expression system disclosed in WO 87/04462, WO 89/01036 and EP 338 841 or other expression systems well known in the art. The purified plasmid with the cloned antibody genes can be introduced in eukaryotic host cells such as CHO cells, NS/0 cells or HEK293 cells or alternatively other eukaryotic cells like a plant derived cells, fungi or yeast cells. The method used to introduce these genes could be methods described in the art such as electroporation, lipofectine, lipofectamine or other. After introducing these antibody genes in the host cells, cells expressing the antibody can be identified and selected. These cells represent the transfectomas which can then be amplified for their expression level and upscaled to produce antibodies. Recombinant antibodies can be isolated and purified from these culture supernatants and/or cells.

Further Recombinant Means for Producing Human Monoclonal Antibodies to CD20

Alternatively, the cloned antibody genes can be expressed in other expression systems, including prokaryotic cells, such as microorganisms, such as *E. coli*, for the production of single chain Fv antibodies, algi, as well as insect cells. Furthermore, the antibodies can be produced in transgenic non-human animals, such as

Samsung Bioepis Exhibit No. 1002
Page 12219

in milk from sheep and rabbits or in eggs from hens, or in transgenic plants. See *e.g.* Verma, R., *et al.* (1998). Antibody engineering: Comparison of bacterial, yeast, insect and mammalian expression systems. *J.Immunol.Meth.* 216:165-181; Pollock, *et al.* (1999). Transgenic milk as a method for the production of recombinant antibodies. *J.Immunol.Meth.* 231:147-157; and Fischer, R., *et al.* (1999). Molecular farming of recombinant antibodies in plants. *Biol.Chem.* 380:825-839.

Use of Partial Antibody Sequences to Express Intact Antibodies

Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties (see, *e.g.*, Riechmann, L. *et al.* (1998) *Nature* 332:323-327; Jones, P. *et al.* (1986) *Nature* 321:522-525; and Queen, C. *et al.* (1989) *Proc. Natl. Acad. Sci.*. U.S.A. 86:10029-10033). Such framework sequences can be obtained from public DNA databases that include germline antibody gene sequences. These germline sequences will differ from mature antibody gene sequences because they will not include completely assembled variable genes, which are formed by V(D)J joining during B cell maturation. Germline gene sequences will also differ from the sequences of a high affinity secondary repertoire antibody at individual evenly across the variable region. For example, somatic mutations are relatively infrequent in the amino terminal portion of framework region 1 and in the carboxy-terminal portion of framework region 4. Furthermore, many somatic mutations do not significantly alter the binding properties of the antibody. For this reason, it is not necessary to obtain the entire DNA sequence of a particular antibody in order to recreate an intact recombinant antibody having binding properties similar to those of the original antibody (see WO 99/45962). Partial heavy and light chain sequence spanning the CDR regions is typically sufficient for this purpose. The partial sequence is used to determine which germline variable and joining gene segments contributed to the recombined antibody variable genes. The germline sequence is then used to fill in missing portions of the variable regions. Heavy and light chain leader sequences are cleaved during protein maturation and do not contribute to the properties of the final antibody. To add missing sequences, cloned cDNA sequences can be combined with synthetic oligonucleotides by ligation or PCR amplification. Alternatively, the entire variable

Samsung Bioepis Exhibit No. 1002
Page 12220

region can be synthesized as a set of short, overlapping, oligonucleotides and combined by PCR amplification to create an entirely synthetic variable region clone. This process has certain advantages such as elimination or inclusion or particular restriction sites, or optimization of particular codons.

The nucleotide sequences of heavy and light chain transcripts from hybridomas are used to design an overlapping set of synthetic oligonucleotides to create synthetic V sequences with identical amino acid coding capacities as the natural sequences. The synthetic heavy and kappa chain sequences can differ from the natural sequences in three ways: strings of repeated nucleotide bases are interrupted to facilitate oligonucleotide synthesis and PCR amplification; optimal translation initiation sites are incorporated according to Kozak's rules (Kozak, 1991, J. Biol. Chem. 266:19867-19870); and HindIII sites are engineered upstream of the translation initiation sites.

For both the heavy and light chain variable regions, the optimized coding and corresponding non-coding, strand sequences are broken down into 30 - 50 nucleotides approximately at the midpoint of the corresponding non-coding oligonucleotide. Thus, for each chain, the oligonucleotides can be assembled into overlapping double stranded sets that span segments of 150 - 400 nucleotides. The pools are then used as templates to produce PCR amplification products of 150 - 400 nucleotides. Typically, a single variable region oligonucleotide set will be broken down into two pools which are separately amplified to generate two overlapping PCR products. These overlapping products are then combined by PCR amplification to form the complete variable region. It may also be desirable to include an overlapping fragment of the heavy or light chain constant region (including the BbsI site of the kappa light chain, or the AgeI site if the gamma heavy chain) in the PCR amplification to generate fragments that can easily be cloned into the expression vector constructs.

The reconstructed heavy and light chain variable regions are then combined with cloned promoter, leader sequence, translation initiation, constant region, 3' untranslated, polyadenylation, and transcription termination, sequences to form expression vector constructs. The heavy and light chain expression constructs can be combined into a single vector, co-transfected, serially transfected, or separately transfected into host cells which are then fused to form a host cell expressing both chains.

Plasmids for use in construction of expression vectors for human IgGκ are described below. The plasmids were constructed so that PCR amplified V heavy and V kappa light chain cDNA sequences could be used to reconstruct complete heavy and light chain minigenes. These plasmids can be used to express completely human, or chimeric IgG1,κ or IgG4,κ antibodies. Similar plasmids can be constructed for

Samsung Bioepis Exhibit No. 1002
Page 12221

expression of other heavy chain isotypes, or for expression of antibodies comprising lambda light chains.

Thus, in another aspect of the invention, the structural features of the human anti-CD20 antibodies of the invention, *e.g.*, 11B8, 2F2, or 7D8, are used to create structurally related human anti-CD20 antibodies that retain at least one functional property of the antibodies of the invention, such as binding to CD20. More specifically, one or more CDR regions of 2F2, 7D8, or 11B8 can be combined recombinantly with known human framework regions and CDRs to create additional, recombinantly-engineered, human anti-CD20 antibodies of the invention.

Accordingly, in another embodiment, the invention provides a method for preparing an anti-CD20 antibody comprising:

preparing an antibody comprising (1) human heavy chain framework regions and human heavy chain CDRs, wherein at least one of the human heavy chain CDRs comprises an amino acid sequence selected from the amino acid sequences of CDRs shown in Figures 53, 55, or 57 (or corresponding amino acid residues in SEQ ID NOs:13-15, 19-21, or 25-27); and (2) human light chain framework regions and human light chain CDRs, wherein at least one of the human light chain CDRs comprises an amino acid sequence selected from the amino acid sequences of CDRs shown in Figures 53, 55, or 57 (or corresponding amino acid residues in SEQ ID NOs: 16-18, 22-24, or 28-30); wherein the antibody retains the ability to bind to CD20.

The ability of the antibody to bind CD20 can be determined using standard binding assays, such as those set forth in the Examples (*e.g.*, a FACS analysis).

Since it is well known in the art that antibody heavy and light chain CDR3 domains play a particularly important role in the binding specificity/affinity of an antibody for an antigen, the recombinant antibodies of the invention prepared as set forth above preferably comprise the heavy and light chain CDR3s of 2F2, 7D8, or 11B8. The antibodies further can comprise the CDR2s of 2F2, 7D8, or 11B8. The antibodies further can comprise the CDR1s of 2F2, 7D8, or 11B8. Accordingly, the invention further provides anti-CD20 antibodies comprising: (1) human heavy chain framework regions, a human heavy chain CDR1 region, a human heavy chain CDR2 region, and a human heavy chain CDR3 region, wherein the human heavy chain CDR3 region is the CDR3 of 2F2, 7D8, or 11B8 as shown in Figures 53, 55, or 57 (or corresponding amino acid residues as shown in SEQ ID NOs: 15, 21, or 27); and (2) human light chain framework regions, a human light chain CDR1 region, a human light chain CDR2 region, and a human light chain CDR3 region, wherein the human light chain CDR3 region is the CDR3 of 2F2, 7D8, or 11B8 as shown in Figures 53, 55, or 57 (or corresponding amino acid residues as shown in SEQ ID NOs:18, 24, or 30), wherein the antibody binds CD20. The antibody may further comprise the heavy chain CDR2 and/or

Samsung Bioepis Exhibit No. 1002
Page 12222

the light chain CDR2 of 2F2, 7D8, or 11B8. The antibody may further comprise the heavy chain CDR1 and/or the light chain CDR1 of 2F2, 7D8, or 11B8.

Preferably, the CDR1, 2, and/or 3 of the engineered antibodies described above comprise the exact amino acid sequence(s) as those of 2F2, 7D8, or 11B8 disclosed herein. However, the ordinarily skilled artisan will appreciate that some deviation from the exact CDR sequences of 2F2, 7D8, or 11B8 may be possible while still retaining the ability of the antibody to bind CD20 effectively (*e.g.*, conservative substitutions). Accordingly, in another embodiment, the engineered antibody may be composed of one or more CDRs that are, for example, 90%, 95%, 98% or 99.5% identical to one or more CDRs of 2F2, 7D8, or 11B8.

In addition to simply binding CD20, engineered antibodies such as those described above may be selected for their retention of other functional properties of antibodies of the invention, such as:

(1) low dissociation rate from CD20;

(2) high affinity binding to CD20;

(3) binding to a unique epitope on CD20, and/or binding in a specific orientation to CD20, and/or binding to a specific form of CD20;

(4) mediation of a high level of CDC on either CD55/59 negative or CD55/59 positive cells;

(5) translocation into lipid rafts upon binding to CD20;

(6) inhibition of the growth of cells which express CD20;

(7) inducement of apoptosis of cells which express CD20;

(8) inducement of homotypic adhesion of cells which express CD20;

(9) prolonged survival of a subject having tumor cells which express CD20;

(10) mediation of ADCC of CD20 targets when mixed with appropriate effector cells;

(11) ability to deplete cells which express CD20; and/or

(12) ability to deplete cells which express low levels of CD20 ($CD20^{low}$ cells).

Characterization of Binding of Human Monoclonal Antibodies to CD20

To purify human anti-CD20 antibodies, selected hybridomas can be grown in two-liter spinner-flasks for monoclonal antibody purification. Supernatants can be filtered and concentrated before affinity chromatography with protein A-sepharose (for IgG1 isotype antibodies) (Pharmacia, Piscataway, NJ) or anti-human IgG coated sepharose or protein G-sepharose in case of IgG3 isotype antibodies. Eluted IgG can be checked by gel electrophoresis and high performance liquid chromatography to

Samsung Bioepis Exhibit No. 1002
Page 12223

ensure purity. The buffer solution can be exchanged into PBS, and the concentration can be determined by OD_{280} using 1.43 extinction coefficient. The monoclonal antibodies can be aliquoted and stored at -80 °C.

To determine if the selected human anti-CD20 monoclonal antibodies bind to unique epitopes, site-directed or multi-site directed mutagenesis can be used.

To determine the isotype of purified antibodies, isotype ELISAs can be performed. Wells of microtiter plates can be coated with 10 μg/ml of anti-human Ig overnight at 4 °C. After blocking with 5% BSA, the plates are reacted with 10 μg/ml of monoclonal antibodies or purified isotype controls, at ambient temperature for two hours. The wells can then be reacted with either human IgGl, IgG2, IgG3 or IgG4 or human IgM-specific alkaline phosphatase-conjugated probes. After washing, the plates are developed with pNPP substrate (1 mg/ml) and analyzed at OD of 405-650.

In order to demonstrate presence of anti-CD20 antibodies in sera of immunized mice or binding of monoclonal antibodies to live cells expressing the CD20, flow cytometry can be used. Briefly, cell lines expressing CD20 (grown under standard growth conditions) are mixed with various concentrations of monoclonal antibodies in PBS containing 0.1% BSA and 0.02% sodium-azide, and incubated at 4 °C for 30 min. After washing, the cells are reacted with fluorescein-labeled anti-human IgG antibody under the same conditions as the primary antibody staining. The samples can be analyzed by flow cytometry with a FACS instrument using light and side scatter properties to gate on single, living cells. An alternative assay using fluorescence microscopy may be used (in addition to or instead of) the flow cytometry assay. Cells can be stained exactly as described above and examined by fluorescence microscopy. This method allows visualization of individual cells, but may have diminished sensitivity depending on the density of the antigen.

Anti-CD20 human IgGs can be further tested for reactivity with CD20 antigen by Western blotting. Briefly, cell extracts from cells expressing CD20 can be prepared and subjected to sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis. After electrophoresis, the separated antigens will be transferred to nitrocellulose membranes, blocked with 20% mouse serum, and probed with the monoclonal antibodies to be tested. Human IgG binding can be detected using anti-human IgG alkaline phosphatase and developed with BCIP/NBT substrate tablets (Sigma Chem. Co., St. Louis, MO).

Phagocytic and Cell Killing Activities of Human Monoclonal Antibodies to CD20

In addition to binding specifically to CD20, human monoclonal anti-CD20 antibodies can be tested for their ability to mediate phagocytosis and killing of cells expressing CD20. The testing of monoclonal antibody activity *in vitro* will provide

Samsung Bioepis Exhibit No. 1002
Page 12224

an initial screening prior to testing *in vivo* models. Briefly, polymorphonuclear cells (PMNs), NK cells, monocytes or other effector cells, from healthy donors can be purified by Ficoll Hypaque density centrifugation, followed by lysis of contaminating erythrocytes. Washed PMNs, can be suspended in RPMI supplemented with 10% heat-inactivated fetal calf serum and mixed with ^{51}Cr labeled cells expressing CD20, at various ratios of effector cells to tumor cells (-effector cells:tumor cells). Purified human anti-CD20 IgGs can then be added at various concentrations. Irrelevant human IgG can be used as negative control. Assays can be carried out for 4 to 20 hours at 37 °C depending on the effector cell type used. Samples can be assayed for cytolysis by measuring ^{51}Cr release into the culture supernatant. Anti-CD20 monoclonal antibodies can also be tested in combinations with each other to determine whether cytolysis is enhanced with multiple monoclonal antibodies.

Human monoclonal antibodies which bind to CD20 also can be tested in an *in vivo* model (*e.g.*, in mice) to determine their efficacy in controlling growth of CD20-expressing tumor cells. These antibodies can be selected, for example, based on the following criteria, which are not intended to be exclusive:

1. binding to live cells expressing CD20;
2. low dissociation rate from CD20;
3. high affinity of binding to CD20;
4. binding to a unique epitope on CD20; and/or binding in a specific orientation to CD20, and/or binding to a specific form of CD20;
5. opsonization of cells expressing CD20;
6. mediation of growth inhibition, phagocytosis and/or killing of cells expressing CD20 in the presence of human effector cells;
7. ability to induce CDC on either CD55/CD59 negative or positive cells;
8. ability to induce homotypic adhesion;
9. ability to induce translocation into lipid rafts upon binding to CD20;
10. ability to induce apoptosis;
11. ability to induce ADCC on cells expressing CD20;
12. ability to deplete cells which express CD20; and/or
13. ability to deplete cells which express low levels of CD20 ($CD20^{low}$ cells).

Preferred human monoclonal antibodies of the invention meet one or more of these criteria.

Human monoclonal anti-CD20 antibodies can be tested for their ability to mediate CDC using a variety of known techniques. For example, serum for complement can be obtained from the blood of healthy subjects which can be centrifuged and harvested. To determine the CDC activity of various mAbs, different methods can be used. ^{51}Cr release can for example be measured or elevated membrane permeability can

Samsung Bioepis Exhibit No. 1002
Page 12225

be assessed using a propidium iodide (PI) exclusion assay. Briefly, target cells can be washed and resuspended in RPMI-1% BSA at 1 x 10^6/ml. Various concentrations of mAb can be added to the cells and allowed to bind for 10-15 min at room temperature. Serum can then be added to a final concentration of 20% (v/v) and the cells incubated at 37 °C for 45 min. All cells from each sample can be added to the PI solution in a FACS tube. The mixture can then be assessed immediately by flow cytometry using a FACScalibur flow cytometer and analysed using CellQuest pro software (BD Biosciences, Mountain view, CA).

To test for the ability to initiate apoptosis, human monoclonal anti-CD20 antibodies can, for example, be incubated with CD20 positive tumor cells, *e.g.*, Daudi at 37 °C for about 20 hours. The cells can be harvested, washed in Annexin-V-FITC binding buffer (BD biosciences), and labeled with Annexin V-FITC (BD biosciences) for 15 min in the dark at 4 °C. All cells from each sample can be added to PI solution (10 µg/ml in PBS) in a FACS tube and assessed immediately by flow cytometry (as above).

In a particular embodiment of the invention, the human monoclonal antibodies are used in combination, *e.g.*, as a pharmaceutical composition comprising two or more anti-CD20 monoclonal antibodies. For example, human anti-CD20 monoclonal antibodies having different but complementary activities can be combined in a single therapy to achieve a desired therapeutic or diagnostic effect. In a preferred embodiment, the composition includes an anti-CD20 human monoclonal antibody that mediates CDC combined with another human anti-CD20 monoclonal antibody that induces apoptosis. In another embodiment, the composition includes an anti-CD20 human monoclonal antibody that mediates highly effective killing of target cells in the presence of effector cells, combined with another human anti-CD20 monoclonal antibody that inhibits the growth of cells expressing CD20.

II. Production of Transgenic Non-human Animals Which Generate Human Monoclonal Anti-CD20 Antibodies

In yet another aspect, the invention provides transgenic and transchromosomal non-human animals, such as transgenic or transchromosomal mice, which are capable of expressing human antibodies that specifically bind to CD20. In a particular embodiment, the invention provides a transgenic or transchromosomal mouse having a genome comprising a human heavy chain transgene, such that the mouse produces human anti- CD20 antibodies when immunized with cells expressing CD20. The human heavy chain transgene can be integrated into the chromosomal DNA of the mouse, as is the case for transgenic, *e.g.*, HuMAb mice, as described in detail herein and exemplified. Alternatively, the human heavy chain transgene can be maintained

Samsung Bioepis Exhibit No. 1002
Page 12226

extrachromosomally, as is the case for transchromosomal (*e.g.*, KM) mice as described in WO 02/43478. Such transgenic and transchromosomal animals are capable of producing multiple isotypes of human monoclonal antibodies to CD20 (*e.g.*, IgG, IgA and/or IgE) by undergoing V-D-J/V-J recombination and isotype switching. The design of a transgenic or transchromosomal non-human animal that responds to foreign antigen stimulation with a heterologous antibody repertoire, requires that the heterologous immunoglobulin transgenes contained within the transgenic animal function correctly throughout the pathway of B cell development. This includes, for example, isotype switching of the heterologous heavy chain transgene. Accordingly, transgenes are constructed so as that isotype switching can be induced and one or more of the following characteristics of antibody genes: (1) high level and cell-type specific expression, (2) functional gene rearrangement, (3) activation of and response to allelic exclusion, (4) expression of a sufficient primary repertoire, (5) signal transduction, (6) somatic hypermutation, and (7) domination of the transgene antibody locus during the immune response.

Not all of the foregoing criteria need be met. For example, in those embodiments wherein the endogenous immunoglobulin loci of the transgenic animal are functionally disrupted, the transgene need not activate allelic exclusion. Further, in those embodiments wherein the transgene comprises a functionally rearranged heavy and/or light chain immunoglobulin gene, the second criteria of functional gene rearrangement is unnecessary, at least for that transgene which is already rearranged. For background on molecular immunology, see, Fundamental Immunology, 2nd edition (1989), Paul William E., ed. Raven Press, N.Y.

In certain embodiments, the transgenic or transchromosomal non-human animals used to generate the human monoclonal antibodies of the invention contain rearranged, unrearranged or a combination of rearranged and unrearranged heterologous immunoglobulin heavy and light chain transgenes in the germline of the transgenic animal. Each of the heavy chain transgenes comprises at least one C_H gene. In addition, the heavy chain transgene may contain functional isotype switch sequences, which are capable of supporting isotype switching of a heterologous transgene encoding multiple C_H genes in the B cells of the transgenic animal. Such switch sequences may be those which occur naturally in the germline immunoglobulin locus from the species that serves as the source of the transgene C_H genes, or such switch sequences may be derived from those which occur in the species that is to receive the transgene construct (the transgenic animal). For example, a human transgene construct that is used to produce a transgenic mouse may produce a higher frequency of isotype switching events if it incorporates switch sequences similar to those that occur naturally in the mouse heavy chain locus, as presumably the mouse switch sequences are optimized to function with the mouse

Samsung Bioepis Exhibit No. 1002
Page 12227

switch recombinase enzyme system, whereas the human switch sequences are not. Switch sequences may be isolated and cloned by conventional cloning methods, or may be synthesized *de novo* from overlapping synthetic oligonucleotides designed on the basis of published sequence information relating to immunoglobulin switch region sequences (Mills *et al.*, *Nucl. Acids Res.* 15:7305-7316 (1991); Sideras *et al.*, *Intl. Immunol.* 1:631-642 (1989)). For each of the foregoing transgenic animals, functionally rearranged heterologous heavy and light chain immunoglobulin transgenes are found in a significant fraction of the B cells of the transgenic animal (at least 10 percent).

The transgenes used to generate the transgenic non-human animals of the invention include a heavy chain transgene comprising DNA encoding at least one variable gene segment, one diversity gene segment, one joining gene segment and at least one constant region gene segment. The immunoglobulin light chain transgene comprises DNA encoding at least one variable gene segment, one joining gene segment and at least one constant region gene segment. The gene segments encoding the light and heavy chain gene segments are heterologous to the transgenic animal in that they are derived from, or correspond to, DNA encoding immunoglobulin heavy and light chain gene segments from a species not consisting of the transgenic non-human animal. In one aspect of the invention, the transgene is constructed such that the individual gene segments are unrearranged, *i.e.*, not rearranged so as to encode a functional immunoglobulin light or heavy chain. Such unrearranged transgenes support recombination of the V, D, and J gene segments (functional rearrangement) and preferably support incorporation of all or a portion of a D region gene segment in the resultant rearranged immunoglobulin heavy chain within the transgenic animal when exposed to CD20 antigen.

In an alternate embodiment, the transgenes comprise an unrearranged "mini-locus". Such transgenes typically comprise a substantial portion of the C, D, and J segments as well as a subset of the V gene segments. In such transgene constructs, the various regulatory sequences, *e.g.* promoters, enhancers, class switch regions, splice-donor and splice-acceptor sequences for RNA processing, recombination signals and the like, comprise corresponding sequences derived from the heterologous DNA. Such regulatory sequences may be incorporated into the transgene from the same or a related species of the non-human animal used in the invention. For example, human immunoglobulin gene segments may be combined in a transgene with a rodent immunoglobulin enhancer sequence for use in a transgenic mouse. Alternatively, synthetic regulatory sequences may be incorporated into the transgene, wherein such synthetic regulatory sequences are not homologous to a functional DNA sequence that is known to occur naturally in the genomes of mammals. Synthetic regulatory sequences are designed according to consensus rules, such as, for example, those specifying the

Samsung Bioepis Exhibit No. 1002
Page 12228

permissible sequences of a splice-acceptor site or a promoter/enhancer motif. For example, a minilocus comprises a portion of the genomic immunoglobulin locus having at least one internal (*i.e.*, not at a terminus of the portion) deletion of a non-essential DNA portion (*e.g.*, intervening sequence; intron or portion thereof) as compared to the naturally-occurring germline Ig locus.

Preferred transgenic and transchromosomal non-human animals, *e.g.*, mice, will exhibit immunoglobulin production with a significant repertoire, ideally substantially similar to that of a human after adjusting for volume.

The repertoire will ideally approximate that shown in a human when adjusted for volume, usually with a diversity at least about 10% as great, preferably 25 to 50% or more. Generally, at least about a thousand different immunoglobulins (ideally IgG), preferably 10^4 to 10^6 or more, will be produced, depending on the number of different V, J and D regions introduced into the mouse genome and driven by the additional diversity generated by V(-D-)J gene segment rearrangements random nucleotide additions at the joining regions. Typically, the immunoglobulins will exhibit an affinity (K_D) for preselected antigens of below 10^{-7} M, such as of below 10^{-8} M, 10^{-9} M or 10^{-10} M or even lower.

Transgenic and transchromosomal non-human animals, *e.g.*, mice, as described above can be immunized with, for example, cells expressing CD20. Alternatively, the transgenic animals can be immunized with DNA encoding human CD20. The animals will then produce B cells which undergo class-switching via switch recombination (cis-switching) and express immunoglobulins reactive with CD20. The immunoglobulins can be human antibodies (also referred to as "human sequence antibodies"), wherein the heavy and light chain polypeptides are encoded by human transgene sequences, which may include sequences derived by somatic mutation and V region recombinatorial joints, as well as germline-encoded sequences; these human antibodies can be referred to as being substantially identical to a polypeptide sequence encoded by a human V_L and J_L or V_H, D_H and J_H gene segments, even though other non-germline sequences may be present as a result of somatic mutation and differential V-J and V-D-J recombination joints. The variable regions of each antibody chain are typically at least 80 percent similar to human germline V, J, and, in the case of heavy chains, D, gene segments; frequently at least 85 percent similar to human germline sequences present on the transgene; often 90 or 95 percent or more similar to human germline sequences present on the transgene. However, since non-germline sequences are introduced by somatic mutation and VJ and VDJ joining, the human sequence antibodies will frequently have some variable region sequences which are not encoded by human V, D, or J gene segments as found in the human transgene(s) in the germline of the mice. Typically, such non-germline sequences (or individual nucleotide

Samsung Bioepis Exhibit No. 1002
Page 12229

positions) will cluster in or near CDRs, or in regions where somatic mutations are known to cluster.

Another aspect of the invention includes B cells derived from transgenic or transchromosomal non-human animals as described herein. The B cells can be used to generate hybridomas expressing human monoclonal antibodies which bind with high affinity (*e.g.*, a dissociation equilibrium constant (K_D) of lower than 10^{-7} M) to human CD20. Thus, in another embodiment, the invention provides a hybridoma which produces a human antibody having an affinity (K_D) of below 10^{-7} M, such as of below 10^{-8} M, 10^{-9} M or 10^{-10} M or even lower when determined by scatchard analysis of CD20 expressing cells using a radio-actively labeled monoclonal antibody or by determination of the half-maximal binding concentration using FACS analysis.

Herein the monoclonal antibody comprises a human sequence light chain composed of (1) a light chain variable region having a polypeptide sequence which is substantially identical to a polypeptide sequence encoded by a human V_L gene segment and a human J_L segment, and (2) a light chain constant region encoded by a human C_L gene segment; and

a human sequence heavy chain composed of a (1) a heavy chain variable region having a polypeptide sequence which is substantially identical to a polypeptide sequence encoded by a human V_H gene segment, a D region, and a human J_H segment, and (2) a constant region encoded by a human C_H gene segment.

The development of high affinity human monoclonal antibodies against CD20 can be facilitated by a method for expanding the repertoire of human variable region gene segments in a transgenic non-human animal having a genome comprising an integrated human immunoglobulin transgene, said method comprising introducing into the genome a V gene transgene comprising V region gene segments which are not present in said integrated human immunoglobulin transgene. Often, the V region transgene is a yeast artificial chromosome comprising a portion of a human V_H or V_L (V_K) gene segment array, as may naturally occur in a human genome or as may be spliced together separately by recombinant methods, which may include out-of-order or omitted V gene segments. Often at least five or more functional V gene segments are contained on the YAC. In this variation, it is possible to make a transgenic animal produced by the V repertoire expansion method, wherein the animal expresses an immunoglobulin chain comprising a variable region sequence encoded by a V region gene segment present on the V region transgene and a C region encoded on the human Ig transgene. By means of the V repertoire expansion method, transgenic animals having at least 5 distinct V genes can be generated; as can animals containing at least about 24 V genes or more. Some V gene segments may be non-functional (*e.g.*,

Samsung Bioepis Exhibit No. 1002
Page 12230

pseudogenes and the like); these segments may be retained or may be selectively deleted by recombinant methods available to the skilled artisan, if desired.

Once the mouse germline has been engineered to contain a functional YAC having an expanded V segment repertoire, substantially not present in the human Ig transgene containing the J and C gene segments, the trait can be propagated and bred into other genetic backgrounds, including backgrounds where the functional YAC having an expanded V segment repertoire is bred into a non-human animal germline having a different human Ig transgene. Multiple functional YACs having an expanded V segment repertoire may be bred into a germline to work with a human Ig transgene (or multiple human Ig transgenes). Although referred to herein as YAC transgenes, such transgenes when integrated into the genome may substantially lack yeast sequences, such as sequences required for autonomous replication in yeast; such sequences may optionally be removed by genetic engineering (*e.g.*, restriction digestion and pulsed-field gel electrophoresis or other suitable method) after replication in yeast is no longer necessary (*i.e.*, prior to introduction into a mouse ES cell or mouse prozygote). Methods of propagating the trait of human sequence immunoglobulin expression, include breeding a transgenic animal having the human Ig transgene(s), and optionally also having a functional YAC having an expanded V segment repertoire. Both V_H and V_L gene segments may be present on the YAC. The transgenic animal may be bred into any background desired by the practitioner, including backgrounds harboring other human transgenes, including human Ig transgenes and/or transgenes encoding other human lymphocyte proteins. The invention also provides a high affinity human sequence immunoglobulin produced by a transgenic mouse having an expanded V region repertoire YAC transgene. Although the foregoing describes a preferred embodiment of the transgenic animal of the invention, other embodiments are contemplated which have been classified in three categories:

I. Transgenic animals containing an unrearranged heavy and rearranged light chain immunoglobulin transgene;

II. Transgenic animals containing an unrearranged heavy and unrearranged light chain immunoglobulin transgene; and

III. Transgenic animal containing rearranged heavy and an unrearranged light chain immunoglobulin transgene.

Of these categories of transgenic animal, the preferred order of preference is as follows II > I > III where the endogenous light chain genes (or at least the K gene) have been knocked out by homologous recombination (or other method) and I > II > III where the endogenous light chain genes have not been knocked out and must be dominated by allelic exclusion.

Samsung Bioepis Exhibit No. 1002
Page 12231

III. Bispecific/ Multispecific Molecules Which Bind to CD20

In yet another embodiment of the invention, human monoclonal antibodies to CD20 can be derivatized or linked to another functional molecule, *e.g.*, another peptide or protein (*e.g.*, an Fab' fragment) to generate a bispecific or multispecific molecule which binds to multiple binding sites or target epitopes. For example, an antibody of the invention can be functionally linked (*e.g.*, by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other binding molecules, such as another antibody, peptide or binding mimetic.

Accordingly, the present invention includes bispecific and multispecific molecules comprising at least one first binding specificity for CD20 and a second binding specificity for a second target epitope. In a particular embodiment of the invention, the second target epitope is an Fc receptor, *e.g.*, human FcγRI (CD64) or a human Fcα receptor (CD89), or a T cell receptor, *e.g.*, CD3. Therefore, the invention includes bispecific and multispecific molecules capable of binding both to FcγR, FcαR or FcεR expressing effector cells (*e.g.*, monocytes, macrophages or polymorphonuclear cells (PMNs)), and to target cells expressing CD20. These bispecific and multispecific molecules target CD20 expressing cells to effector cell and, like the human monoclonal antibodies of the invention, trigger Fc receptor-mediated effector cell activities, such as phagocytosis of a CD20 expressing cells, antibody dependent cellular cytotoxicity (ADCC), cytokine release, or generation of superoxide anion.

Bispecific and multispecific molecules of the invention can further include a third binding specificity, in addition to an anti-Fc binding specificity and an anti-CD20 binding specificity. In one embodiment, the third binding specificity is an anti-enhancement factor (EF) portion, *e.g.*, a molecule which binds to a surface protein involved in cytotoxic activity and thereby increases the immune response against the target cell. The "anti-enhancement factor portion" can be an antibody, functional antibody fragment or a ligand that binds to a given molecule, *e.g.*, an antigen or a receptor, and thereby results in an enhancement of the effect of the binding determinants for the F_c receptor or target cell antigen. The "anti-enhancement factor portion" can bind an F_c receptor or a target cell antigen. Alternatively, the anti-enhancement factor portion can bind to an entity that is different from the entity to which the first and second binding specificities bind. For example, the anti-enhancement factor portion can bind a cytotoxic T cell (*e.g.*, via CD2, CD3, CD8, CD28, CD4, CD40, ICAM-1 or other immune cell that results in an increased immune response against the target cell).

In one embodiment, the bispecific and multispecific molecules of the invention comprise as a binding specificity at least one antibody, including, *e.g.*, an Fab, Fab', $F(ab')_2$, Fv, or a single chain Fv. The antibody may also be a light chain or heavy chain dimer, or any minimal fragment thereof such as a Fv or a single chain construct as

Samsung Bioepis Exhibit No. 1002
Page 12232

described in Ladner *et al.* US 4,946,778. The antibody may also be a binding-domain immunoglobulin fusion protein as disclosed in US 2003/0118592 and US 2003/0133939.

In one embodiment bispecific and multispecific molecules of the invention comprise a binding specificity for an FcγR or an FcαR present on the surface of an effector cell, and a second binding specificity for a target cell antigen, *e.g.*, CD20.

In one embodiment, the binding specificity for an Fc receptor is provided by a human monoclonal antibody, the binding of which is not blocked by human immunoglobulin G (IgG). As used herein, the term "IgG receptor" refers to any of the eight γ-chain genes located on chromosome 1. These genes encode a total of twelve transmembrane or soluble receptor isoforms which are grouped into three Fcγ receptor classes: FcγRI (CD64), FcγRII(CD32), and FcγRIII (CD16). In one preferred embodiment, the Fcγ receptor is a human high affinity FcγRI.

The production and characterization of these preferred monoclonal antibodies are described by Fanger *et al.* in WO 88/00052 and in US 4,954,617. These antibodies bind to an epitope of FcγRI, FcγRII or FcγRIII at a site which is distinct from the Fcγ binding site of the receptor and, thus, their binding is not blocked substantially by physiological levels of IgG. Specific anti-FcγRI antibodies useful in this invention are mAb 22, mAb 32, mAb 44, mAb 62 and mAb 197. In other embodiments, the anti-Fcγ receptor antibody is a humanized form of monoclonal antibody 22 (H22). The production and characterization of the H22 antibody is described in Graziano, R.F. *et al.* (1995) J. Immunol 155 (10): 4996-5002 and WO 94/10332. The H22 antibody producing cell line was deposited at the American Type Culture Collection on November 4, 1992 under the designation HA022CL1 and has the accession No. CRL 11177.

In still other preferred embodiments, the binding specificity for an Fc receptor is provided by an antibody that binds to a human IgA receptor, *e.g.*, an Fc-alpha receptor (FcαRI (CD89)), the binding of which is preferably not blocked by human immunoglobulin A (IgA). The term "IgA receptor" is intended to include the gene product of one α-gene (FcαRI) located on chromosome 19. This gene is known to encode several alternatively spliced transmembrane isoforms of 55 to 110 kDa. FcαRI (CD89) is constitutively expressed on monocytes/macrophages, eosinophilic and neutrophilic granulocytes, but not on non-effector cell populations. FcαRI has medium affinity for both IgA1 and IgA2, which is increased upon exposure to cytokines such as G-CSF or GM-CSF (Morton, H.C. *et al.* (1996) Critical Reviews in Immunology 16:423-440). Four FcαRI-specific monoclonal antibodies, identified as A3, A59, A62 and A77, which bind FcαRI outside the IgA ligand binding domain, have been described (Monteiro, R.C. *et al.* (1992) *J. Immunol.* 148:1764).

Samsung Bioepis Exhibit No. 1002
Page 12233

FcαRI and FcγRI are preferred trigger receptors for use in the invention because they are (1) expressed primarily on immune effector cells, *e.g.*, monocytes, PMNs, macrophages and dendritic cells; (2) expressed at high levels (*e.g.*, 5,000-100,000 per cell); (3) mediators of cytotoxic activities (*e.g.*, ADCC, phagocytosis); (4) mediate enhanced antigen presentation of antigens, including self-antigens, targeted to them.

In another embodiment the bispecific molecule is comprised by two human monoclonal antibodies according to the invention which have complementary functional activities, such as one antibody predominately working by inducing CDC and the other antibody predominately working by inducing apoptosis, *e.g.*, 2F2 in combination with 11B8.

In other embodiments, bispecific and multispecific molecules of the invention further comprise a binding specificity which recognizes, *e.g.*, binds to, a target cell antigen, *e.g.*, CD20. In a preferred embodiment, the binding specificity is provided by a human monoclonal antibody of the present invention.

An "effector cell specific antibody" as used herein refers to an antibody or functional antibody fragment that binds the Fc receptor of effector cells. Preferred antibodies for use in the subject invention bind the Fc receptor of effector cells at a site which is not bound by endogenous immunoglobulin.

As used herein, the term "effector cell" refers to an immune cell which is involved in the effector phase of an immune response, as opposed to the cognitive and activation phases of an immune response. Exemplary immune cells include a cell of a myeloid or lymphoid origin, *e.g.*, lymphocytes (*e.g.*, B cells and T cells including cytolytic T cells (CTLs)), killer cells, natural killer cells, macrophages, monocytes, eosinophils, neutrophils, polymorphonuclear cells, granulocytes, mast cells, and basophils. Some effector cells express specific Fc receptors and carry out specific immune functions. In preferred embodiments, an effector cell is capable of inducing antibody-dependent cellular cytotoxicity (ADCC), *e.g.*, a neutrophil capable of inducing ADCC. For example, monocytes, macrophages, which express FcR are involved in specific killing of target cells and presenting antigens to other components of the immune system, or binding to cells that present antigens. In other embodiments, an effector cell can phagocytose a target antigen, target cell, or microorganism. The expression of a particular FcR on an effector cell can be regulated by humoral factors such as cytokines. For example, expression of FcγRI has been found to be up-regulated by interferon gamma (IFN-γ). This enhanced expression increases the cytotoxic activity of FcγRI-bearing cells against targets. An effector cell can phagocytose or lyse a target antigen or a target cell.

Samsung Bioepis Exhibit No. 1002
Page 12234

"Target cell" shall mean any undesirable cell in a subject (*e.g.*, a human or animal) that can be targeted by a composition (*e.g.*, a human monoclonal antibody, a bispecific or a multispecific molecule) of the invention. In preferred embodiments, the target cell is a cell expressing or overexpressing CD20. Cells expressing CD20 typically include B cells and B cell tumors.

While human monoclonal antibodies are preferred, other antibodies which can be employed in the bispecific or multispecific molecules of the invention are murine, chimeric and humanized monoclonal antibodies. Such murine, chimeric and humanized monoclonal antibodies can be prepared by methods known in the art.

Bispecific and multispecific molecules of the present invention can be made using chemical techniques (see *e.g.*, D. M. Kranz *et al.* (1981) *Proc. Natl. Acad. Sci.* USA 78:5807), "polydoma" techniques (See US 4,474,893, to Reading), or recombinant DNA techniques.

In particular, bispecific and multispecific molecules of the present invention can be prepared by conjugating the constituent binding specificities, *e.g.*, the anti-FcR and anti-CD20 binding specificities, using methods known in the art and described in the examples provided herein. For example, each binding specificity of the bispecific and multispecific molecule can be generated separately and then conjugated to one another. When the binding specificities are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC) (see *e.g.*, Karpovsky *et al.* (1984) *J. Exp. Med.* 160:1686; Liu, MA *et al.* (1985) *Proc. Natl. Acad. Sci.* USA 82:8648). Other methods include those described by Paulus (Behring Ins. Mitt. (1985) No. 78, 118-132); Brennan *et al.* (*Science* (1985) 229:81-83), and Glennie *et al.* (*J. Immunol.* (1987) 139: 2367-2375). Preferred conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, IL).

When the binding specificities are antibodies, they can be conjugated via sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains. In a particularly preferred embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues, preferably one, prior to conjugation.

Alternatively, both binding specificities can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the bispecific and multispecific molecule is a mAb x mAb, mAb x Fab, Fab x $F(ab')_2$ or ligand x Fab fusion protein. A bispecific and multispecific molecule of the invention, *e.g.*, a bispecific molecule can be a single chain molecule, such as a single

Samsung Bioepis Exhibit No. 1002
Page 12235

chain bispecific antibody, a single chain bispecific molecule comprising one single chain antibody and a binding determinant, or a single chain bispecific molecule comprising two binding determinants. Bispecific and multispecific molecules can also be single chain molecules or may comprise at least two single chain molecules. Methods for preparing bi- and multispecific molecules are described for example in US 5,260,203; US 5,455,030; US 4,881,175; US 5,132,405; US 5,091,513; US 5,476,786; US 5,013,653; US 5,258,498; and US 5,482,858.

Binding of the bispecific and multispecific molecules to their specific targets can be confirmed by enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay (RIA), FACS analysis, a bioassay (*e.g.*, growth inhibition), or a Western Blot Assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (*e.g.*, an antibody) specific for the complex of interest. For example, the FcR-antibody complexes can be detected using *e.g.*, an enzyme-linked antibody or antibody fragment which recognizes and specifically binds to the antibody-FcR complexes. Alternatively, the complexes can be detected using any of a variety of other immunoassays. For example, the antibody can be radioactively labeled and used in a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986). The radioactive isotope can be detected by such means as the use of a γ counter or a scintillation counter or by autoradiography.

IV. Immunoconjugates

In another aspect, the present invention features a human anti-CD20 monoclonal antibody conjugated to a therapeutic moiety, such as a cytotoxin, a drug (*e.g.*, an immunosuppressant) or a radioisotope. Such conjugates are referred to herein as "immunoconjugates". Immunoconjugates which include one or more cytotoxins are referred to as "immunotoxins." A cytotoxin or cytotoxic agent includes any agent that is detrimental to (*e.g.*, kills) cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof.

Suitable therapeutic agents for forming immunoconjugates of the invention include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, fludarabin, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine

Samsung Bioepis Exhibit No. 1002
Page 12236

(BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine). In a preferred embodiment, the therapeutic agent is a cytotoxic agent or a radiotoxic agent. In another embodiment, the therapeutic agent is an immunosuppressant. In yet another embodiment, the therapeutic agent is GM-CSF. In a preferred embodiment, the therapeutic agent is doxorubicin, cisplatin, bleomycin, sulfate, carmustine, chlorambucil, cyclophosphamide or ricin A.

Antibodies of the present invention also can be conjugated to a radioisotope, *e.g.*, iodine-131, yttrium-90 or indium-111, to generate cytotoxic radiopharmaceuticals for treating a CD20-related disorder, such as a cancer. The antibody conjugates of the invention can be used to modify a given biological response, and the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, an enzymatically active toxin, or active fragment thereof, such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor or interferon-γ; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982).

Samsung Bioepis Exhibit No. 1002
Page 12237

In a further embodiment, the human monoclonal antibodies according to the invention are attached to a linker-chelator, *e.g.*, tiuxetan, which allows for the antibody to be conjugated to a radioisotope.

V. Pharmaceutical Compositions

In another aspect, the present invention provides a composition, *e.g.*, a pharmaceutical composition, containing one or a combination of human monoclonal antibodies of the present invention. The pharmaceutical compositions may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995. In one embodiment, the compositions include a combination of multiple (*e.g.*, two or more) isolated human antibodies of the invention which act by different mechanisms, *e.g.*, one antibody which predominately acts by inducing CDC in combination with another antibody which predominately acts by inducing apoptosis.

Pharmaceutical compositions of the invention also can be administered in combination therapy, *i.e.*, combined with other agents. For example, the combination therapy can include a composition of the present invention with at least one anti-inflammatory agent or at least one immunosuppressive agent. In one embodiment such therapeutic agents include one or more anti-inflammatory agents, such as a steroidal drug or a NSAID (nonsteroidal anti-inflammatory drug). Preferred agents include, for example, aspirin and other salicylates, Cox-2 inhibitors, such as rofecoxib (Vioxx) and celecoxib (Celebrex), NSAIDs such as ibuprofen (Motrin, Advil), fenoprofen (Nalfon), naproxen (Naprosyn), sulindac (Clinoril), diclofenac (Voltaren), piroxicam (Feldene), ketoprofen (Orudis), diflunisal (Dolobid), nabumetone (Relafen), etodolac (Lodine), oxaprozin (Daypro), and indomethacin (Indocin).

In another embodiment, such therapeutic agents include one or more DMARDs, such as methotrexate (Rheumatrex), hydroxychloroquine (Plaquenil), sulfasalazine (Asulfidine), pyrimidine synthesis inhibitors, *e.g.*, leflunomide (Arava), IL-1 receptor blocking agents, *e.g.*, anakinra (Kineret), and TNF-α blocking agents, *e.g.*, etanercept (Enbrel), infliximab (Remicade) and adalimumab.

In another embodiment, such therapeutic agents include one or more immunosuppressive agents, such as cyclosporine (Sandimmune, Neoral) and azathioprine (Imural).

Samsung Bioepis Exhibit No. 1002
Page 12238

In yet another embodiment, such therapeutic agents include one or more chemotherapeutics, such as doxorubicin (Adriamycin), cisplatin (Platinol), bleomycin (Blenoxane), carmustine (Gliadel), cyclophosphamide (Cytoxan, Procytox, Neosar), and chlorambucil (Leukeran).

In another embodiment, human antibodies of the present invention may be administered in combination with chlorambucil and prednisolone; cyclophosphamide and prednisolone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, vincristine, doxorubicin, and prednisone; fludarabine and anthracycline; or in combination with other common multi-drugs regimens for NHL, such as disclosed, *e.g.*, in Non-Hodgkin's Lymphomas: Making sense of Diagnosis, Treatment, and Options, Lorraine Johnston, 1999, O'Reilly and Associates, Inc.

In yet another embodiment, the human antibodies may be administered in conjunction with radiotherapy and/or autologous peripheral stem cell or bone marrow transplantation.

In still another embodiment, the human antibodies may be administered in combination with one or more antibodies selected from anti-CD25 antibodies, anti-CD19 antibodies, anti-CD21 antibodies, anti-CD22 antibodies, anti-CD37 antibodies, anti-CD38 antibodies, anti-IL6R antibodies, anti-IL8 antibodies, anti-IL15 antibodies, anti-IL15R antibodies, anti-CD4 antibodies, anti-CD11a antibodies (*e.g.*, efalizumab), anti-alpha-4/beta-1 integrin (VLA4) antibodies (*e.g.*, natalizumab), and CTLA4-Ig.

In a particular embodiment, the human monoclonal antibodies are administered in combination with an anti-CD25 antibody for the treatment of bullous pemphigoid, *e.g.*, in patients with graft-versus-host disease.

In another particular embodiment, the human monoclonal antibodies are administered in combination with one or more antibodies selected from anti-CD19 antibodies, anti-CD21 antibodies, anti-CD22 antibodies, anti-CD37 antibodies, and anti-CD38 antibodies for the treatment of malignant diseases.

In still another particular embodiment, the human antibodies are administered in combination with one or more antibodies selected from anti-IL6R antibodies, anti-IL8 antibodies, anti-IL15 antibodies, anti-IL15R antibodies, anti-CD4 antibodies, anti-CD11a antibodies (*e.g.*, efalizumab), anti-alpha-4/beta-1 integrin (VLA4) antibodies (*e.g* natalizumab), and CTLA4-Ig for the treatment of inflammatory diseases.

In yet a further embodiment, the human antibodies may be administered in combination with an anti-C3b(i) antibody in order to enhance complement activation.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably,

Samsung Bioepis Exhibit No. 1002
Page 12239

the carrier is suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e.g.*, by injection or infusion). Depending on the route of administration, the active compound, *i.e.*, antibody, bispecific and multispecific molecule, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

A "pharmaceutically acceptable salt" refers to a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects (see *e.g.*, Berge, S.M., *et al.* (1977) J. Pharm. Sci. 66:1-19). Examples of such salts include acid addition salts and base addition salts. Acid addition salts include those derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorous and the like, as well as from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, aromatic acids, aliphatic and aromatic sulfonic acids and the like. Base addition salts include those derived from alkaline earth metals, such as sodium, potassium, magnesium, calcium and the like, as well as from nontoxic organic amines, such as N,N'-dibenzylethylenediamine, N-methylglucamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine and the like.

A composition of the present invention can be administered by a variety of methods known in the art. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for the preparation of such formulations are generally known to those skilled in the art. *See, e.g., Sustained and Controlled Release Drug Delivery Systems*, J.R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

To administer a compound of the invention by certain routes of administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the compound may be administered to a subject in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes (Strejan *et al.* (1984) *J. Neuroimmunol.* 7:27).

Samsung Bioepis Exhibit No. 1002
Page 12240

Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Dosage regimens are adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical

Samsung Bioepis Exhibit No. 1002
Page 12241

carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

For the therapeutic compositions, formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the composition which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.01 per cent to about ninety-nine percent of active ingredient, preferably from about 0.1 per cent to about 70 per cent, most preferably from about 1 per cent to about 30 per cent.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate. Dosage forms for the topical or transdermal administration of compositions of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

Samsung Bioepis Exhibit No. 1002
Page 12242

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of presence of microorganisms may be ensured both by sterilization procedures, supra, and by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In one embodiment the human monoclonal antibodies of the invention are administered in crystalline form by subcutaneous injection, cf. Yang *et al.* (2003) *PNAS*, 100(12):6934-6939

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given alone or as a pharmaceutical composition containing, for example, 0.01 to 99.5% (more preferably, 0.1 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in

Samsung Bioepis Exhibit No. 1002
Page 12243

combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, a suitable daily dose of a composition of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. It is preferred that administration be intravenous, intramuscular, intraperitoneal, or subcutaneous, preferably administered proximal to the site of the target. If desired, the effective daily dose of a therapeutic composition may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

In one embodiment, the human monoclonal antibodies according to the invention may be administered by infusion in a weekly dosage of 10 to 500 mg/m^2, such as 200 to 400 mg/m^2. Such administration may be repeated, *e.g.*, 1 to 8 times, such as 3 to 5 times. The administration may be performed by continuous infusion over a period of from 2 to 24 hours, such as of from 2 to 12 hours.

In another embodiment, the human monoclonal antibodies are administered by slow continuous infusion over a long period, such as more than 24 hours, in order to reduce toxic side effects.

In still another embodiment the human monoclonal antibodies are administered in a weekly dosage of from 250 mg to 2000 mg, such as for example 300 mg, 500 mg, 700 mg, 1000 mg, 1500 mg or 2000 mg, for up to 8 times, such as from 4 to 6 times. The administration may be performed by continuous infusion over a period of from 2 to 24 hours, such as of from 2 to 12 hours. Such regimen may be repeated one or more times as necessary, for example, after 6 months or 12 months. The dosage can be determined or adjusted by measuring the amount of circulating monoclonal anti-CD20 antibodies upon administration in a biological sample by using anti-idiotypic antibodies which target the anti-CD20 antibodies.

Samsung Bioepis Exhibit No. 1002
Page 12244

In yet another embodiment, the human monoclonal antibodies are administered by maintenance therapy, such as, *e.g.*, once a week for a period of 6 months or more.

In still another embodiment, the human monoclonal antibodies according to the invention may be administered by a regimen including one infusion of a human monoclonal antibody against CD20 followed by an infusion of a human monoclonal antibody against CD20 conjugated to a radioisotope. The regimen may be repeated, *e.g.*, 7 to 9 days later.

Therapeutic compositions can be administered with medical devices known in the art. For example, in a preferred embodiment, a therapeutic composition of the invention can be administered with a needleless hypodermic injection device, such as the devices disclosed in US 5,399,163; US 5,383,851; US 5,312,335; US 5,064,413; US 4,941,880; US 4,790,824; or US 4,596,556. Examples of well-known implants and modules useful in the present invention include: US 4,487,603, which discloses an implantable micro-infusion pump for dispensing medication at a controlled rate; US 4,486,194, which discloses a therapeutic device for administering medicants through the skin; US 4,447,233, which discloses a medication infusion pump for delivering medication at a precise infusion rate; US 4,447,224, which discloses a variable flow implantable infusion apparatus for continuous drug delivery; US 4,439,196, which discloses an osmotic drug delivery system having multi-chamber compartments; and US 4,475,196, which discloses an osmotic drug delivery system. Many other such implants, delivery systems, and modules are known to those skilled in the art.

In certain embodiments, the human monoclonal antibodies of the invention can be formulated to ensure proper distribution *in vivo*. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds. To ensure that the therapeutic compounds of the invention cross the BBB (if desired), they can be formulated, for example, in liposomes. For methods of manufacturing liposomes, see, *e.g.*, US 4,522,811; US 5,374,548; and US 5,399,331. The liposomes may comprise one or more moieties which are selectively transported into specific cells or organs, thus enhance targeted drug delivery (*see, e.g.*, V.V. Ranade (1989) *J. Clin. Pharmacol.* 29:685). Exemplary targeting moieties include folate or biotin (see, *e.g.*, US 5,416,016 to Low *et al.*); mannosides (Umezawa *et al.*, (1988) *Biochem. Biophys. Res. Commun.* 153:1038); antibodies (P.G. Bloeman *et al.* (1995) *FEBS Lett.* 357:140; M. Owais *et al.* (1995) *Antimicrob. Agents Chemother.* 39:180); surfactant protein A receptor (Briscoe *et al.* (1995) *Am. J. Physiol.* 1233:134), different species of which may comprise the formulations of the inventions, as well as components of the invented molecules; p120 (Schreier *et al.* (1994) *J. Biol. Chem.* 269:9090); see also K. Keinanen; M.L.

Samsung Bioepis Exhibit No. 1002
Page 12245

Laukkanen (1994) *FEBS Lett.* 346:123; J.J. Killion; I.J. Fidler (1994) *Immunomethods* 4:273. In one embodiment of the invention, the therapeutic compounds of the invention are formulated in liposomes; in a more preferred embodiment, the liposomes include a targeting moiety. In a most preferred embodiment, the therapeutic compounds in the liposomes are delivered by bolus injection to a site proximal to the desired area, *e.g.*, the site of inflammation or infection, or the site of a tumor. The composition must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

In a further embodiment, human monoclonal antibodies of the invention can be formulated to prevent or reduce their transport across the placenta. This can be done by methods known in the art, *e.g.*, by PEGylation of the antibodies or by use of F(ab)2' fragments. Further references can be made to "Cunningham-Rundles C, Zhuo Z, Griffith B, Keenan J. (1992) Biological activities of polyethylene-glycol immunoglobulin conjugates. Resistance to enzymatic degradation. *J Immunol Methods.* 152:177-190; and to "Landor M. (1995) Maternal-fetal transfer of immunoglobulins, *Ann Allergy Asthma Immunol* 74:279-283. This is particularly relevant when the antibodies are used for treating or preventing recurrent spontaneous abortion.

A "therapeutically effective dosage" for tumor therapy can be measured by objective tumor responses which can either be complete or partial. A complete response (CR) is defined as no clinical, radiological or other evidence of disease. A partial response (PR) results from a reduction in aggregate tumor size of greater than 50%. Median time to progression is a measure that characterizes the durability of the objective tumor response.

A "therapeutically effective dosage" for tumor therapy can also be measured by its ability to stabilize the progression of disease. The ability of a compound to inhibit cancer can be evaluated in an animal model system predictive of efficacy in human tumors. Alternatively, this property of a composition can be evaluated by examining the ability of the compound to inhibit cell growth or apoptosis by *in vitro* assays known to the skilled practitioner. A therapeutically effective amount of a therapeutic compound can decrease tumor size, or otherwise ameliorate symptoms in a subject. One of ordinary skill in the art would be able to determine such amounts based on such factors as the subject's size, the severity of the subject's symptoms, and the particular composition or route of administration selected.

A "therapeutically effective dosage" for rheumatoid arthritis preferably will result in an ACR20 Preliminary Definition of Improvement in the patients, more preferred in an ACR50 Preliminary Definition of Improvement and even more preferred in an ARC70 Preliminary Definition of Improvement.

Samsung Bioepis Exhibit No. 1002
Page 12246

ACR20 Preliminary Definition of Improvement is defined as: ≥20% improvement in: Tender Joint Count (TCJ) and Swollen Joint Count (SWJ) and ≥ 20% improvement in 3 of following 5 assessments: Patient Pain Assessment (VAS), Patient Global assessment (VAS), Physician Global Assessment (VAS), Patent Self-Assessed Disability (HAQ), Acute Phase Reactant (CRP or ESR).

ACR50 and ACR70 are defined in the same way with ≥50% and ≥70% improvements, respectively. For further details see Felson *et al.* in American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis; Arthritis Rheumatism (1995) 38: 727-735.

The composition must be sterile and fluid to the extent that the composition is deliverable by syringe. In addition to water, the carrier can be an isotonic buffered saline solution, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. Proper fluidity can be maintained, for example, by use of coating such as lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition. Long-term absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

When the active compound is suitably protected, as described above, the compound may be orally administered, for example, with an inert diluent or an assimilable edible carrier.

VI. Uses and Methods of the Invention

The human antibodies (including immunoconjugates, bispecifics/multispecifics, compositions and other derivatives described herein) of the present invention have numerous *in vitro* and *in vivo* diagnostic and therapeutic utilities involving the diagnosis and treatment of disorders involving cells expressing CD20. For example, the antibodies can be administered to cells in culture, *e.g.*, *in vitro* or *ex vivo*, or to human subjects, *e.g.*, *in vivo*, to treat, prevent and to diagnose a variety of disorders. As used herein, the term "subject" is intended to include human and non-human animals which respond to the human antibodies against CD20. Preferred subjects include human patients having disorders that can be corrected or ameliorated by inhibiting or controlling B cells (normal or malignant).

For example, in one embodiment, human antibodies of the present invention can be used to treat a subject with a tumorigenic disorder, *e.g.*, a disorder characterized by the presence of tumor cells expressing CD20 including, for example, B cell lymphoma, *e.g.*, NHL. Examples of tumorigenic diseases which can be treated

Samsung Bioepis Exhibit No. 1002
Page 12247

and/or prevented include B cell lymphoma, *e.g.*, NHL, including precursor B cell lymphoblastic leukemia/lymphoma and mature B cell neoplasms, such as B cell chronic lymhocytic leukemia(CLL)/small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), including low-grade, intermediate-grade and high-grade FL, cutaneous follicle center lymphoma, marginal zone B cell lymphoma (MALT type, nodal and splenic type), hairy cell leukemia, diffuse large B cell lymphoma, Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant lymphoproliferative disorder, Waldenström's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL).

Further examples of B cell non-Hodgkin's lymphomas are lymphomatoid granulomatosis, primary effusion lymphoma, intravascular large B cell lymphoma, mediastinal large B cell lymphoma, heavy chain diseases (including γ, μ, and α disease), lymphomas induced by therapy with immunosuppressive agents, such as cyclosporine-induced lymphoma, and methotrexate-induced lymphoma.

In a further embodiment, the human antibodies of the present invention can be used to treat Hodgkin's lymphoma.

Examples of immune disorders in which CD20 expressing B cells are involved which can be treated and/or prevented include autoimmune disorders, such as psoriasis, psoriatic arthritis, dermatitis, systemic scleroderma and sclerosis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis, glomerulonephritis, eczema, asthma, atherosclerosis, leukocyte adhesion deficiency, multiple sclerosis, Raynaud's syndrome, Sjögren's syndrome, juvenile onset diabetes, Reiter's disease, Behçet's disease, immune complex nephritis, IgA nephropathy, IgM polyneuropathies, immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, hemolytic anemia, myasthenia gravis, lupus nephritis, systemic lupus erythematosus, rheumatoid arthritis (RA), atopic dermatitis, pemphigus, Graves' disease, Hashimoto's thyroiditis, Wegener's granulomatosis, Omenn's syndrome, chronic renal failure, acute infectious mononucleosis, HIV, and herpes virus associated diseases. Further examples are severe acute respiratory distress syndrome and choreoretinitis. Furthermore, other diseases and disorders include those caused by or mediated by infection of B-cells with virus, such as Epstein-Barr virus (EBV).

Further examples of inflammatory, immune and/or autoimmune disorders in which autoantibodies and/or excessive B lymphocyte activity are prominent and which can be treated and/or prevented, include the following:

Samsung Bioepis Exhibit No. 1002
Page 12248

vasculitides and other vessel disorders, such as microscopic polyangiitis, Churg-Strauss syndrome, and other ANCA-associated vasculitides, polyarteritis nodosa, essential cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, Kawasaki disease, Takayasu arteritis, giant cell arthritis, Henoch-Schönlein purpura, primary or isolated cerebral angiitis, erythema nodosum, thrombangiitis obliterans, thrombotic thrombocytopenic purpura (including hemolytic uremic syndrome), and secondary vasculitides, including cutaneous leukocytoclastic vasculitis (*e.g.*, secondary to hepatitis B, hepatitis C, Waldenström's macroglobulinemia, B-cell neoplasias, rheumatoid arthritis, Sjögren's syndrome, or systemic lupus erythematosus); further examples are erythema nodosum, allergic vasculitis, panniculitis, Weber-Christian disease, purpura hyperglobulinaemica, and Buerger's disease;

skin disorders, such as contact dermatitis, linear IgA dermatosis, vitiligo, pyoderma gangrenosum, epidermolysis bullosa acquisita, pemphigus vulgaris (including cicatricial pemphigoid and bullous pemphigoid), alopecia areata (including alopecia universalis and alopecia totalis), dermatitis herpetiformis, erythema multiforme, and chronic autoimmune urticaria (including angioneurotic edema and urticarial vasculitis);

immune-mediated cytopenias, such as autoimmune neutropenia, and pure red cell aplasia;

connective tissue disorders, such as CNS lupus, discoid lupus erythematosus, CREST syndrome, mixed connective tissue disease, polymyositis/dermatomyositis, inclusion body myositis, secondary amyloidosis, cryoglobulinemia type I and type II, fibromyalgia, phospholipid antibody syndrome, secondary hemophilia, relapsing polychondritis, sarcoidosis, stiff man syndrome, and rheumatic fever; a further example is eosinophil fasciitis;

arthritides, such as ankylosing spondylitis, juvenile chronic arthritis, adult Still's disease, and SAPHO syndrome; further examples are sacroileitis, reactive arthritis, Still's disease, and gout;

hematologic disorders, such as aplastic anemia, primary hemolytic anemia (including cold agglutinin syndrome), hemolytic anemia secondary to CLL or systemic lupus erythematosus; POEMS syndrome, pernicious anemia, and Waldemström's purpura hyperglobulinaemica; further examples are agranulocytosis, autoimmune neutropenia, Franklin's disease, Seligmann's disease, μ-chain disease, paraneoplastic syndrome secondary to thymoma and lymphomas, and factor VIII inhibitor formation;

endocrinopathies, such as polyendocrinopathy, and Addison's disease; further examples are autoimmune hypoglycemia, autoimmune hypothyroidism, autoimmune insulin syndrome, de Quervain's thyroiditis, and insulin receptor antibody-mediated insulin resistance;

Samsung Bioepis Exhibit No. 1002
Page 12249

hepato-gastrointestinal disorders, such as celiac disease, Whipple's disease, primary biliary cirrhosis, chronic active hepatitis, and primary sclerosing cholangiitis; a further example is autoimmune gastritis;

nephropathies, such as rapid progressive glomerulonephritis, post-streptococcal nephritis, Goodpasture's syndrome, membranous glomerulonephritis, and cryoglobulinemic nephritis; a further example is minimal change disease;

neurological disorders, such as autoimmune neuropathies, mononeuritis multiplex, Lambert-Eaton's myasthenic syndrome, Sydenham's chorea, tabes dorsalis, and Guillain-Barré's syndrome; further examples are myelopathy/tropical spastic paraparesis, myasthenia gravis, acute inflammatory demyelinating polyneuropathy, and chronic inflammatory demyelinating polyneuropathy;

cardiac and pulmonary disorders, such as fibrosing alveolitis, bronchiolitis obliterans, allergic aspergillosis, cystic fibrosis, Löffler's syndrome, myocarditis, and pericarditis; further examples are hypersensitivity pneumonitis, and paraneoplastic syndrome secondary to lung cancer;

allergic disorders, such as bronchial asthma and hyper-IgE syndrome; a further example is amaurosis fugax;

ophthalmologic disorders, such as idiopathic chorioretinitis;

infectious diseases, such as parvovirus B infection (including hands-and-socks syndrome); and

gynecological-obstretical disorders, such as recurrent abortion, recurrent fetal loss, and intrauterine growth retardation; a further example is paraneoplastic syndrome secondary to gynaecological neoplasms;

male reproductive disorders, such as paraneoplastic syndrome secondary to testicular neoplasms; and

transplantation-derived disorders, such as allograft and xenograft rejection, and graft-versus-host disease.

In one embodiment, the disease is an inflammatory, immune and/or autoimmune disorder selected from ulcerative colitis, Crohn's disease, juvenile onset diabetes, multiple sclerosis, immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, hemolytic anemia (including autoimmune hemolytic anemia), myasthenia gravis, systemic sclerosis, and pemphigus vulgaris.

In another embodiment, human antibodies of the invention can be used to detect levels of CD20, or levels of cells which contain CD20 on their membrane surface, which levels can then be linked to certain disease symptoms. Alternatively, the antibodies can be used to deplete or interact with the function of CD20 expressing cells, thereby implicating these cells as important mediators of the disease. This can be

Samsung Bioepis Exhibit No. 1002
Page 12250

achieved by contacting a sample and a control sample with the anti-CD20 antibody under conditions that allow for the formation of a complex between the antibody and CD20. Any complexes formed between the antibody and CD20 are detected and compared in the sample and the control.

Human antibodies of the invention can be initially tested for binding activity associated with therapeutic or diagnostic use *in vitro*. For example, the antibodies can be tested using flow cytometric assays described in the Examples below. Moreover, activity of the antibodies in triggering at least one effector-mediated effector cell activity, including inhibiting the growth of and/or killing of cells expressing CD20, can be assayed. For example, the ability of the antibodies to trigger CDC and/or apoptosis can be assayed. Protocols for assaying for CDC, homotypic adhesion, molecular clustering or apoptosis are described in the Examples below.

Human antibodies of the invention also have additional utility in therapy and diagnosis of a variety of CD20-related diseases. For example, the human antibodies can be used to elicit *in vivo* or *in vitro* one or more of the following biological activities: to inhibit the growth of and/or differentiation of a cell expressing CD20; to kill a cell expressing CD20; to mediate phagocytosis or ADCC of a cell expressing CD20 in the presence of human effector cells; to mediate CDC of a cell expressing CD20 in the presence of complement; to mediate apoptosis of a cell expressing CD20; to induce homotypic adhesion; and/or to induce translocation into lipid rafts upon binding CD20.

In a particular embodiment, the human antibodies are used *in vivo* to treat, prevent or diagnose a variety of CD20-related diseases. Examples of CD20-related diseases include, among others, B cell lymphoma, *e.g.*, NHL, and immune diseases, *e.g.*, autoimmune diseases, such as those listed above.

In a particular embodiment, the antibodies of the invention are used to treat or to prevent NHL, as the antibodies deplete the CD20 bearing tumor cells).

Non-Hodgkin's lymphoma is a type of B cell lymphoma. Lymphomas, *e.g.*, B cell lymphomas, are a group of related cancers that arise when a lymphocyte (a blood cell) becomes malignant. The normal function of lymphocytes is to defend the body against invaders: germs, viruses, fungi, even cancer. There are many subtypes and maturation stages of lymphocytes and, therefore, there are many kinds of lymphomas. Like normal cells, malignant lymphocytes can move to many parts of the body. Typically, lymphoma cells form tumors in the lymphatic system: bone marrow, lymph nodes, spleen, and blood. However, these cells can migrate to other organs. Certain types of lymphoma will tend to grow in locations in which the normal version of the cell resides. For example, it's common for follicular NHL tumors to develop in the lymph nodes.

Samsung Bioepis Exhibit No. 1002
Page 12251

CD20 is usually expressed at elevated levels on neoplastic (*i.e.*, tumorigenic) B cells associated with NHL. Accordingly, CD20 binding antibodies of the invention can be used to deplete CD20 bearing tumor cells which lead to NHL and, thus, can be used to prevent or treat this disease.

Human antibodies (*e.g.*, human monoclonal antibodies, multispecific and bispecific molecules) of the present invention also can be used to block or inhibit other effects of CD20. For example, it is known that CD20 is expressed on B lymphocytes and is involved in the proliferation and/or differentiation of these cells. Since B lymphocytes function as immunomodulators, CD20 is an important target for antibody mediated therapy to target B lymphocytes, *e.g.*, to inactivate or kill B lymphocytes, involved in autoimmune disorders. Such autoimmune disorders include, for example, the above listed diseases

Suitable routes of administering the antibody compositions (*e.g.*, human monoclonal antibodies, multispecific and bispecific molecules and immunoconjugates) of the invention *in vivo* and *in vitro* are well known in the art and can be selected by those of ordinary skill. For example, the antibody compositions can be administered by injection (*e.g.*, intravenous or subcutaneous). Suitable dosages of the molecules used will depend on the age and weight of the subject and the concentration and/or formulation of the antibody composition. Furthermore, tumor load can be determined and used to calculate suitable dosages.

As previously described, human anti-CD20 antibodies of the invention can be co-administered with one or other more therapeutic agents, *e.g.*, a cytotoxic agent, a radiotoxic agent or an immunosuppressive agent. The antibody can be linked to the agent (as an immunocomplex) or can be administered separate from the agent. In the latter case (separate administration), the antibody can be administered before, after or concurrently with the agent or can be co-administered with other known therapies, *e.g.*, an anti-cancer therapy, *e.g.*, radiation. Such therapeutic agents include, among others, anti-neoplastic agents such as doxorubicin, cisplatin, bleomycin, carmustine, chlorambucil, and cyclophosphamide. Co-administration of the human anti-CD20 antibodies of the present invention with chemotherapeutic agents provides two anti-cancer agents which operate via different mechanisms which yield a cytotoxic effect to human tumor cells. Such co-administration can solve problems due to development of resistance to drugs or a change in the antigenicity of the tumor cells which would render them unreactive with the antibody.

Target-specific effector cells, *e.g.*, effector cells linked to compositions (*e.g.*, human antibodies, multispecific and bispecific molecules) of the invention can also be used as therapeutic agents. Effector cells for targeting can be human leukocytes such as macrophages, neutrophils or monocytes. Other cells include eosinophils, natural

Samsung Bioepis Exhibit No. 1002
Page 12252

killer cells and other IgG- or IgA-receptor bearing cells. If desired, effector cells can be obtained from the subject to be treated. The target-specific effector cells, can be administered as a suspension of cells in a physiologically acceptable solution. The number of cells administered can be in the order of 10^8 to 10^9 but will vary depending on the therapeutic purpose. In general, the amount will be sufficient to obtain localization at the target cell, *e.g.*, a tumor cell expressing CD20, and to effect cell killing by, *e.g.*, phagocytosis. Routes of administration can also vary.

Therapy with target-specific effector cells can be performed in conjunction with other techniques for removal of targeted cells. For example, anti-tumor therapy using the compositions (*e.g.*, human antibodies, multispecific and bispecific molecules) of the invention and/or effector cells armed with these compositions can be used in conjunction with chemotherapy. Additionally, combination immunotherapy may be used to direct two distinct cytotoxic effector populations toward tumor cell rejection. For example, anti-CD20 antibodies linked to anti-Fc-γRI or anti-CD3 may be used in conjunction with IgG- or IgA-receptor specific binding agents.

Bispecific and multispecific molecules of the invention can also be used to modulate FcγR or FcαR levels on effector cells, such as by capping and elimination of receptors on the cell surface. Mixtures of anti-Fc receptors can also be used for this purpose.

The compositions (*e.g.*, human antibodies, multispecific and bispecific molecules and immunoconjugates) of the invention which have complement binding sites, such as portions from IgG1, -2, or -3 or IgM which bind complement, can also be used in the presence of complement. In one embodiment, *ex vivo* treatment of a population of cells comprising target cells with a binding agent of the invention and appropriate effector cells can be supplemented by the addition of complement or serum containing complement. Phagocytosis of target cells coated with a binding agent of the invention can be improved by binding of complement proteins. In another embodiment target cells coated with the compositions (*e.g.*, human antibodies, multispecific and bispecific molecules) of the invention can also be lysed by complement. In yet another embodiment, the compositions of the invention do not activate complement.

The compositions (*e.g.*, human antibodies, multispecific and bispecific molecules and immunoconjugates) of the invention can also be administered together with complement. Accordingly, within the scope of the invention are compositions comprising human antibodies, multispecific or bispecific molecules and serum or complement. These compositions are advantageous in that the complement is located in close proximity to the human antibodies, multispecific or bispecific molecules. Alternatively, the human antibodies, multispecific or bispecific molecules of the invention and the complement or serum can be administered separately. Binding of the

Samsung Bioepis Exhibit No. 1002
Page 12253

compositions of the present invention to target cells causes translocation of the CD20 antigen-antibody complex into lipid rafts of the cell membrane. Such translocation creates a high density of antigen-antibody complexes which may efficiently activate and/or enhance CDC.

Also within the scope of the present invention are kits comprising the antibody compositions of the invention (*e.g.*, human antibodies and immunoconjugates) and instructions for use. The kit can further contain one or more additional reagents, such as an immunosuppressive reagent, a cytotoxic agent or a radiotoxic agent, or one or more additional human antibodies of the invention (*e.g.*, a human antibody having a complementary activity).

Accordingly, patients treated with antibody compositions of the invention can be additionally administered (prior to, simultaneously with, or following administration of a human antibody of the invention) with another therapeutic agent, such as a cytotoxic or radiotoxic agent, which enhances or augments the therapeutic effect of the human antibodies.

In other embodiments, the subject can be additionally treated with an agent that modulates, *e.g.*, enhances or inhibits, the expression or activity of Fcγ or Fcα receptors by, for example, treating the subject with a cytokine. Preferred cytokines for administration during treatment with the multispecific molecule include of granulocyte colony-stimulating factor (G-CSF), granulocyte- macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFN-γ), and tumor necrosis factor (TNF).

The compositions (*e.g.*, human antibodies, multispecific and bispecific molecules) of the invention can also be used to target cells expressing FcγR or CD20, for example for labeling such cells. For such use, the binding agent can be linked to a molecule that can be detected. Thus, the invention provides methods for localizing *ex vivo* or *in vitro* cells expressing Fc receptors, such as FcγR, or CD20. The detectable label can be, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor.

In a particular embodiment, the invention provides methods for detecting the presence of CD20 antigen in a sample, or measuring the amount of CD20 antigen, comprising contacting the sample, and a control sample, with a human monoclonal antibody which specifically binds to CD20, under conditions that allow for formation of a complex between the antibody or portion thereof and CD20. The formation of a complex is then detected, wherein a difference complex formation between the sample compared to the control sample is indicative the presence of CD20 antigen in the sample.

Samsung Bioepis Exhibit No. 1002
Page 12254

In other embodiments, the invention provides methods for treating a disorder involving cells expressing CD20 in a subject, *e.g.*, non-Hodgkin's lymphoma or rheumatoid arthritis, by administering to the subject the human antibodies described above. Such antibodies and derivatives thereof are used to inhibit CD20 induced activities associated with certain disorders, *e.g.*, proliferation and/or differentiation. By contacting the antibody with CD20 (*e.g.*, by administering the antibody to a subject), the ability of CD20 to induce such activities is inhibited and, thus, the associated disorder is treated.

Accordingly, in another embodiment, the present invention provides a method for treating or preventing a tumorigenic disorder involving CD20 expressing cells, *e.g.*, NHL. The method involves administering to a subject an antibody composition of the present invention in an amount effective to treat or prevent the disorder. The antibody composition can be administered alone or along with another therapeutic agent, such as a cytotoxic or a radiotoxic agent which acts in conjunction with or synergistically with the antibody composition to treat or prevent the diseases involving CD20 expressing cells. In a particularly preferred embodiment, the present invention provides a method for treating non-Hodgkin's lymphoma.

In another embodiment, the present invention provides a method for treating or preventing an autoimmune disorder involving human CD20 expressing cells, *e.g.*, those diseases as listed above. The method involves administering to a subject an antibody composition of the present invention in an amount effective to treat or prevent the disorder. The antibody composition can be administered alone or along with another therapeutic agent, such as an immunosuppressant which acts in conjunction with or synergistically with the antibody composition to treat or prevent the disease involving cells expressing CD20.

In still another embodiment, the invention provides a method for detecting the presence or quantifying the amount of CD20-expressing cells *in vivo* or *in vitro*. The method comprises (i) administering to a subject a composition (*e.g.*, a multi- or bispecific molecule) of the invention conjugated to a detectable marker; (ii) exposing the subject to a means for detecting said detectable marker to identify areas containing CD20-expressing cells.

In yet another embodiment; immunoconjugates of the invention can be used to target compounds (*e.g.*, therapeutic agents, labels, cytotoxins, radiotoxins immunosuppressants, *etc.*) to cells which have CD20 expressed on their surface by linking such compounds to the antibody. Thus, the invention also provides methods for localizing *ex vivo* or *in vitro* cells expressing CD20, such as Reed-Sternberg cells (*e.g.*, with a detectable label, such as a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor). Alternatively, the immunoconjugates can be used to kill cells

Samsung Bioepis Exhibit No. 1002
Page 12255

which have CD20 expressed on their surface by targeting cytotoxins or radiotoxins to CD20.

The present invention is further illustrated by the following examples which should not be construed as further limiting.

EXAMPLES

B-cell lines used in the examples

Cell line	Origin	Obtained from
Daudi	Negroid Burkitt's Lymphoma	ECACC (85011437)
ARH-77	IgG plasma cell leukemia	DSMZ (ACC 512)
DOHH	Refractory immunoblastic B cell lymphoma	DSMZ (ACC 47)
Raji	Negroid Burkitt's Lymphoma	ECACC (85011429)
SU-DHL-4	B-NHL, diffuse histiocytic lymphoma	DSMZ (ACC 495)
Ramos-EHRB	Burkitt's Lymphoma	ECACC (85030804)
Tanoue	Human B-cell leukemia	DSMZ (ACC 399)

Daudi, ARH-77, DOHH, Raji, Ramos-EHRB, and Tanoue B-cell lines were cultured in RPMI 1640 culture medium supplemented with 10% fetal calf serum (FCS) (Optimum C241, Wisent Inc., st. Bruno, Canada), 2 mM L-glutamine, 100 IU/ml penicillin, 100 μg/ml streptomycin, and 1 mM sodium pyruvate (all Gibco BRL, Life Technologies, Paisley, Scotland).

SU-DHL-4 B-cell line was cultured in the same medium but without sodium pyruvate.

Cultures were maintained at 37 °C in a humidified 5% CO_2 incubator, split and harvested at 80-90% confluence. Medium was refreshed twice a week. At this time cells were split and seeded out to 1-1.5 x 10^6 cells/ml to ensure viability and optimal growth.

Example 1 Production of Human Antibodies Against CD20

HCo7 and KM Mice: Fully human monoclonal antibodies to CD20 were prepared using HCo7 and KM mice which express human antibody genes. In the KM mouse strain, the endogenous mouse kappa light chain gene has been homozygously disrupted as described in Chen *et al.* (1993) *EMBO J.* 12:811-820 and the endogenous mouse heavy chain gene has been homozygously disrupted as described in Example 1 of

Samsung Bioepis Exhibit No. 1002
Page 12256

PCT Publication WO 01/09187. This mouse strain carries a human kappa light chain transgene, KCo5, as described in Fishwild *et al.* (1996) *Nature Biotechnology* 14:845-851. This mouse strain also carries a human heavy chain transchromosome composed of chromosome 14 fragment hCF (SC20) as described in WO 02/43478.

The HCo7 mice have a JKD disruption in their endogenous light chain (kappa) genes (as described in Chen *et al.* (1993) *EMBO J.* 12: 821-830), a CMD disruption in their endogenous heavy chain genes (as described in Example 1 of WO 01/14424), a KCo5 human kappa light chain transgene (as described in Fishwild *et al.* (1996) *Nature Biotechnology* 14:845-851), and a HCo7 human heavy chain transgene (as described in US 5,770,429).

HCo7 and KM Mice Immunizations: HCo7 and KM mice were immunized with human CD20 transfected NS/0 cells. For the first immunization, per mouse, $1x10^7$ cells in 150 µl PBS were mixed 1:1 with Complete Freunds Adjuvant and injected intraperitoneally (i.p.). Subsequent i.p. immunizations were done using a similar amount of cells without adjuvant. Three and two days prior to fusion the mice were intravenously boosted with 0.5×10^7 cells suspended in PBS.

The presence of antibodies directed against human CD20 in the serum of the mice was monitored by flow cytometry using FACS analysis, using human CD20 transfected NS/0 cells as well as CD20 negative parental NS/0 cells.

Generation of Hybridomas Producing Human Monoclonal Antibodies to CD20: The mouse splenocytes were isolated from the HCo7 and KM mice and fused with PEG to a mouse myeloma cell line based upon standard protocols. The resulting hybridomas were then screened for human IgG,κ production by ELISA and for CD20 specificity using human CD20 transfected NS/0 and SKBR3 cells by FACS analysis. Single cell suspensions of splenic lymphocytes from immunized mice were fused to one-fourth the number of SP2/0 nonsecreting mouse myeloma cells (ATCC, CRL 1581) with 50% PEG (Sigma). Cells were plated at approximately 1×10^5/well in flat bottom microtiter plate, followed by about two week incubation in selective medium containing 10% fetal bovine serum, 10% P388D1 (ATCC, CRL TIB-63) conditioned medium, 3-5% origen (IGEN) in DMEM (Mediatech, CRL 10013, with high glucose, L-glutamine and sodium pyruvate) plus 5 mM HEPES, 0.055 mM 2-mercaptoethanol, 50 mg/ml gentamycin and 1x HAT (Sigma, CRL P-7185). After 1-2 weeks, cells were cultured in medium in which the HAT was replaced with HT. Individual wells were then screened by flow cytometry for human anti-CD20 monoclonal IgG antibodies. Once extensive hybridoma growth occurred, medium was monitored usually after 10-14 days. The antibody secreting hybridomas were replated, screened again and, if still positive for

Samsung Bioepis Exhibit No. 1002
Page 12257

human IgG, anti-CD20 monoclonal antibodies were subcloned by limiting dilution. The stable subclones were then cultured *in vitro* to generate small amounts of antibody in tissue culture medium for characterization. One clone from each hybridoma, which retained the reactivity of parent cells (by FACS), was chosen. 5-10 vial cell banks were generated for each clone and stored in liquid nitrogen.

Selection of Human Monoclonal Antibodies Binding to CD20/Primary Screens: To determine the isotype of antibodies, an isotype ELISA was performed. Wells of microtiter plates were coated with 1 μg/ml of mouse anti-human kappa light chain, 50 μl/well in PBS incubated 4 °C overnight. After blocking with 5% chicken serum, the plates were reacted with supernatant and purified isotype control. Plates were then incubated at ambient temperature for 1-2 hours. The wells were then reacted with either human IgG1, IgG2, IgG3 or IgG4-specific Horseradish peroxidase – conjugated probes. Plates were developed and analyzed as described above.

Four hybridoma cell lines were generated, three from fusion of KM mouse and one from fusion of HCo7 mouse, expressing the following antibodies:

2F2: a human monoclonal IgG1,κ antibody with the nucleotide sequences: SEQ ID NOs: 1 and 3 and the amino acid sequences: SEQ ID NOs: 2 and 4.

4C9: a human monoclonal IgG1,κ antibody with exactly the same amino acid sequences as 2F2: SEQ ID NOs: 2 and 4.

7D8: a human monoclonal IgG1,κ antibody with the nucleotide sequences: SEQ ID NOs: 5 and 7 and the amino acid sequences: SEQ ID NOs: 6 and 8.

11B8: a human monoclonal IgG3, κ antibody with the nucleotide sequences: SEQ ID NOs: 9 and 11 and the amino acid sequences: SEQ ID NOs: 10 and 12.

The term "2F2" is used herein to designate both the antibody derived from hybridoma clone 2F2 and the identical antibody derived from hybridoma clone 4C9.

The antibodies of the invention can be switched to other isotypes as determined by the transgenic or transchromosomal non-human animal from which they are derived. In one embodiment of the invention, the 11B8 human monoclonal IgG3,κ antibody can be switched to a human monoclonal IgG1,κ isotype having exactly the same V_H and V_L sequences. In another embodiment, the 2F2 IgG1,κ antibody or 7D8 IgG1,κ antibody can be switched to a human monoclonal IgG2, IgG4, IgA1, IgA2 or IgE isotype having exactly the same V_H and V_L sequences.

Samsung Bioepis Exhibit No. 1002
Page 12258

Example 2 Antibody Sequencing of Human Antibodies Against CD20

Sequencing of the V_L and V_H Regions

RNA preparation: Total RNA was prepared from $5x10^6$ cells of all HuMAb CD20 hybridoma cell lines (2F2, 7D8 and 11B8) with RNeasy kit (Qiagen, Westburg, Leusden, Netherlands) according to the manufacturer's protocol.

cDNA preparation of 2F2 and 7D8: 5'-RACE-Ready Complementary DNA (cDNA) of RNA was prepared from 1 μg total RNA, using the SMART RACE cDNA Amplification kit (Clonetech), following the manufacturer's protocol.

V_H and V_L regions were amplified using an advantage HF 2 PCR Kit (Clonetech, BD) and using the following primers:

V_K RACE2	5' GCA GGC ACA CAA CAG AGG CAG TTC CAG ATT TC	anneals in C-kappa
V_H RACE2	5' GCT GTG CCC CCA GAG GTG CTC TTG GAG G	anneals in C_{H1}

cDNA preparation of 11B8: Complementary DNA (cDNA) of RNA from 11B8 cells was prepared from 3 μg total RNA with AMV Reverse Transcriptase with buffer (Roche Diagnostics GmbH, Mannheim, Germany), oligo $d(T)_{15}$ (Promega, Madison, WI, USA), dNTP (Roche Diagnostics GmbH, Mannheim, Germany) and RNAsin (Promega) according to the manufacturer's protocol (2000, version 3).

PCR primers used to amplify V_H and V_L regions for cloning:

Primer pairs used:

V_H: FR1 5' primers

AB62	CAg gTK CAg CTg gTg CAg TC
AB63	SAg gTg CAg CTg KTg gAg TC
AB65	gAg gTg CAg CTg gTg CAg TC

V_H leader 5' primers

AB85	ATg gAC Tgg ACC Tgg AgC ATC
AB86	ATg gAA TTg ggg CTg AgC Tg
AB87	ATg gAg TTT ggR CTg AgC Tg
AB88	ATg AAA CAC CTg Tgg TTC TTC
AB89	ATg ggg TCA ACC gCC ATC CT

Samsung Bioepis Exhibit No. 1002
Page 12259

V_H 3' primer

AB90	TgC CAg ggg gAA gAC CgA Tgg

V_K:

FR1 5' primers

AB8	RAC ATC CAg ATg AYC CAg TC
AB9	gYC ATC YRg ATg ACC CAg TC
AB10	gAT ATT gTg ATg ACC CAg AC
AB11	gAA ATT gTg TTg ACR CAg TC
AB12	gAA ATW gTR ATg ACA CAg TC
AB13	gAT gTT gTg ATg ACA CAG TC
AB14	gAA ATT gTg CTg ACT CAg TC

V_K leader 5' primers

AB123	CCC gCT Cag CTC CTg ggg CTC CTg
AB124	CCC TgC TCA gCT CCT ggg gCT gC
AB125	CCC AgC gCA gCT TCT CTT CCT CCT gC
AB126	ATg gAA CCA Tgg AAg CCC CAg CAC AgC

V_K 3' primer

AB16	Cgg gAA gAT gAA gAC AgA Tg

wherein K = T or G, S = C or G, R = A or G, Y = C or T, and W = A or T.

PCR conditions used to amplify V_H and V_L regions for cloning 2F2 and 7D8: Polymerase chain reactions (PCR) were performed with HF polymerase mix (Clonetech.) on a T1 cycler (Biometra, Westburg).

Samsung Bioepis Exhibit No. 1002
Page 12260

PCR conditions:

94 °C 30 sec 5 cycles
72 °C 1 min

94 °C 30 sec
70 °C 30 sec 5 cycles
72 °C 1 min

94 °C 30 sec
68 °C 30 sec 27-30 cycles
72 °C 1 min

PCR conditions used to amplify V_H and V_L regions for cloning 11B8: Polymerase chain reactions (PCR) were performed with AmpliTaq polymerase (Perkin Elmer) on a T1 Cycler (Biometra, Westburg, Leusden, Netherlands).

PCR cycling protocol:

94 °C 2 min
11 cycles 94 °C 30 sec
65 °C 30 sec, minus 1 °C per cycle
72 °C 30 sec
30 cycles 94 °C 30 sec
55 °C 30 sec
72 °C 30 sec
72 °C 10 min
cool down to 4 °C

Cloning of V_H and V_L in pGEMT-Vector System II (2F2, 7D8, and 11B8): After analysing the PCR products on an agarose gel, the products were purified with the QIAEX II Gel Extraction Kit (Qiagen, Westburg, Leusden, Netherlands). Two independently amplified PCR products of each V_H and V_L region were cloned in pGEMT-Vector System II (Promega) according to manufacturer's protocol (1999, version 6).

After transformation to *E. coli* JM109, individual colonies were screened by colony PCR using T7 and SP6 primers, 30 annealing cycles at 55 °C. Plasmid DNA from colonies was purified using Qiaprep Spin miniprep kit (Qiagen). To further

Samsung Bioepis Exhibit No. 1002
Page 12261

analyse the V_H and V_L regions, a *Nco*1/*Not*1 (NE Biolabs, Westburg, Leusden, Netherlands) digestion was performed and analysed on agarose gel.

Sequencing (2F2, 7D8 and 11B8): The V-regions regions were sequenced after cloning in the pGEMT-Vector System II. Sequencing was performed at Baseclear (Leiden, Netherlands). The sequences were analyzed by aligning germline V-gene sequences in Vbase (www.mrc-cpe.cam.ac.uk/imt-doc/public/intro.htm).http://www.mrc-cpe.cam.ac.uk/vbase-ok.php?menu=901.

The sequences obtained are shown in Figures 53-58.

Example 3 Recombinant production of 2F2 and 11B8 in GS-NS/0 cell line

2F2T: The heavy chain and light chain variable regions of the 2F2 antibody were amplified, using PCR, from a standard cloning vector, pGem-5Zf (Promega), using primers which included an optimal Kozak sequence and suitable restriction sites to clone the fragments in the GS constant region vectors pCONγ1f and PCONκ (Lonza).

After amplification, the fragments were purified and digested with the restriction enzymes for cloning and ligated in the two vectors. The heavy chain variable fragment was digested with *Hind* III and *Bsi* WI and ligated into the pCONγ1f vector which had been digested with *Hind* III and *Bsi* WI, and dephosphorylated with alkaline phosphatase. The light chain variable fragment was digested with *Hind* III and *Apa* I and ligated into the PCONκ vector which had been digested with *Hind* III and *Apa* I, and dephosphorylated with alkaline phosphatase. The pCONγ1f/variable-heavy and PCONκ/variable-light vectors are shown in Figures 1 and 2, respectively. Transformed *E. coli* colonies were checked by colony PCR and 2 positive colonies of each the heavy chain (HC) and light chain (LC) construct were grown for plasmid isolation. Isolated plasmid of these 4 clones was sequenced to confirm the sequence. Both of the HC clones and one of the LC clones were found to have the correct sequences.

The two HC and one LC constructs were combined to give two combinations of LC-HC and transiently co-transfected in CHO-K1 cells to check the constructs for proper production of 2F2 antibody. Normal production levels were reached for all combinations in this expression experiment and 1 clone of each of the HC and LC constructs were chosen for construction of a double-gene vector.

Standard cloning procedures were used to combine the HC and LC constructs in a double-gene cloning vector, designated pCONγ1f/κ2F2, by ligating the complete expression cassette from the heavy chain vector, pCONγ1f/variable-heavy,

Samsung Bioepis Exhibit No. 1002
Page 12262

into the light chain vector, pCONκ/variable-light. The pCONγ1f/κ2F2 vector is shown in Figure 3.

This construct was again functionally tested in a transient transfection in CHO-K1 cells and showed normal expression levels.

The variable regions of the pCONγ1f/κ2F2 plasmid were sequenced to reconfirm the correct sequences.

Linear plasmid was prepared for stable transfections by digesting pCONγ1f/κ2F2 with a unique restriction enzyme, *Pvu I,* cutting outside regions vital for expression. Complete linearization was confirmed by agarose gel electrophoresis and the DNA was purified and stored at -20 °C until use.

Six transfections of NS/0 host cells were performed, by electroporation with plasmid DNA, using the above linear DNA plasmid. Following transfection, the cells were distributed into 96-wells plates and incubated. Selective medium (containing 10% dialysed fetal calf serum (dFCS) and 10 μM of the GS-inhibitor L-methionine sulphoximine but lacking glutamine) was added and the plates were monitored to determine when the non-transfected cells died to leave foci of transfected cells. For further details concerning GS vector systems, see WO 87/04462. The transfected plates were incubated for approximately three weeks to allow colony formation. The resulting colonies were examined microscopically to verify that the colonies were of a suitable size for assay (covering greater than 60% of the bottom of the well), and that only one colony was present in each well. Cell supernatants from 436 transfectants were screened for assembled antibody by IgG,κ-ELISA. Using this data, 111 transfectants were selected for progression and further assessment in static culture. Cultures of the selected cell lines were expanded and adapted to low-serum containing medium (containing bovine serum albumin (BSA) and added 1% dFCS) and a further assessment of productivity in static culture was undertaken (ELISA and measurement of percentage confluence). The 65 highest ranking cell lines were selected for progression. A preliminary assessment of the productivity of the selected cell lines was made in batch shake flask suspension culture in low serum-containing medium (containing BSA and added 1% dFCS). Based upon harvest antibody concentration (by ELISA) and acceptable growth characteristics, 30 cell lines were selected for further evaluation in serum-free medium using a batch shake flask suspension culture. The 10 cell lines that produced the highest antibody concentrations were further evaluated in duplicate fed-batch shake flask suspension cultures in serum-free medium. Product concentrations at harvest were determined by protein A high performance liquid chromatography (HPLC), according to well-known standard methods. All cell lines produced 2F2 antibody (denoted 2F2T) in good yields in the range of from 671-1333 mg/L as determined by protein A HPLC.

Samsung Bioepis Exhibit No. 1002
Page 12263

11B8T: In a similar way a GS-NS/0 cell line was established for recombinant production of 11B8 (denoted 11B8T) modifying the transfection procedure slightly as follows.

Four transfections of NS/0 host cells were performed, by electroporation with plasmid DNA, using the above linear DNA plasmid. After examining the resulting colonies microscopically to verify that the colonies were of a suitable size for assay (covering greater than 60% of the bottom of the well) and that only one colony was present in each well, cell supernatants from 596 transfectants were screened for assembled antibody by IgG,κ-ELISA. Using this data, 100 transfectants were selected for progression and further assessment in static culture. Cultures of the selected cell lines were expanded and adapted to low-serum containing medium (containing bovine serum albumin (BSA) and added 1% dFCS) and a further assessment of productivity in static culture was undertaken (ELISA and measurement of percentage confluence). The 60 highest ranking cell lines were selected for progression, and an additional 13 cell lines for which productivity data was unavailable were also progressed. A preliminary assessment of the productivity of the selected cell lines was made in batch shake flask suspension culture in low serum-containing medium (containing BSA and added 1% dFCS). Based upon harvest antibody concentration (by ELISA) and acceptable growth characteristics, 10 cell lines were selected for further evaluation in duplicate fed-batch shake flask suspension cultures in low serum-containing medium (containing BSA and added 1% dFCS). Product concentrations at harvest were determined by protein A high performance liquid chromatography (HPLC), according to well-known standard methods. Based on this one of the cell lines was discarded. The resulting 9 cell lines all produced 11B8 antibody (denoted "11B8T") in good yields in the range of from 354-771 mg/L as determined by protein A HPLC.

Example 4 Comparison of hybridoma-derived 2F2 and transfectoma-derived recombinant 2F2T

By use of gel electrophoresis (SDS-PAGE and native agarose gel electrophoresis) it was shown that 2F2 and 2F2T are of the same size, and only slightly differ in electric charge.

Furthermore, 2F2 and 2F2T bind to CD20-transfected NS/0 cells and Raji cells with similar affinity as measured by flow cytometry using FACScalibur™ (Becton Dickinson, San Diego, CA, USA). No binding to non-transfected NS/0 cells was observed demonstrating the specificity of 2F2 and 2F2T. 2F2 and 2F2T also induce CDC in a concentration-dependent manner to the same extent in ARH-77 cells (IgG plasma cell leukemia), Daudi cells, DOHH cells (refractory immunoblastic B cell

Samsung Bioepis Exhibit No. 1002
Page 12264

lymphoma progressed from follicular centroblastic/centrolytic lymphoma, DSMZ, Braunschweig, Germany) and Raji cells, measuring cell lysis (number of PI-positive cells) by flow cytometry (FACScalibur). In a second experiment, the concentrations of 2F2 and 2F2T were kept constant while serum was added in different concentrations. No significant differences between 2F2 and 2F2T were observed.

Finally, 2F2 and 2F2T bound to cell-associated CD20 binds complement factor C1q strongly and to the same extent. The experiment was performed in Daudi cells, DOHH cells, and Raji cells using fluorescein-conjugated anti-C1q polyclonal antibodies for detecting binding of C1q.

Example 5 Binding Characteristics of Human Antibodies Against CD20

Binding to different cell lines: NS/0, NS/0 transfected with human CD20, Daudi and Raji cells were incubated for 30 min at 4 °C with culture supernatant containing human antibodies 2F2, 7D8, and 11B8 followed by incubation with FITC-conjugated anti-human IgG Ab. Binding was assessed by flow cytometry using a FACScalibur flow cytometer. Fluorescence intensities were compared with negative control isotype matched samples. As shown in Figure 4, all three antibodies bound to NS/0 cells transfected with human CD20, whereas no binding was observed to parental, non-transfected NS/0 cells. All three antibodies also bound to the two different Burkitt lymphoma B cell lines (Raji and Daudi) indicating that 2F2, 7D8, and 11B8 are CD20 specific. Supernatant containing 7D8 or 11B8 were tested under non-saturating conditions, therefore, lower mean fluorescence intensities compared to 2F2 are observed.

EC_{50} value of 2F2 as determined by flow cytometry: In order to determine the apparent affinity of 2F2 for CD20 expressed on human B cells, a binding curve was made of 2F2 using isolated PBMCs from three human donors and gating of CD3-negative cells. The isolated PBMCs were incubated for 1 hour with a concentration range of FITC labeled 2F2 and analysed on FACS, and the mean fluorescence intensity (MFI) determined. The MFI values are shown in Figures 5A and 5B as a function of the antibody concentration. The EC_{50} values were calculated by use of Graph Pad Prism 3.02 by non-linear regression. The EC_{50} value of 2F2 in humans was similar for all three donors with a mean (± s.e.m.) of 287 ± 12.7 ng/ml (1.9 ± 0.1 nM).

Binding of ^{125}I-labeled mAbs to CD20 expressing cells: mAbs were iodinated using Iodobeads (Pierce Chemical Co., Rockford, IL). ^{125}I-labelled mAbs were serially diluted and incubated with Ramos-EHRB (cells for 2 hours at 37 °C in the

Samsung Bioepis Exhibit No. 1002
Page 12265

presence of sodium azide and 2-deoxyglucose to prevent endocytosis. The cell bound and free ^{125}I labeled mAbs were then separated by centrifugation at 14,000 x g for 2 min through a mixture of phthalate oils, allowing rapid separation without disturbing the binding equilibrium. The pelleted cells together with bound antibody were then counted using a gamma counter (Wallac UK Ltd, Milton Keynes, UK).

As shown in Figure 6, 2F2 and 11B8 exhibit similar K_D (or similar saturation points) indicating that both antibodies bind with similar affinity. However, 11B8 saturates at a lower level than 2F2 indicating that it recognized a different form of CD20. This is also in agreement with a further experiment showing that a similar number of 2F2 and rituximab antibody molecules binds to CD20 on Ramos-EHRB cells and Daudi cells, as shown by the similar levels of binding saturation (approximately 2-3 x 10^5 antibody molecules per cell). 11B8 and B1, in contrast, saturate at half this level and only about 1-2 x 10^5 antibody molecules bind to the Ramos-EHRB cells (Figure 7A) and Daudi cells (Figure 7B).

To exclude the possibility that the iodinated antibodies bind via Fc-receptors, binding curves were confirmed by use of anti-CD20 $F(ab')_2$ fragments. Again, similar numbers of 2F2 and rituximab-$F(ab')_2$ fragments bound to both Ramos-EHRB and Daudi cells. Also in these experiments, the number of 2F2 or rituximab antibody molecules bound to Ramos-EHRB cells and Daudi cells saturates at approximately twice the number of 11B8 and B1 molecules bound to the cells.

Dissociation rate: To determine the dissociation rate of the mAbs, Ramos-EHRB cells (final volume of 1 ml in the presence of azide/2DOG) were incubated for 2 hours at 37 °C with 2 μg/ml ^{125}I mAbs to achieve maximum binding. Following centrifugation in a microfuge (2000 rpm for 2 min), the supernatant was removed, the pellet quickly resuspended in 1 ml medium, and immediately transferred to 9 ml medium at 37 °C in a 15 ml conical tube. At various times over the next 2 hours, 0.4 ml samples were removed and separated on phthalate oils to determine the level of radiolabeled mAbs remaining on the cell surface. As shown in Figure 8, both 2F2 and 11B8 dissociated significantly more slowly from CD20 than rituximab or B1.

Dissociation rates of anti-CD20 $F(ab)_2$ fragments: Ramos-EHBR cells were saturated with 2 μg/ml of ^{125}I-labeled $F(ab)_2$ fragments of 2F2, 11B8, and rituximab, respectively. The Ramos-EHBR cells were washed and incubated in the presence of a high concentration of the unlabeled antibody. The maximal (initial) binding to Ramos-EHRB cells was set at 100%. At several time points over the next 3 hours following loading, 0.4 ml samples were removed and separated on phthalate oil to determine the levels of radiolabeled mAb remaining on the cell surface. As can be seen

Samsung Bioepis Exhibit No. 1002
Page 12266

from Figure 9, 2F2 and 11B8 dissociated much more slowly from the surface of CD20 than rituximab. At 90 min, approximately 50% of the $F(ab)_2$ rituximab molecules were bound to the cell, whereas half of the $F(ab)_2$ 2F2 molecules were dissociated after 3 hours. The k_d (k_{off}) values for 2F2, 11B8T, and rituximab are calculated as follows:

$F(ab)_2$ 2F2: $k_d = \ln 2/t_{½}$ (sec) = ln 2/10800 (sec) = 6.4×10^{-5} sec^{-1}

$F(ab)_2$ 11B8T: $k_d = \ln 2/t_{½}$ (sec) = ln 2/9000 (sec) = 7.7×10^{-5} sec^{-1}

$F(ab)_2$ rituximab: $k_d = \ln 2/t_{½}$ (sec) = ln 2/5400 (sec) = 1.3×10^{-4} sec^{-1}

Anti-CD20 mAb functional off rates: The impact of the slow 2F2 dissociation rate compared to rituximab was assessed in a functional CDC assay. To this end, Daudi or SU-DHL4 cells were pre-incubated with 10 µg/ml anti-CD20 mAb or an isotype control antibody, washed and incubated in medium for different time points. At these time points after start of the assay, samples were incubated with complement (normal human serum 20 vol/vol%) and then incubated for another 45 min at 37 °C. Thereafter, cell lysis was determined on FACS by using PI (propidium iodide) staining method. The % lysed cells (PI-positive cells) are shown in Figure 10A (Daudi cells) or Figure 10B (SU-DHL4 cells) as a function of incubation time. 2F2 induced high CDC in both cell lines, and still lysed up to 90% of the cells after 6 hours, indicating that the CD20 saturation of the cells remained sufficiently high to induce complement-mediated lysis of most of the cells. Rituximab, in contrast and in agreement with the above dissociation rate studies, dissociated rapidly from the cells and failed to induce specific lysis following the 6 hour incubation period. 11B8 was used as a control and did not induce CDC.

Example 6 CDC of Human Antibodies Against CD20

Serum preparation: Serum for complement lysis was prepared by drawing blood from healthy volunteers into autosep gel and clot activator vacutainer tubes (BD biosciences, Rutherford, NJ) which were held at room temperature for 30-60 min and then centrifuged at 3000 rpm for 5 min. Serum was harvested and stored at -80 °C.

Samsung Bioepis Exhibit No. 1002
Page 12267

Flow cytometry: For flow cytometry a FACScalibur flow cytometer was used with CellQuest pro software (BD Biosciences, Mountain view, CA). At least 5000 events were collected for analysis with cell debris excluded by adjustment of the forward sideward scatter (FCS) threshold.

CDC kinetics: In a first set of experiments (n=3) the kinetics of CDC of five different B-cell lines, *i.e.*, Daudi, SU-DHL-4, Raji, DOHH and ARH-77, were determined by adding 10 μg/ml 2F2, rituximab and an IgG control antibody, respectively, for 10 min before human serum was added. At several time intervals (up to one hour) after induction of CDC, the cells were suspended in PI solution and cell lysis (number of PI-positive cells) was measured by flow cytometry. The results are depicted in Figures 11A (ARH-77 cells), 11 B (Daudi cells), 11C (Raji cells), 11D (DOHH) and 11 E (SU-DHL-4). As seen, addition of antibodies induced cell lysis within 5 min. Interestingly, addition of 2F2 resulted in a marked cell lysis of more than 80% in all five B-cell lines. Rituximab induced more than 80% cell lysis only in the SU-DHL-4 and Daudi cell lines, whereas the cell lysis of the DOHH cell line was ~50%, and less than 20% in the ARH-77 and Raji cell lines. No lysis was observed with the IgG control antibody (data only shown in Figure 11B).

CDC serum titration: In a separate set of experiments (n=5), NHS (normal human serum) was titrated at two different antibody concentrations of 0.5 μg/ml and 5 μg/ml. Cells were pre-incubated with 2F2 or rituximab for 10 min, before a concentration range of NHS was added. At 45 min after induction of CDC, cells were resuspended in PI solution. Cell lysis (number of PI-positive cells) was measured by flow cytometry. Figures 12A-D show the percentage of lysed (PI-positive) cells as a function of NHS concentration. Figure 12A shows cell lysis of Daudi cells, Figure 12B cell lysis of ARH-77 cells, Figure 12C cell lysis of DOHH cells, and Figure 12D cell lysis of Raji cells. Increased lysis of cells was observed with increased NHS concentration. Addition of 2F2 caused maximal lysis of Daudi cells at the highest NHS and antibody concentration. Rituximab induced about 50% cell lysis of Daudi cells at the highest NHS concentration.

In ARH-77 cells, only the highest concentration of NHS and 2F2 led to approximately 75% cell lysis. Lower antibody concentrations were insufficient to induce ARH-77 cell lysis. Rituximab was not able to induce cell lysis of ARH-77 cells in this experiment.

2F2 was able to induce NHS-concentration dependent cell lysis of DOHH cells at both the high and the low concentration, whereas rituximab was not able to induce lysis under these conditions.

Samsung Bioepis Exhibit No. 1002
Page 12268

Finally, 2F2 induced NHS-concentration-dependent lysis of Raji cells, which was only apparent by use of 5 μg/ml mAb. No lysis was observed with rituximab.

In these experiments, no lysis was observed with the isotype control antibody (data not shown).

CDC antibody titration: To measure the ability of the anti-CD20 antibodies to induce CDC at low concentrations, an experiment was performed where the antibodies were titrated (n=6). Various cell lines were pre-incubated with a concentration range of 2F2 and rituximab, respectively, for 10 min before NHS was added. After 45 min incubation at 37 °C (when maximal lysis occurs) the cells were resuspended in PI solution and cell lysis (number of PI-positive cells) was measured by flow cytometry. Figures 13A (Daudi cells), 13B (DOHH cells), 13C (ARH-77 cells), and 13D (Raji cells) show the percentage of lysed (PI-positive) cells as a function of antibody concentration. Both 2F2 and rituximab induced a concentration-dependent increase in cell lysis. 2F2 induced more than 80% lysis of Daudi cells upon addition of 2 μg/ml, whereas with rituximab this level was not reached even after addition of 10 μg/ml. Furthermore, 2F2 induced more than 80% lysis of DOHH cells at 0.4 μg/ml, whereas minimal lysis was observed with rituximab at this concentration. The maximal lysis of DOHH cells with rituximab (~30% of total cell analyzed) was reached at 10 μg/ml. Induction of lysis of ARH-77 and Raji cells by 2F2 was lower, but still ~70% lysis was reached at an antibody concentration of 10 μg/ml. At its highest concentration, rituximab induced lysis in only ~23% of ARH-77 cells, and in only ~6% of Raji cells.

In a similar experiment, 2F2, 2F2T, 11B8T, and rituximab were investigated for their ability to induce CDC of Daudi and Raji cell lines, see Figures 14A and 14B. Also in this experiment more than 80% lysis of Daudi cells was observed with (transfectoma-derived) 2F2T at 10 μg/ml, whereas rituximab reached only to 60% lysis even at 10 μg/ml, cf. Figure 14A. Lysis of Daudi cells with 2F2T was identical to the lysis obtained with hybridoma-derived 2F2.

Lysis of Raji cells was more difficult, but again both 2F2 and 2F2T induced lysis of Raji cells to a similar extent (Figure 14B). Rituximab was not able to induce CDC of Raji cells which is in agreement with the experiment shown in Figure 13D.

As can be seen from Figures 14A and 14B neither Daudi nor Raji cells were susceptible to CDC by 11B8T. B1 induced lysis of Daudi cells, but only to a small extent, and was not able to induce lysis of Raji cells.

Samsung Bioepis Exhibit No. 1002
Page 12269

CDC activity of anti-CD20 in Daudi cells: To determine the CDC activity of each antibody, elevated membrane permeability was assessed using FACS analysis of propidium iodide (PI)-stained cells. Briefly, the Daudi cells were washed and resuspended in RPMI/1% BSA at 1 x 10^6 cells/ml. Various concentrations of human monoclonal antibodies were added to the Daudi cells and allowed to bind to CD20 on the cells for 10-15 min at room temperature. Thereafter, serum as a source of complement was added to a final concentration of 20% (v/v) and the mixtures were incubated for 45 min at 37 °C. The cells were then kept at 4 °C until analysis. Each sample (150 µl) was then added to 10 µl of PI solution (10 µg/ml in PBS) in a FACS tube. The mixture was assessed immediately by flow cytometry. As shown in Figure 15A, 2F2 and 7D8 showed superior CDC activity compared to rituximab.

In a second experiment, cells were labeled with human monoclonal antibodies as above, then washed and incubated in PBS for 45 min at 37 °C prior to the addition of human serum. This ensured that only antibody bound to the cell at the time of serum addition was available to activate complement for cell lysis. As shown in Figure 15B, decreased CDC activity was found for rituximab compared to 2F2 and 7D8 indicating that the human antibodies (2F2 and 7D8) are not affected by washing the cells prior to the addition of serum.

CDC activity of anti-CD20 in Raji cells: CDC activity was assessed using Raji cells which have relatively high surface expression of CD55 and CD59 and, therefore, are more resistant to complement attack. Human antibodies were added to Raji cells and allowed to bind for 15 min. Human serum (20%) was added and the mixtures incubated for 45 min at 37 °C. As shown in Figure 16A, rituximab was ineffective in mediating CDC of Raji cells whereas significant levels of cell lysis occurred in Raji cells opsonized with 2F2 or 7D8. Accordingly, 2F2 and 7D8 have a unique capacity to lyse CD55/59 positive target cells.

In a separate experiment, Raji cells were pre-incubated with saturating concentrations of anti-CD55 mAb (final concentration of 5 µg/ml) and anti-CD59 mAb (final concentration of 5 µg/ml) to block the effects of these complement defense molecules. Human anti-CD20 antibodies were then added along with serum (20%) as above for 45 min at 37 °C. As shown in Figure 16B, the blockade of CD55 and CD59 molecules resulted in almost 100% lysis of Raji cells with human antibodies 2F2 or 7D8 whereas only a 25% increase in cell lysis was observed using rituximab.

Role of complement inhibitors I – Expression of surface molecules: Since complement inhibitors such as CD55 and CD59 appear to play an important role in susceptibility to rituximab-induced CDC, an experiment was performed to determine

Samsung Bioepis Exhibit No. 1002
Page 12270

the expression of these molecules on the B-cell lines under investigation (Raji, Daudi, DOHH, ARH-77, and SU-DHL-4).

The cells were stained with FITC-conjugated anti-CD55, anti-CD59 and anti-CD20 antibodies and molecules expression was analyzed by flow cytometry. The results are shown in the below Table 1.

Table 1

Expression	CD20	CD55	CD59
ARH-77	++	++++	++
Raji	+	++	+++
DOHH	++	+++	++
SU-DHL-4	+++	+	++
Daudi	++	+	+

Role of complement inhibitors II – Blockade of CD55 and CD59: To further study the roles of CD55 and CD59 in anti-CD20-induced CDC, both complement inhibitor molecules were blocked by specific antibodies prior to induction of CDC (n=3). Raji cells were used because only partial lysis was induced by 2F2 alone. Raji cells (1 x 10^5 cells/50 µl) were pre-incubated with a concentration range of 2F2 and rituximab together with anti-CD55 (5 µg/ml) or anti-CD59 (5 µg/ml) antibodies for 10 min, before pooled NHS (20%) was added. At 45 min after induction of CDC, cells were resuspended in PI solution. Cell lysis (number of PI-positive cells) was measured by flow cytometry. Figures 17A-C show the percentage of lysed (PI-positive) cells as a function of antibody concentration, and show one experiment which is exemplary of three experiments. Figure 17A shows incubation of Raji cells with anti-CD55 antibody, Figure 17B incubation of Raji cells with anti-CD59 antibody, and Figure 17C incubation of Raji cells with anti-CD55 and anti-CD59 antibodies.

As can be seen in Figure 17A, addition of anti-CD55 antibody did not influence 2F2 or rituximab-induced CDC. Addition of anti-CD59 antibody increased susceptibility of the cells to both 2F2 and to rituximab with ~30% (Figure 17B). Addition of both anti-CD55 and anti-CD59 further enhanced anti-CD20-induced lysis of cells with ~30% (Figure 17C).

Role of complement factors, as determined by flow cytometry I – C1q binding: Anti-CD20 antibodies (2F2 and rituximab) and an isotype control antibody were added to various B-cell lines. After 10 min incubation, NHS (1 vol/vol%) was added. After further incubation for 10 min at 37 °C and washing of the cells, the supernatant was discarded and the cell pellet was incubated with FITC-conjugated anti-

Samsung Bioepis Exhibit No. 1002
Page 12271

C1q antibody. Data show mean fluorescence intensity of cells stained with C1q and are depicted in Figures 18A (Daudi), 18B (ARH-77), 18C (DOHH), and 18D (Raji) (n=6). The results indicated antibody concentration-dependent increase in binding of C1q by 2F2, irrespective of the B-cell line investigated. Moreover, C1q binding by 2F2 was always higher than binding by rituximab, in all cell lines tested. No increase in mean fluorescence was observed with the isotype control antibody (data not shown).

Role of complement factors, as determined by flow cytometry II – Complement activation via the classical route: Fixation of C4c to antibody-coated cells is an indication of activation of complement activation via the classical route. Anti-CD20 antibodies (2F2 and rituximab) and an isotype control antibody were added to various B-cell lines. After 10 min incubation at 37 °C, NHS (1 vol/vol%) was added. After further incubation and washing of the cells, the supernatant was discarded and the cell pellet was incubated with FITC-conjugated anti-C4c antibody. Data show mean fluorescence intensity of cells stained with C4c and are depicted in Figures 19A (Daudi), 19B (ARH-77), 19C (DOHH), and 19D (Raji) (n=6). Complement factor C4c fixation to 2F2 was demonstrated in all B-cell lines tested (n=3), with a maximum reached at ~1 µg/ml of antibody. Fixation of C4c after 2F2 binding was much higher than after rituximab, irrespective of the cell line tested. No increase in mean fluorescence was observed with the isotype control antibody (data not shown).

CDC in heat-inactivated serum: Cells (Daudi cells, ARH-77 cells or Raji cells) and antibodies (rituximab, 2F2, 2F2T, 11B8, and isotype control antibody HuMab-KLH IgG1) were pre-incubated in a concentration range of anti-CD20 antibodies for 10 min, before NHS (active or heat-inactivated in a water bath at 57 °C at 30 min) was added. At 45 min after induction of CDC, cells were resuspended in PI solution. Cell lysis (number of PI-positive cells) was measured by flow cytometry. No lysis of the cells was observed in the presence of heat-inactivated serum, irrespective of the cell-line and CD20-antibody used, no CDC was observed in the presence of heat-inactivated serum.

Example 7 ADCC of Human Antibodies Against CD20 ADCC Assay I

Enrichment of human neutrophils: Polymorphonuclear cells (neutrophils, PMNs) were enriched from heparinized whole blood. Blood was diluted twice in RPMI 1640 and was layered on Ficoll (Lymphocyte Separation Medium 1077 g/ml, 710 g, RT, 20 min; BioWhittaker, cat. 17-829E, lot no. 0148 32) and centrifuged at 2000 rpm for 20 min. The mononuclear cell layer was removed, and erythrocytes within the pellet

Samsung Bioepis Exhibit No. 1002
Page 12272

containing neutrophils were hypotonically lysed using ice-cold NH_4Cl solution (155 mM NH_4Cl, 10 mM $NaHCO_3$, 0.1 mM EDTA, pH 7.4). The remaining neutrophils were washed twice and resuspended in RPMI 1640 supplemented with 10% FCS (RPMI-10).

Enrichment of human peripheral blood mononuclear cells: Human blood was diluted twice in RPMI 1640 and blood cells were layered on Ficoll (Lymphocyte Separation Medium 1077 g/ml, 710 g, RT, 20 min; BioWhittaker, Cambrex Bio Science Verviers, Verviers, Belgium, cat. 17-829E, lot no. 0148 32). Peripheral blood mononuclear cells (MNCs) were collected from the interphase, washed and resuspended in RPMI 1640 culture medium supplemented with 10% FCS, 2 mM L-glutamine, 5 U/ml penicillin, 50 µg/ml streptomycin (all derived from BioWhittaker) to which 25 mM HEPES (BioWhittaker) was added.

ADCC set up: Target B-cells (freshly isolated B-cells or from B-cell lines) were labeled with 20 µCi ^{51}Cr (Amersham Biosciences, Uppsala, Sweden) for 2 hours. After extensive washing in RPMI-10, the cells were adjusted to 1 x 10^5 cells/ml. Whole blood or isolated effector cells (50µl; MNCs, PMNs) or plasma (50 µl), sensitizing antibodies (50 µl), and RPMI-10 (50 µl) were added to round-bottom microtiter plates (Greiner Bio-One GmbH, Frickenhausen, Germany). Assays were started by adding target cells (50 µl) giving a final volume of 200 µl. For isolated effector cells, an effector to target (E:T) ratio of 40:1 was used. For whole blood, an amount of 33 vol/vol% was used corresponding to an estimated effector to target ratio of 40:1. After incubation (3 hours, 37 °C), assays were stopped by centrifugation, and ^{51}Cr release from triplicates was measured in counts per minute (cpm) in a scintillation counter. Percentage of cellular cytotoxicity was calculated using the following formula:

% specific lysis = (experimental cpm – basal cpm)/(maximal cpm – basal cpm) x 100

with maximal ^{51}Cr release determined by adding perchloric acid (3% final concentration) to target cells, and basal release measured in the absence of sensitizing antibodies and effector cells.

Statistics: Data were analyzed by one-way ANOVA, followed by Tukey's multi comparison post-hoc test. Analysis was performed using Graph Pad Prism (version 3.02 for Windows, Graph Pad Software, San Diego, CA, USA).

Samsung Bioepis Exhibit No. 1002
Page 12273

Lysis of ARH-77 cells: In a first set of experiments, ARH-77 cells were used as target cells (Figure 20). Addition of 2F2 (n=3), rituximab (n=3) or 11B8T (n=1) resulted in MNC-mediated lysis of ARH-77 cells of approximately 50%. No specific lysis was observed in the presence of neutrophils. Addition of plasma (to evaluate the role of complement) induced lysis of ARH-77 cells after incubation with 2F2, but not after incubation with rituximab ($p<0.05$, 2F2 vs. no antibody, ANOVA) or 11B8T. In the presence of whole blood, lysis of ARH-77 cells increased after incubation with 2F2 ($p<0.05$, 2F2 vs. rituximab and 2F2 vs. no antibody, ANOVA), but not with rituximab. Specific lysis induced by rituximab was in fact very low in the presence of whole blood. 11B8T induced cell lysis of approximately 25% (n=1) in the presence of whole blood. In the absence of antibody, non-specific lysis of 10-15% was observed.

Lysis of B-CLL cells: In a second set of experiments, chronic B-lymphocytic leukaemia (B-CLL) cells obtained from B-CLL patients (n=12) were subcloned for 5 rounds and then used as target cells in the experiment (Figure 21). In the absence of antibody, no specific lysis was observed, but addition of 2F2, 11B8T or rituximab (10 μg/ml) increased MNC-mediated specific lysis to 10-20% ($p<0.001$, ANOVA). Incubation of target cells with plasma and 2F2 induced specific lysis of B-CLL cells, whereas no specific lysis was observed with 11B8T or rituximab ($p<0.001$, ANOVA). Moreover, 2F2 mediated specific lysis of B-CLL cells after incubation in whole blood. No specific lysis of B-CLL cells by whole blood was observed with 11B8T ($p<0.01$, ANOVA) or rituximab ($p<0.001$, ANOVA). No specific lysis was observed in the presence of neutrophils.

Because rituximab was able to mediate effective ADCC but not CDC of the tumor cells tested, it is likely that whole blood-induced B-cell lysis by 2F2 is mediated via complement.

Lysis of hairy cell leukaemia (HCL) cells: In a third set of experiments lysis of HCL cells by 2F2, 11B8T, and rituximab by ADCC or in the presence of plasma or whole blood was determined. Data are shown in Figure 22. Whereas neutrophils could not mediate ADCC irrespective of the mAb used, 11B8T was able to induce MNC-mediated lysis of HCL cells more efficiently than 2F2 ($p<0.001$, ANOVA) or rituximab ($p<0.05$, ANOVA). 2F2 and rituximab were not able to induce MNC-mediated lysis of HCL cells. Plasma-mediated lysis of the cells was strongly enhanced with 2F2, as compared to rituximab ($p<0.05$, ANOVA), 11B8T ($p<0.01$, ANOVA) or without antibody ($p<0.001$, ANOVA). When lysis induced by anti-CD20 in the presence of whole blood was studied, 2F2 induced complete lysis of cells, and was

Samsung Bioepis Exhibit No. 1002
Page 12274

superior to rituximab ($p<0.01$, ANOVA), 11B8T or no antibody added ($p<0.001$, ANOVA).

Lysis of B-ALL cells: Using cells from two patients the ability of 2F2 and rituximab to induce lysis B-ALL cells by ADCC or complement was investigated (Figure 23). As was observed in the previous experiments, 2F2 and rituximab induced MNC-mediated ADCC of B-ALL cells to a similar extent. But again 2F2 was able to induce plasma- and whole blood-mediated lysis of B-ALL cells, whereas rituximab was not.

Lysis of follicular lymphoma cells: When lysis of follicular lymphoma cells (n=2) was investigated, a different picture emerged (Figure 24). A minor PMN-mediated lysis of cells with 2F2 was observed, and both 2F2 and rituximab were not able to induce MNC-mediated ADCC. 11B8T was still able to induce MNC-mediated lysis of approximately 20%. Although a relatively high plasma-mediated lysis was induced by rituximab, complete plasma-mediated lysis was observed with 2F2. Also with whole blood, complete lysis was observed with 2F2, whereas 70% lysis with rituximab. Minimal plasma- or whole blood-mediated lysis by 11B8T was observed.

Lysis of primary mantle cell lymphoma cells: Specific lysis of mantle cell lymphoma cells was more difficult to induce (n=1, Figure 25). Minimal or no lysis by 2F2, 11B8T or rituximab was observed after addition of PMN or MNC and CD20 mAbs. However, 2F2 was still able to induce approximately 40% lysis by plasma or whole blood, whereas with rituximab only 10-20% of the cells were lysed. 11B8T was not able to induce lysis of primary mantle cell lymphoma cells.

Antibody concentration-dependent lysis of ARH-77 cells in whole blood: In a further experiment (n=4) dose-dependency regarding the induction of ADCC on ARH-77 cells in the presence of whole blood was analyzed. As can be seen in Figure 26, titration of 2F2 induced a dose-dependent increase in the percentage of specific lysis ($p<0.05$: treatment-effect, two-way ANOVA) of ARH-77 cells. No specific lysis of ARH-77 cells was observed with rituximab.

ADCC assay II

Preparation ^{51}Cr-labeled target cells: ARH-77 cells and Raji cells were collected (3 x 10^6 cells) in RPMI++, spun down (1500 rpm; 5 min), resuspended in 140 µl ^{51}Cr (Chromium-51; CJS11-1mCi, batch 12; 140 µl is about 100 µCi) and incubated

Samsung Bioepis Exhibit No. 1002
Page 12275

(37 °C water bath; 1 hour). After washing cells (1500 rpm, 5 min, in PBS, 3x), cells were resuspended in RPMI++ and counted by trypan blue exclusion. Cells were brought at concentration of 2 x 10^4 cells/ml.

Preparation of effector cells: Fresh peripheral blood mononuclear cells (MNC) were isolated from 40 ml of heparin blood by Ficoll (Bio Whittaker; lymphocyte separation medium, cat 17-829E) via manufacturer's instructions. After resuspension of cells in RPMI++, cells were counted by trypan blue exclusion and adjusted to a concentration of 1 x 10^6 cells/ml.

ADCC set up: 50 µl RPMI++ was pipetted into 96 wells plates, and 50 µl of ^{51}Cr-labeled targets cells were added. Thereafter, 50 µl of antibody was added, diluted in RPMI++ (final concentrations 10, 1, 0.1, 0.01 µg/ml). Cells were incubated (RT, 10 min), and 50 µl effector cells were added, resulting in an effector to target ratio of 50:1 (for determination of maximal lysis, 50 µl 5% Triton-X-100 was added instead of effector cells). Cells were spun down (500 rpm, 5 min), and incubated (37 °C, 5% CO_2, 4 hours). After spinning down the cells (1500 rpm, 5 min), 100 µl of supernatant was harvested into micronic tubes, and counted in a gamma counter. The percentage specific lysis was calculated as follows:

% specific lysis = (cpm sample- cpm target cells only)/(cpm maximal lysis –cpm target cells only) x 100

Statistics: Data were analyzed by one-way ANOVA, followed by Tukey's multi comparison post-hoc test. Analysis was performed using Graph Pad Prism (version 3.02 for Windows, Graph Pad Software, San Diego, CA, USA).

Antibody concentration-dependent lysis of ARH-77and Raji cells: 2F2T and 11B8T were tested for their ability to induce ADCC of ARH-77 and Raji cells (n=3) in comparison with rituximab.

A dose-effect relation with CD20 mAbs was observed in ADCC of ARH-77 cells using MNC as effector cells (Figure 27). Both 2F2T and 11B8T induced specific lysis of ARH-77 cells which was maximal (50%) at 10 µg/ml of mAb. Rituximab induced only 25% lysis of target cells. Addition of the isotype control antibody (HuMab-KLH) did not induce ADCC. No specific lysis was observed without addition of MNCs (data not shown).

Samsung Bioepis Exhibit No. 1002
Page 12276

When Raji cells were used as target cells, a similar picture as with ARH-77 cells emerged (Figure 28). Both 2F2T and 11B8T induced MNC-mediated lysis of Raji cells, albeit that 2F2T seemed more potent than 11B8T at low concentrations. The maximum lysis reached with 2F2T and 11B8T was approximately 35%. Rituximab induced MNC-mediated lysis of Raji cells, although only 20% of target cells were susceptible to rituximab. Addition of the isotype control antibody (HuMab-KLH) did not induce ADCC. No specific lysis was observed without addition of MNCs (data not shown).

Example 8 FRET and Triton-X insolubility analysis

Preparation of Cy3- and Cy5-conjugated mAb for fluorescence resonance energy transfer (FRET): Monoclonal antibodies were directly conjugated to bifunctional NHS-ester derivatives of Cy3 and Cy5 (Amserham Biosciences UK Ltd) as described in the manufacturer's instructions. Briefly, mAb were dialyzed against 0.1 M carbonate/bicarbonate buffer (pH 9). Thereafter, dye was dissolved in H_2O, immediately added to 1 mg of the mAb, and incubated at room temperature in the dark for 45 min. The labeled mAbs were separated from the unconjugated dye by gel chromatography using a PD10-Sephadex G25 column equilibrated in PBS. Molar ratios of coupling were determined spectrophotometrically from ε_{552} = 150/mM/cm for Cy3, ε_{650} = 250/mM/cm for Cy5, and ε_{280} = 170/mM/cm for protein, and ranged from 5- to 8-fold excess dye:protein.

FRET analysis: Daudi cells were resuspended at 5 x 10^6 cells/ml in PBS/0.1% BSA, and equimolar donor (Cy3)-conjugated and acceptor (Cy5)-conjugated mAb were combined and added to the cell suspension (final concentration 10 μg/ml). Cells were incubated for 30 min in the dark, at 4 °C or 37 °C. Each experiment included cells labeled with donor- and acceptor-conjugated mAb after pre-incubation with a 20-fold molar excess of unconjugated mAb, and cells labeled with donor-or acceptor-conjugated mAb in the presence of equimolar unlabeled mAb. To assess the association of labeled antigens, flow cytrometric FRET measurement was carried out using a FACScalibur (BD Biosciences). The fluorescence intensities at 585 nm (FL2) and 650 nm (FL3), both excited at 488 nm, and the fluorescence intensities at 661 nm (FL4), excited at 635 nm, were detected and used to calculate FRET according to the equitation below, where A is acceptor (Cy5), and D is donor (Cy3). All values obtained were corrected for autofluoresence using the following formula:

FRET = FL3(D,A)-FL2(D,A)/a-FL4(D,A)/b
where a = FL2(D)/FL3(D), and b = FL4(A)/FL3(A)

Samsung Bioepis Exhibit No. 1002
Page 12277

Correction parameters were obtained using data collected from single-labeled cells, and side angle light scattering was used to gate out debris and dead cells. FRET between donor and acceptor mAb derivatives on dually labeled cells is expressed in terms of acceptor sensitized emission at 488 nm. Larger FRET values indicate closer physical association of the donor- and acceptor labeled antibodies or a higher density of acceptor-labeled mAb in the vicinity of donor-labeled mAb.

Assessment of raft associated antigen by Triton X-100 (TX) insolubility: As a rapid assessment of the presence of antigen in raft microdomains, a flow cytometry method based on Triton X-100 (TX) insolubility at low temperatures was used, as described previously. In brief, Daudi cells were washed in RPMI/ 1% BSA and resuspended at 2.5 x 10^6/ml. The cells (100 µl) were then incubated with 10 µg/ml of FITC conjugated mAb for 15 min at 37 °C, washed in cold PBS/ 1% BSA/ 20 mM sodium azide (PBS-BS), and the sample was divided in half. All samples were kept on ice throughout the remainder of the assay. One half was maintained on ice to allow calculation of 100% surface antigen levels, whilst the other was treated with 0.5% TX for 15 min on ice to determine to proportion of antigens remaining in the insoluble raft fraction. Cells were then maintained at 4 °C throughout the remainder of the assay, washed once in PBS-BS, resuspended in PBS-BS and assessed by flow cytometry. To determine the constitutive level of raft association of the target antigens, cells were first treated with 0.5% TX for 15 min on ice and washed in PBS-BS prior to binding of FITC-labeled mAb.

As shown in Figures 29A, 29B, and 29, fluorescence resonance energy transfer (FRET) analysis indicates clustering of CD20 upon incubation with 2F2 or 7D8. No such clustering was observed upon incubation with 11B8. These results are consistent with the TX treatment data, cf. Figure 29C, (*i.e.*, 2F2 and 7D8, unlike 11B8 remain with the insoluble fraction of the cell following binding) and support the concept that 2F2 and 7D8, upon binding, translocate CD20 into lipid raft compartment of the B cell membrane.

As shown if Figure 30 (FRET values and s.e.m. of three experiments using one-way ANOVA followed by Tukey's multi comparison post-hoc test) the FRET analysis indicates clustering of rituximab and 2F2, whereas no clustering was observed with 11B8T. These data are in agreement with the data obtained after treatment with 0.5% TX prior to binding of FITC-labeled mAbs as shown in Figure 31 (n=2).

Samsung Bioepis Exhibit No. 1002
Page 12278

Preparation of lipid raft fractions and Western blotting: Another way to examine the association of CD20 with lipid rafts, is to investigate the distribution of CD20 between the raft and non-raft membrane fractions using the sucrose gradient fractionation method as disclosed by Deans, J.P., et al., *J. Biol. Chem.*, 1998. **273**(1): pp 344-348, except that Optiprep (Sigma) was used instead of sucrose. Monoclonal antibodies directed against CD20 (10 μg/ml) were allowed to bind to Daudi cells (1 x 10^7) for 20 min at 37 °C. Following this incubation, the cells were pelleted, washed twice with PBS and lysed in ice-cold lysis buffer (1.0% TX in MES-buffered saline (25 mM MES, pH 6.5, 150 mM NaCl, 1 mM phenylmethylsulfonyl fluoride, 5 μg/ml aprotinin, 5 μg/ml leupeptin, 10 mM EDTA)). The cell pellet was resuspended thoroughly and incubated for 20 min on ice. Thereafter, the lysate was mixed with 400 μl cold 60% Optiprep (Sigma). The sample was overlaid with a 600 μl step of each 35%, 30%, 25%, 20%, 0% Optiprep in lysis buffer. The gradients were spun at 40.000 rpm at 4 °C for 18 hours. Six fractions from the top were collected, resolved on a 4-15% SDS-PAGE gel, transferred onto nitrocellulose membranes and incubated with primary antibody (mouse anti-CD20 polysera; Serotec, UK), followed by HRP-conjugated secondary antibody (rabbit anti mouse-HRP; Jackson, Bar Harbor, Maine, USA). Blots were visualised using Supersignal West Dura extended duration substrate (Pierce, Woburn, MA, USA).

The results are shown in Figure 32. As it can be seen, CD20 molecules are confined to the high-density fraction 5 (untreated cells). Cells treated with rituximab showed a distinct shift in CD20 distribution with a significant proportion in the lower density membrane fractions 2 and 3, coincident with the fraction where membrane rafts are expected to sediment. Cells treated with 2F2 also showed this shift to fractions 2 and 3. In contrast, cells treated with 11B8T for 20 min showed a similar distribution to untreated cells, with CD20 molecules in fraction 5. In conclusion binding to 2F2 and rituximab induces a shift of CD20 molecules to the lower density membrane fractions, whereas binding to 11B8T does not.

Example 9 Apoptosis of Burkitt Cell Lines with Human Antibodies Against CD20

Apoptosis: Daudi cells, 0.5 x 10^6 in 1 ml tissue culture medium, were placed into 24-well flat-bottom plates with 1 or 10 μg/ml mAb or control antibodies, and incubated at 37 °C. After 20 hours, cells were harvested, washed in Annexin-V-FITC binding buffer (BD biosciences) and labeled with Annexin V-FITC (BD biosciences) for 15 min in the dark at 4 °C. The cells were kept at 4 °C until analysis. Each sample (150 μl) was added to 10 μl of PI solution (10 μg/ml in PBS) in a FACS tube. The mixture was assessed immediately by flow cytometry using a FACScalibur flow cytometer with

Samsung Bioepis Exhibit No. 1002
Page 12279

CellQuest pro software (BD Biosciences, Mountain view, CA). At least 10,000 events were collected for analysis.

Induction of apoptosis in Daudi cells: Daudi cells were incubated for 20 hours in the presence of human antibodies against CD20 (1 μg/ml) (without the addition of a secondary cross-linking antibody). Induction of apoptosis was assessed by AnnexinV/PI staining using flow cytometry.

As shown in Figures 33A-G, 11B8 shows clear evidence of inducing apoptosis (similar to that induced by an anti-IgM antibody). 2F2 and 7D8 did not induce apoptosis of Daudi cells. An apoptosis-inducing mouse anti-CD20 antibody, AT80, was used as a control.

Induction of apoptosis in Raji cells: Induction of apoptosis of Raji cells was tested with a concentration range of CD20 mAbs. Figure 34 shows the percentage of annexin-V-positive cells. As can be seen from Figure 34, the positive control mouse anti-human CD20-mAb, B1, induced a concentration-dependent increase in apoptosis of Raji cells with a maximum of approximately 70% at 10 μg/ml mAb. Also 11B8 was a strong inducer of apoptosis, resulting in apoptosis of Raji cells with a maximum of 53.4% at 10 μg/ml mAb. On the other hand, 2F2 and rituximab were very poor in inducing apoptosis of Raji cells, with slightly elevated levels of apoptosis compared to negative control levels.

Induction of apoptosis in Daudi cells: The same picture emerged when Daudi cells were used as target cells, after addition of 1.0 μg/ml CD20 mAb (Figures 35A and 35B). Data in Figure 35A show the total of annexin-V positive cells, and data in Figure 35B (the X-axis showing annexin-V, and the Y-axis showing PI) show the percentages of Daudi cells in early apoptosis (annexin-V positive and PI negative) and late apoptosis (annexin-V positive and PI positive). Again, Both B1 (65.9%) and 11B8T (56.3%) were strong inducers of apoptosis (Figure 36), when used at a concentration of 1.0 μg/ml. Addition of 2F2T resulted in a low level of apoptotic Daudi cells (17%). Addition of rituximab resulted in approximately 29% apoptosis of Daudi cells. Addition of isotype control antibody HuMab-KLH did not induce apoptosis of Daudi cells (6%).

Samsung Bioepis Exhibit No. 1002
Page 12280

Example 10 Homotypic Adhesion of Cells with Human Antibodies Against CD20

Homotypic aggregation correlates with induction of apoptosis. Therefore, the ability of the anti-CD20 mAbs to induce homotypic aggregation of B cells was investigated

Homotypic aggregation of Ramos-EHRB cells: Ramos-EHRB cells (0.5 x 10^6 in 1 ml tissue culture medium) were incubated at 37 °C for 4 hours in the presence of anti-CD20 antibodies 11B8, 2F2, or 7D8 (without cross-linking) and induction of homotypic adhesion was assessed by light microscopy (as described above).

As shown in Figures 36A-E, 11B8 caused extensive aggregation of Ramos-EHRB cells (similar to the aggregation caused by murine anti-CD20 antibody, AT80). 2F2, and 7D8 did not induce homotypic aggregation of Ramos cells.

Homotypic aggregation of Daudi cells: Daudi cells were placed into 24-well flat-bottom plates with 1 or 10 µg/ml anti-CD20 mAbs or control antibody, and incubated at 37 °C for 4 hours. The extent of homotypic aggregation was determined by light microscopy. As can be seen from Figure 37, 2F2 hardly induced homotypic aggregation of Daudi cells, with 1.0 µg/ml (and 10 µg/ml, data not shown). Rituximab gave little homotypic aggregation of Daudi cells. In contrast, the B1 antibody was a strong inducer of homotypic aggregation.

Example 11 Immunotherapy Using Human Antibodies Against CD20

Therapy with high dose (100 µg) 2F2 and 7D8 of SCID mice challenged with Daudi cells: The SCID mice were obtained from Harlan UK Ltd., Blackthorn, Oxon, UK, and bred and maintained under pathogen free conditions. Daudi cells (2.5 x 10^6) were injected i.v. into the tail vein of cohorts of 12-16 weeks old SCID mice, followed 7 days later by injection of 100 µg of 2F2 or 7D8 via the same route. Animals were sacrificed upon presentation of limb paralysis, according to the instructions of the animal ethics committee. As shown in Figure 38, survival of the mice is prolonged after treatment with 2F2 or 7D8.

Therapy with high dose (100 µg) 2F2 and rituximab of SCID mice challenged with Tanoue cells: Tanoue cells (2.5 x 10^6 in 200 µl PBS) were injected i.v. into the tail vein of cohorts of 12-16 week old SCID mice (Harlan UK Ltd., Blackthorn, Oxon, UK) followed 7 days later by the injection of 100 µg (in 200 µl PBS) of anti-CD20 mAb via the same route. In this experiment, 2F2 was compared to rituximab and B1. Animals were sacrified upon presentation of rear-limb paralysis. The results are shown in Figure 39. At day 39, the first two control mice died, and death within this

Samsung Bioepis Exhibit No. 1002
Page 12281

group was complete at day 54. Only one mouse died within this time interval following 2F2 treatment and survival was considerably increased for the other mice in this group. One mouse died 81 days following injection of the tumor cells and the remaining mice (60% of the total number) survived beyond the termination of the experiment at 100 days post tumor challenge. Rituximab in contrast only increased survival for 2 out of 5 mice (dying at 66 and 83 days post challenge) and none of the mice survived until the end of the experiment. In the B1-group, the survival of SCID mice was similar to that in the 2F2 group, with two mice dying on day 48, and one mouse on day 76. In this group, forty percent was alive at the time the experiment was terminated.

Dose response of 2F2 and rituximab treatment of SCID mice challenged with Daudi cells: To assess the efficacy of 2F2 in comparison to rituximab in protection against tumorigenesis, a dose titration was performed in therapy of SCID mice challenged with Daudi tumor cells. Daudi cells express more CD20 than Tanoue cells and are more sensitive to killing *in vitro*. 10 groups of SCID mice (4 per group) and 1 control group (5 SCID mice) were injected with 2.5 x 10^6 Daudi cells (in 200 µl PBS) i.v. on day 0, and then treated with 20, 5, 2, 0.5 or 0.1 µg (in 200 µl PBS) rituximab, 2F2 or PBS (control) i.v. on day 7. Animals were sacrificed upon presentation of rear-limb paralysis. The results are shown in Figure 40.

In the control group, all mice died within the time interval of 26-29 days. However, a clear dose-effect relation was observed with 2F2 (Figure 40, upper graph). Whereas no effect was observed with doses of 0.1 µg and 0.5 µg 2F2, as little as 2 µg 2F2 substantially extended survival until day 41, 5 µg 2F2 extended survival until day 47, and 20 µg 2F2 extended survival even until day 50.

In contrast, rituximab even tested at the highest dose of 20 µg only slightly increased survival and no dose-effect relation was therefore observed at the lower concentrations tested (Figure 40, lower graph).

Therapy of SCID mice with Daudi tumors by 11B8T and B1: Daudi cells (2.5 x 10^6) in 200 µl PBS were injected i.v. into the tail vein of cohorts of 12-16 week old SCID mice, followed 7 days later by the injection of 100 µg 11B8 or B1 in 200 µl PBS via the same route. Animals were sacrificed upon presentation of rear-limb paralysis. In control mice treated with PBS, all mice died within a time interval of 35-53 days (Figure 41). 11B8T treatment strongly protected the mice, with mice dying between 72 and 98 days post tumor challenge. In the B1-treatment group, most mice survived until day 98 and 40% of the mice survived beyond the end of the experiment, *i.e.*, day 100.

Samsung Bioepis Exhibit No. 1002
Page 12282

Example 12 Evaluation of anti-CD20 antibodies in a Daudi-luc xenograft model using SCID mice

The therapeutic efficacy of anti-CD20 antibodies was evaluated in a mouse model in which disseminated outgrowth of human B-cell tumor cells is followed using external optical imaging. In this model tumor cells are transfected with firefly luciferase. Upon administration of luciferin (Molecular Probes, Leiden, The Netherlands) to the mice the labeled cells can be detected in *vivo* by bioluminescent imaging using a highly sensitive CCD camera, cf. Wetterwald *et al.* (2002) *American Journal of Pathology*, 160(3):1143-1153.

Daudi cells were transfected with gWIZ luciferase from Gene Therapy Systems (San Diego, CA) and cultured in RPMI with 10% FCS, Pen/Strep, Sodium Pyruvate and 1 ug/ml puromycin (Sigma). Cells were analysed for luciferase expression (expressed in RLU/1 x 10^5 cells) in a luminometer and for CD20 expression by FACS. 2.5 x 10^6 luciferase-transfected Daudi cells/mouse were injected i.v. into SCID mice. Eight days after inoculation, the mice received a single dose (10 μg) treatment of 2F2T, 11B8T, rituximab, B1 or isotype control antibody (huIgG1) (6 mice per treatment group). For imaging, mice were anesthetized by i.p. injection of a mixture of ketamine /xylazine /atropine. Synthetic D-Luciferin (sodium salt, Molecular Probes) was given i.p. at a dose of 25 mg/ml. Mice were then placed in a light tight box and after 3 min, imaging was started using a VersArray 1300B liquid nitrogen cooled CCD detector (Roper Scientific). Photons emitted from the luciferase were counted over an exposure period of 5 min. Under illumination black and white images were made for reference. MetaVue software (Universal Imaging Corp) was used for data collection and image analysis. Statistical significance of differences between groups was established using one-way analysis of variance with a Newman-Keuls post test using GraphPad PRISM version 3.02 (Graphpad Software Inc).

Imaging from the back side was performed at one-week intervals. On day 8, the day of treatment, light emission was only detected at the inoculation sites in the tail. Tumor formation at distant sites was detected on day 14 in all mice from the isotype control group (huIgG1) and in one mouse from the rituximab group. In the following weeks light emission steadily increased. Figure 42 gives the images of all mice made on day 39 (31 days after treatment), in which bioluminescence is represented in red color (the dark areas in the mice) (light intensity > 50 photons per 5 min) as overlay on the black and white body image of the mice. The tumor mass in each mouse was quantified on day 25, 32, 39, and 46 by integrating the light signals over the body surface, cf. Figure 43. The fastest tumor growth was observed in the isotype control group. Treatment with rituximab gave significant inhibition of tumor growth. However,

Samsung Bioepis Exhibit No. 1002
Page 12283

tumor growth inhibition by 2F2T, 11B8T and B1 was significantly more potent (see below Table 2 for significance levels.

Table 2

Significance levels of differences in integrated light intensity between groups at different time points

	Day 25	**Day32**	**Day 39**	**Day 46**
B1 vs. rituximab	$P > 0.05$	$P < 0.05$	$P < 0.01$	$P < 0.001$
B1 vs. 11B8T	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
B1 vs. 2F2T	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
B1 vs. huIgG1	$P < 0.001$	$P < 0.001$	$P < 0.001$	
rituximab vs. 11B8T	$P > 0.05$	$P < 0.05$	$P < 0.01$	$P < 0.001$
rituximab vs. 2F2T	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P < 0.001$
rituximab vs. huIgG1	$P < 0.001$	$P > 0.05$	$P < 0.05$	
11B8T vs. 2F2T	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
11B8T vs. huIgG1	$P < 0.001$	$P < 0.001$	$P < 0.001$	
2F2T vs. huIgG1	$P < 0.001$	$P < 0.01$	$P < 0.01$	

Example 13 Pilot and Pharmacokinetic study in cynomolgus monkeys

The objective was to determine the pharmacokinetic pattern and pharmacological effects of 2F2 in cynomolgus monkeys (approximately 2 years old; weight range of 2.1-2.6 kg) following once daily intravenous infusion administrations (*via* the saphenous vein) for 4 consecutive days. The study also compared the pharmacological effects of rituximab in order to determine its equivalent potential. For this purpose, 6 male and 6 female cynomolgus monkeys were assigned to 6 dose groups that received 2F2 or rituximab at dose levels of 1.25, 6.25 and 12.5 mg/kg/day at a constant dose volume of 10 ml/kg for 4 consecutive days, in total 5, 25 and 50 mg/kg, respectively. On completion of the last dose administration, the animals were retained for a post dose observation period of 130 days. The practices and procedures adopted during this study were consistent with the OECD Principles of Good Laboratory Practice as set forth by the United Kingdom Department of Health. All animals were observed at regular intervals for signs of ill health or reaction to treatment and were subjected to a physical examination. Laboratory investigations of haematology, coagulation, clinical chemistry and urine analysis were performed during the study. Blood samples and lymph node biopsies were obtained (from the superficial lymph nodes) for flow cytometry analysis throughout the dosing and post dose observation periods. The following cell phenotypes were analysed by flow cytometry: CD3, CD4, CD8, CD20

Samsung Bioepis Exhibit No. 1002
Page 12284

and CD21. On completion of the post dose observation period the animals were sacrificed and subjected to a detailed necropsy.

There were no adverse clinical signs or any findings that were considered to be related to treatment with 2F2 or rituximab. Figures 44 and 45 shows the flow cytometry analysis of CD20 and CD21 expressing cells in peripheral blood of treated animals, respectively. Figure 46 shows the flow cytometry analysis of CD20 expressing cells in lymph nodes. Together, both phenotypes analysed during the study indicate a strong and efficient B cell depletion after administration of 2F2 and rituximab at 6.25 mg/kg/day (25 mg/kg in total) and 12.5 mg/kg/day (50 mg/kg in total). In addition, data shows that repopulation of CD20 expressing cells in the lymph nodes and peripheral blood of 2F2 treated animals restarted approximately at day 75 post dosing of 25 mg/kg and 50 mg/kg, *i.e.*, markedly later than in rituximab treated animals.

Furthermore, Figures 47A-C show the flow cytometric analysis of $CD20^{low}CD23^{+}CD40^{high}$ expressing cell subpopulations in the peripheral blood (Y. Vugmeyster *et al.* (2003) Cytometry 52A:101-109).

Peripheral blood cells obtained from either 2F2 or rituximab treated monkeys at dose levels of 1.25 mg/kg (Figure 47A), 6.25 mg/kg (Figure 47B), and 12.5 mg/kg (Figure 47C) once daily by intravenous infusion administrations for 4 consecutive days were incubated with anti-human CD20 FITC murine monoclonal antibody (Coulter) at room temperature for 10 min. Afterwards, count beads were added together with PBS and the cells were washed twice (300 g for 10 min), followed by immediate analysis of $CD20^{low}CD23^{+}CD40^{high}$ vs. $CD20^{high}$ $CD23^{+}CD40^{low}$ expressing cell subpopulation in a flow cytometer (Beckman Coulter). Results of $CD20^{low}$ $CD23^{+}CD40^{high}$ cells shown are expressed as cells per μl. As can be seen from the Figure 47 2F2 was capable of inducing a complete and longer depletion of $CD20^{low}CD23^{+}CD40^{high}$ expressing cells compared to rituximab.

Example 14 Epitope mapping using site-directed mutagenesis

Epitope mapping studies using a mutagenesis approach have indicated that alanine at position 170 (A170) and proline at position 172 (P172) in the second extracellular loop are critical for the recognition of human CD20 by known anti-CD20 antibodies. In studies by Deans and colleagues (M.J. Polyak, *et al.*, *Blood*, (2002) 99(9): pp 3256-3262; M.J. Polyak, *et al.*, *J. Immunol.*, (1998) 161(7): pp 3242-3248) the binding of all anti-CD20 mAbs tested was abrogated by changing A170 and P172 into the corresponding murine CD20 residues S170 and S172. Some heterogeneity in the recognition of the AxP epitope has been recognized however as most antibodies like rituximab recognize murine CD20 with S170 and S172 mutated to the human A170xP172 sequence whereas some others require additional mutations immediately N-

Samsung Bioepis Exhibit No. 1002
Page 12285

terminal of the AxP sequence. To verify whether the A170xP172 motive is also important for the binding of the antibodies according to the invention the AxP sequence was mutated into SxS using site-directed mutagenesis (AxP mutant = A170S, P172S), cells were transfected with the AxP mutant and wild-type (WT) CD20 DNA, and the binding characteristics of the anti-CD20 mAbs were compared.

Further mutants were prepared, P172S (proline at position 172 mutated to serine), N166D (asparagine at position 166 mutated to aspartic acid), and N163D (asparagine at position 163 mutated to aspartic acid), using site-directed mutagenesis to evaluate whether the mutated amino acid residues are important for binding of the antibodies of the invention.

To examine this, a CD20 expression vector was constructed by amplifying the CD20 coding sequence using suitable primers introducing restriction sites and an ideal Kozak sequence for optimal expression. The amplified fragment was digested and ligated in the expression vector pEE13.4. After transformation in *E. coli*, colonies were screened for inserts and two clones were selected for sequencing to confirm the correct sequence. The construct was named pEE13.4CD20HS.

Mutagenesis was performed to introduce the AxP mutation and to introduce 20 mouse mutations in the extracellular loop regions of human CD20. Mutagenesis was checked by restriction enzyme digestion and sequencing. The constructs were transiently transfected in CHO cells (for AxP mutations) or HEK293F cells and analyzed 24 or 48 hours post-transfection using flow cytometry.

Oligonucleotide PCR Primers: Oligonucleotide primers were synthesized and quantified by Isogen BV (Maarssen, The Netherlands). Primers were reconstituted in water in a concentration of 100 pmol/µl and stored at -20 °C until required. A summary of PCR and sequencing primers is shown in Table 3.

Optical density determination of nucleic acids: Optical density was determined using an Ultrospec 2100 pro Classic (Amersham Biosciences, Uppsala, Sweden) according to the manufacturer's instructions. The DNA concentration was measured by analysis of the OD_{260nm}, where one OD_{260nm} unit = 50 µg/ml. The reference solution was identical to the solution used to dissolve the nucleic acids.

Plasmid DNA isolation from E. coli culture: Plasmid DNA was isolated from *E. coli* cultures using kits from Qiagen according to the manufacturer's instructions (Westburg BV, Leusden, The Netherlands). For 'bulk' plasmid preparation either a Hi-Speed plasmid Maxi kit or a Hi-Speed plasmid Midi kit were used (Qiagen). For a small scale plasmid preparation (*i.e.*, 2 ml of *E coli* culture) a Qiaprep Spin Miniprep Kit

Samsung Bioepis Exhibit No. 1002
Page 12286

(Qiagen) was used and the DNA eluted in 50 µl TE (Tris-HCl 10 mM pH 8.0, EDTA 1 mM).

PCR amplification: PCR reactions were performed according to the manufacturer's instructions for the Pfu-Turbo© Hotstart DNA polymerase (Stratagene, Amsterdam, The Netherlands). Each 20 µl reaction contained 1 x PCR reaction buffer, 200 µM mixed dNTPs, 6.7 pmol of each forward and reverse primer, approximately 1 ng template DNA and 1 unit of Pfu-Turbo© Hotstart DNA polymerase. PCR reactions were performed on a T-gradient Thermocycler 96 (Biometra GmbH, Goettingen, Germany) using a 30 cycle program of: +95 °C for 2 min, followed by 30 cycles of: +95 °C for 30 sec, anneal: a gradient of 45-65 °C for 30 sec and extension: +72 °C for 2 min, followed by a final extension step of 10 min at 72 °C and subsequent storage at 4 °C. The completed reactions were analysed by agarose gel electrophoresis.

Agarose gel electrophoresis: Agarose gel electrophoresis was performed according to Sambrook (Molecular Cloning Laboratory Manual, 3rd edition) using gels of 50 ml, in 1 x Tris/acetic acid/EDTA (TAE) buffer. DNA was visualized by the inclusion of ethidium bromide in the gel and observation under UV light. Gel images were recorded by a CCD camera and an image analysis system (GeneGnome; Syngene, Cambridge, UK).

Restriction enzyme digestions: Restriction enzymes were supplied by New England Biolabs (Beverly, MA) and used according to the supplier's recommendations. In general, 100 ng was digested with 5 units of enzyme(s) in appropriate buffer in a final volume of 10 µl. Reaction volumes were scaled up as appropriate. Digestions were incubated for a minimum of 60 min at the manufacturer's recommended temperature.

For fragments requiring double digestions with restriction enzymes which have incompatible buffer or temperature requirements, digestions were performed sequentially so as to offer favourable conditions for each enzyme in turn.

Alkaline phosphatase treatment: Shrimp alkaline phosphatase (USB, Cleveland, OH) was used according to the supplier's recommendations. Alkaline phosphatase removes 5'-phosphate groups from the ends of DNA fragments thereby preventing self-ligation. This is of particular relevance when self re-ligation of a DNA fragment could result in a replication-competent vector. The enzyme is active in most restriction enzyme buffers and was added as appropriate. After the digestion, the enzyme was inactivated by raising the temperature to 70 °C for 15 min.

Samsung Bioepis Exhibit No. 1002
Page 12287

Purification of PCR and restriction enzyme reaction products: Purification was carried out using the mini-elute PCR Purification kit (supplied by Qiagen), according to the manufacturer's instructions. Briefly, DNA samples were diluted in 5 volumes of binding buffer I (Qiagen) and loaded onto a mini-elute column within an Eppendorf centrifuge tube. The assembly was centrifuged in a bench-top microcentrifuge. The column was washed twice with buffer II (Qiagen): Following buffer application, the assembly was centrifuged and the flow-through was discarded. The column was dried by centrifugation in the absence of added buffer. DNA was eluted by adding elution buffer to the column and the eluate collected by centrifugation. Isolated DNA was quantified by UV spectroscopy and quality assessed by agarose gel electrophoresis.

Isolation of DNA fragments from agarose gel: Where appropriate (*i.e.*, when multiple fragments were present), digested DNA samples were separated by gel electrophoresis and the desired fragment excised from the gel and recovered using the QIAEX II gel extraction kit (Qiagen), according to the manufacturer's instructions. Briefly, DNA bands were excised from the agarose gel and melted in an appropriate buffer at +55 °C. QIAEX II resin was added and incubated for 5 min. QIAEX II resin was pelleted by a short centrifugation step (1 min, 14000 g, RT) and washed twice with 500 µl of wash buffer PE. The final pellet was dried in a hood and DNA was eluted with the appropriate volume of TE and temperature (depending on the size of the DNA).

Ligation of DNA fragments: Ligations were performed with the Quick Ligation Kit (New England Biolabs) according to the manufacturer's instructions. For each ligation, the vector DNA was mixed with approximately 3-fold molar excess of insert DNA such that the total amount of DNA was lower than 200 ng in 10 µl, with volume adjusted with water as appropriate. To this was added 10 µl 2 x Quick Ligation Buffer and 1 µl Quick T4 DNA ligase and the ligation mix was incubated for 5-30 min at room temperature.

Transformation of DNA into bacteria: Samples of DNA were used to transform One Shot DH5α-T1R competent *E. coli* cells (Invitrogen, Breda, The Netherlands) using the heat-shock method according to the manufacturer's instructions. Briefly, 1-5 µl of DNA solution (typically 2 µl of DNA ligation mix) was added to an aliquot of transformation-competent bacterial cells and the mixture incubated on ice for 30 min. The cells were then heat-shocked by transferring to a waterbath at 42 °C for 30 sec followed by a further incubation on ice for 5 min. Cells were left to recover by

Samsung Bioepis Exhibit No. 1002
Page 12288

incubation in a non-selective culture medium (SOC) for 1 hour with agitation at 37 °C and were subsequently spread onto agar plates containing appropriate selective agent (ampicillin at 50 µg/ml). Plates were incubated for 16-18 hours at +37 °C or until colonies of bacteria became evident.

Screening of bacterial colonies by PCR: Bacterial colonies were screened for the presence of vectors containing the desired sequences using the PCR colony screening technique. 20 µl of PCR reaction mix containing 0.5 volumes of HotStarTaq Master Mix (Qiagen), 4 pmol of the forward and reverse primers and completed with water was added to a PCR tube. A colony was lightly touched with a 20 µl pipet tip, once touched in 2 ml LB in a culture tube (for growing bacteria containing the corresponding plasmid) and resuspended in the 20 µl PCR mix. PCR was performed on a T-gradient Thermocycler 96 (Biometra) using a 35 cycle program of: +95 °C for 15 min, followed by 35 cycles of: +94 °C for 30 sec, anneal: 55 °C for 30 sec and extension: +72 °C for 2 min, followed by a final extension step of 10 min at 72 °C and subsequent storage at 4°C. The completed reactions were analyzed by agarose gel electrophoresis. See Table 3 for details of primer pairs used for colony PCR.

DNA sequencing: Plasmid DNA samples were send to AGOWA (Berlin, Germany) for sequence analysis. Sequences were analyzed using the VectorNTI software package (Informax, Frederick, MD, USA).

Table 3

Name	Application	Length	Oligo Sequence
CD20P172S	CD20 *mutagenesis*	36	TGGGGAGTTTTTCTCAGAGGAATTCGATGGTTCACAGTTGTA
CD20N166D	CD20 mutagenesis	39	TGTAACAGTATTGGGTAGATGGG
CD20N163D	CD20 mutagenesis	36	AATCATGGACATACTTAATATTA
cd20exfor	CD20 construction	41	TATAGCCCGGGGCCGCCACCATGACAACACCCAGAAATTCA
cd20exrev	CD20 construction	38	GCGTCTCATGTACATTAAGGAGAGCTGTCATTTTCTAT
pee13.4seqrev2	Colony PCR	23	TCGGACATCTCATGACTTTCTTT
pConKseq1	Colony PCR	23	GTAGTCTGAGCAGTACTCGTTGC
cd20hsapmutr (AxP)	CD20 mutagenesis	42	TGGGGAGTTTTTCTCAGAGGAATTCGATGGTTCACAGTTGTA
cd20hsapmutf (AxP)	CD20 mutagenesis	42	TACAACTGTGAACCATCGAATTCCTCTGAGAAAAACTCCCCA
CD20seq2	CD20 sequencing	23	TGTAACAGTATTGGGTAGATGGG
cd20seq1	CD20 sequencing	23	AATCATGGACATACTTAATATTA

Samsung Bioepis Exhibit No. 1002
Page 12289

Mutagenesis: The mutagenesis was performed, using either the QuikChange® XL Site-Directed Mutagenesis kit (Cat 200517-5, Lot 1120630, Stratagene Europe) according to the manufacturer's instructions.

Mutagenesis reactions were concentrated using ethanol precipitation and transformed into either oneshot DH5α-T1R competent *E. coli* cells or electroporated into ElectroTen-Blue® Electroporation-Competent Cells. Colonies were checked by colony PCR and restriction digestion prior to transfection.

HEK293F cell transfection: HEK293F cells were obtained from Invitrogen and transfected according to the manufacturer's instructions, using 293fectin. The HEK293F cells were used for all the single mutant sequences.

CHO cell transfection: CHO cells grown to approximately 95% confluence were transiently transfected with CD20 wild-type, mutant cDNA or a combination of both constructs using lipofectamine 2000 (M668-019, Invitrogen, Breda, Netherlands). To this end, 24 μg precipitated DNA was diluted (1μg/μl) in 500 μl optimem, in ratios of AxP 100% : WT 0%; AxP 33.3% : WT 66.6%; AxP 66.6% : WT 33.3%;AxP 0% :WT 100%. For each transfection 24 μl lipofectamine was diluted in 500 μl optimem. Then, the diluted lipofectamine was incubated (RT, 5 min), and the diluted DNA combined with the diluted lipofectamine. After gently mixing and incubating the solution (RT, 20 min), 1000 μl DNA/lipofectamine was added to the CHO cells, thoroughly mixed and incubated for 48 hours at 37 °C, 5% CO_2. Two days after transfection of CHO cells, cells were washed twice with FACS buffer (PBS supplemented with 0.1% BSA and 0.002% NaN_3). CHO cells were treated with trypsin/EDTA (Gibco BRL, Life Technologies, Paisley, Scotland) and lifted off the culture plates.

Anti-CD20 Antibody binding: HEK293F cells and CHO cells were taken up in PBS in a concentration of 2 x 10^6/ml, and added to round bottom plates (1 x 10^5/well). Then, 50 μl CD20 mAb was added, in serial dilutions of 10, 5, 2.5, or 0 μg per well (4 °C, 30 min). After washing in FACS buffer (PBS supplemented with 0.1% BSA and 0.002% NaN_3), the cells were analyzed on a flow cytometer (Becton Dickinson, San Diego, CA, USA), and 5,000 events per sample were acquired at high flow rate.

As can be seen from Figures 48A-E, all anti-CD20 mAbs bound efficiently to CHO cells expressing WT CD20. As expected, rituximab did not bind the AxP mutant (Figure 48A), and B1 bound this mutant poorly (Figure 48D). Both 2F2 and 11B8 in contrast bound to WT and AxP mutant CD20 equally well (Figure 48B and

Samsung Bioepis Exhibit No. 1002
Page 12290

Figure 48C). Titrating the amount of WT CD20 on the surface indeed titrated the binding of rituximab and B1. Both 2F2 and 11B8 again were insensitive to the absence or presence of the mutation.

This study indicates that the binding of 2F2 and 11B8 to human CD20 is insensitive to mutations at amino acid positions 170 and 172. 2F2 and 11B8 therefore represent a new class of CD20 mAbs recognizing a novel CD20 epitope.

Figure 49A shows percentage binding of 2F2, 11B8T, B1 or rituximab to mutant P172S vs. WT CD20, Figure 49B shows percentage binding of 2F2T, 11B8T, B1, CAT (CAT 13.6E12, a mouse monoclonal IgG2A anti-CD20 antibody, Diatec.Com), a control isotype antibody (KLH), or rituximab to mutant CD20 (AxP) vs. WT CD20.

For the mutant wherein asparagine at position 166 has been replaced with aspartic acid (CD20N166D) 2F2 showed very low binding, whereas B1, rituximab and 11B8T were able to bind, see Figure 49C. In a similar experiment CAT 13.6E12 and rituximab were able to bind to CD20N166D, whereas 2F2T only showed very low binding, see Figure 49D. For the mutant wherein asparagine at position 163 has been replaced by aspartic acid (CD20N163D) again rituximab, 11B8T, and B1 were able to bind to CD20N163D, whereas 2F2 and 2F2T only showed very low binding, see Figure 49E. In a similar experiment CAT 13.6E12 and rituximab were able to bind to CD20N163D, whereas 2F2T only showed very low binding, see Figure 49F.

These experiments indicate that 2F2 and 11B8 bind to different epitopes.

Example 15 Epitope mapping using Pepscan method

Synthesis of peptides: 7-, 9-, and 15-mer peptides were synthesized according to standard methods. In some cases chemical linkage of the legs of a 15-mer peptide helps to identify amino acid sequences of a potentially discontinuous epitope. According to known procedures (H.M. Geysen *et al.* (1984) *Proc. Natl. Acad. Sci. USA,* 81:3998; J.W. Slootstra *et al.* (1996) *Mol. Divers.* 1:87; and WO 01/60769), 7-, 9-, and 15-mer peptides were synthesized that could be possible binding sites or epitopes involved in binding of 2F2 or 11B8 to the human CD20 molecule. The 9- and 15-mers were synthesized as loops and screened using credit-card format mini-PEPSCAN cards (455 peptide format/card). In all looped peptides amino acids at varied positions were replaced by a cysteine (*e.g.*, acetyl-XCXXXXXXXXXXXCX-minicard). The peptides were synthesized using standard Fmoc-chemistry and deprotected using TFA with scavengers. Subsequently, the deprotected peptides were reacted on the microarray with an 0.5 mM solution of 1,3-bis(bromomethyl)benzene in ammonium bicarbonate (20 mM, pH 7.9), supplemented with acetonitrile (1:1 (v/v)). The microarrays were gently shaken in the solution for 30-60 min, while completely covered in the solution. Finally,

Samsung Bioepis Exhibit No. 1002
Page 12291

the microarrays were washed extensively with excess of Millipore H_2O and sonicated in disrupt-buffer containing 1% sodium dodecylsulfate, 0.1% β-mercaptoethanol, in PBS (pH 7.2) at 70 °C for 30 min, followed by sonication in millipore H_2O for another 45 min. Subsequently, the microwells were ready for screening in an ELISA-assay.

Pepscan ELISA-assay: The 455-well credit card-format polyethylene cards, containing the covalently linked peptides, were incubated with serum (diluted 1:1000 in blocking solution which contains 5% horse serum (v/v) and 5% ovalbumin (w/v)) (4 °C, over night). After washing, the peptides were incubated with anti-human antibody peroxidase (dilution 1:1000, 1 hour, 25 °C), and after washing the peroxidase substrate, 2,2'-azino-di-3-ethylbenzthiazoline sulfonate and 2 µl/ml 3% H_2O_2 were added. After one hour, the color development was measured. The color development of the ELISA was quantified with a CCD-camera and an image processing system. The set up consists of a CCD-camera and a 55 mm lens (Sony CCD Video Camera XC-77RR, Nikon micro-nikk or 55 mm f/2.8 lens), a camera adaptor (Sony Camera adaptor DC-77RR) and the Image Processing Software package Optimas, version 6.5 (Media Cybernetics, Silver Spring, MD 20910, U.S.A.). Optimas runs on a pentium II computer system.

The absorbances (OD values) for the peptides at different antibody concentrations are shown in below Table 4 and Table 5.

Samsung Bioepis Exhibit No. 1002
Page 12292

GMI-055PC

Table 4

	11B8 10 μg/ml	11B8 100 μg/ml	7D8 10 μg/ml	7D8 100 μg/ml	rituximab 10 μg/ml	2F2 10 μg/ml	2F2 100 μg/ml	B1 10 μg/ml	B1 100 μg/ml
KMECLNFIRAHCPYI	**763**	**2997**	134	41	90	48	66	147	304
LKMECLNFIRCHTPY	165	738	160	41	120	49	87	179	216
KMESCNFIRACTPYI	**625**	**3090**	142	52	123	39	78	170	308
MESLCFIRAHCPYIN	179	956	127	55	102	41	65	119	178
CFIRAHTPC	188	534	181	69	134	91	114	170	212
CIRAHTPYC	151	449	186	60	132	57	92	151	195
CRAHTPYIC	**427**	**1605**	188	64	145	48	87	179	216
CAHTPYINC	179	452	174	65	125	42	106	161	172
IPAGIYA	217	950	164	76	177	48	85	165	192
PAGIYAP	**449**	**2501**	170	64	111	43	85	165	300
AGIYAPI	**251**	**2207**	188	73	110	44	98	187	143
GIYAPIC	99	251	152	64	141	34	93	177	147
IYAPICV	137	313	174	58	159	58	99	175	90
GIYAPIA	172	857	177	96	156	62	96	165	121
IYAPIAV	161	654	181	58	116	62	76	161	106

Samsung Bioepis Exhibit No. 1002
Page 12293

Table 5

	11B8 10 μg/ml	7D8 10 μg/ml	rituximab 10 μg/ml	2F2 10 μg/ml
PCINIYNAEPANPCE	118	163	152	65
YCNIYNAEPANPSCK	287	181	**2418**	86
ICIYNAEPANPSECN	138	192	142	78
NCYNAEPANPSEKCS	93	121	**2649**	49
ICNAEPANPSEKNCP	115	165	**3283**	43
YCAEPANPSEKNSCS	106	188	**3770**	65
NCEPANPSEKNSPCT	159	183	**3476**	61
ACPANPSEKNSPSCQ	146	148	**250**	77
ECANPSEKNSPSTCY	134	179	188	68

As appears from Table 4, 11B8 showed binding to AGIYAP of the small first extracellular loop of human CD20 at both 10 μg/ml and 100 μg/ml, whereas the other antibodies tested did not show significant binding to AGIYAP.

Furthermore, 11B8 showed binding to MESLNFIRAHTPYI of the second extracellular loop of human CD20 at both 10 μg/ml and 100 μg/ml, whereas the other antibodies tested did not show significant binding to MESLNFIRAHTPYI.

As appears from Table 5, rituximab showed binding to EPANPSEK of the second extracellular loop of human CD20 at both **1** μg/ml and 10 μg/ml, whereas the other antibodies tested did not show significant binding to EPANPSEK.

Example 16 Anti-idiotypic antibodies

Generation of anti-idiotypic antibodies: Mouse anti-idiotypic antibodies were made by immunizing Balb/C mice with 2F2 or 11B8T, and generating hybridomas from spleens of these mice by fusion with NS1 myeloma cells using standard techniques. The following anti-idiotypic antibodies were generated: anti-2F2 sab 1.1, anti-2F2 sab 1.2, anti-2F2 sab 1.3, anti-11B8T sab 2.2, anti-11B8T sab 2.3, anti-11B8T sab 2.4, anti-11B8T sab 2.5, and anti-11B8T sab 2.6. These were tested for specific binding to 2F2T, 7D8 and 11B8T. ELISA plates were coated with purified 2F2T, 7D8 or 11B8T (diluted in PBS to a final concentration of 1-2 μg/ml, 37 °C, 2 hours). Plates were blocked with PBS containing 0.05% Tween-20 and 2% chicken serum (RT, 1 hour). Subsequently, the plates were incubated with supernatants from cultures of the anti-idiotypic antibodies (final concentration adjusted to 1-10 μg/ml, RT, 2 hours). Bound mouse anti-idiotypic antibodies were detected with rabbit-anti-mouse IgG-HRP conjugated antibody (Jackson ImmunoResearch).

Samsung Bioepis Exhibit No. 1002
Page 12294

As shown in Figure 50 anti-2F2 sab 1.1, anti-2F2 sab 1.2, and anti-2F2 sab 1.3 bind to 2F2T and 7D8, but not to 11B8T or an unrelated, isotype control human antibody. Since 2F2T and 7D8 are very homologous in V_L and V_H sequence, reaction of anti-2F2 idiotypic antibodies with 7D8 was expected.

Figure 51 shows that anti-11B8T sab 2.2, anti-11B8T sab 2.3, anti-11B8T sab 2.4, anti-11B8T sab 2.5, and anti-11B8T sab 2.6 all bind to 11B8T to a similar extent.

Anti-idiotypic antibodies as an immunodiagnostic tool: The 2F2/7D8 and 11B8T specific anti-idiotypic antibodies can be used as an immunodiagnostic tool to detect and quantify levels of human monoclonal antibodies against CD20 in laboratory or patient samples. This may be useful for examining pharmakokinetics of the anti-CD20 antibody or for determining and adjusting the dosage of the anti-CD20 antibody and for monitoring the disease and the effect of treatment in a patient. As an example of such an assay, ELISA plates were coated with 4 μg/ml anti-2F2 sab 1.1, anti-2F2 sab 1.2 or anti-2F2 sab 1.3. Plates were blocked with PBS containing 0.05% Tween-20 and 2% chicken serum (RT, 1 hour). Subsequently, the plates were incubated with a serial dilution of 2F2T (10,000-9.77 ng/ml, RT, 2 hours). Bound 2F2T was detected with mouse-anti-human IgG HRP-conjugated antibody. As shown in Figures 52A-C a dose dependent binding of 2F2T was observed.

Equivalents

Those skilled in the art will recognize or be able to ascertain, using no more than routine experimentation, many equivalents of the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims. Any combination of the embodiments disclosed in the dependent claims are also contemplated to be within the scope of the invention.

Incorporation by Reference

All patents, pending patent applications and other publications cited herein are hereby incorporated by reference in their entirety.

Samsung Bioepis Exhibit No. 1002
Page 12295

We claim:

1. An isolated human monoclonal antibody which binds to human CD20.

2. The antibody of claim 1, selected from the group consisting of an IgG1, an IgG2, an IgG3, an IgG4, an IgM, an IgA1, an IgA2, a secretory IgA, an IgD, and an IgE antibody.

3. The antibody of claim 2, wherein the antibody is an IgG1 antibody.

4. The antibody of claim 2, wherein the antibody is an IgG3 antibody.

5. The antibody of claim 2, wherein the antibody is an IgG4 antibody.

6. The antibody of claim 2, wherein the antibody is an IgA1 or IgA2 antibody.

7. The antibody of any one of the preceding claims, wherein the antibody dissociates from human CD20 with a dissociation rate constant (k_d) of about 10^{-5} sec^{-1} or less.

8. The antibody of any one of the preceding claims, wherein the antibody binds to human CD20 with an affinity constant (K_D) of about 5 nM or less.

9. The antibody of any one of the preceding claims, wherein the antibody has one or more of the characteristics selected from the group consisting of:

(i) capable of inducing complement dependent cytotoxicity (CDC) of cells expressing CD20 in the presence of complement;

(ii) capable of inducing complement dependent cytotoxicity (CDC) of cells expressing CD20 and high levels of CD55 and/or CD59 in the presence of complement;

(iii) capable of inducing apoptosis of cells expressing CD20;

(iv) capable of inducing antibody dependent cellular cytotoxicity (ADCC) of cells expressing CD20 in the presence of effector cells;

Samsung Bioepis Exhibit No. 1002
Page 12296

(v) capable of inducing homotypic adhesion of cells which express CD20;

(vi) capable of translocating into lipid rafts upon binding to CD20;

(vii) capable of prolonging the survival of a subject having tumor cells which express CD20;

(viii) capable of depleting cells expressing CD20; and

(ix) capable of depleting cells expressing low levels of CD20 ($CD20^{low}$ cells).

10. The antibody of claim 9, which has one or more of the following characteristics selected from the group consisting of:

(i) capable of inducing at least 20%, and preferably at least 30% CDC mediated lysis of B-CLL cells in the presence of 33 vol/vol% plasma within 3 hours at 37 °C at an antibody concentration of 10 μg/ml;

(ii) capable of inducing at least 20%, and preferably at least 30% lysis of B-CLL cells in the presence of 33 vol/vol% whole blood cells within 3 hours at 37 °C at an antibody concentration of 10 μg/ml;

(iii) capable of prolonging the 50% survival rate of SCID mice injected with Daudi cells by more than 30% at a dose of 20 μg; and

(iv) capable of depleting peripheral B cells expressing low levels of CD20 ($CD20^{low}$ B cells) to undetectable levels for more than 50 days in cynomolgus monkeys at a dosage of 6.25 mg/kg per day for 4 consecutive days.

11. The antibody of claim 10, which is capable of capable of inducing at least 20%, and preferably at least 30% CDC mediated lysis of B-CLL cells in the presence of 33 vol/vol% plasma within 3 hours at 37 °C at an anti-CD20 antibody concentration of 10 μg/ml.

12. The antibody of any of the preceding claims 1-11 encoded by human heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:1 and SEQ ID NO:3, respectively, and conservative sequence modifications thereof.

13. The antibody of any of the preceding claims 1-11 encoded by human heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:5 and SEQ ID NO:7, respectively, and conservative sequence modifications thereof.

Samsung Bioepis Exhibit No. 1002
Page 12297

14. The antibody of any of the preceding claims 1-11 encoded by human heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NO:9 and SEQ ID NO:11, respectively, and conservative sequence modifications thereof.

15. The antibody of any of the preceding claims 1-11 having a human heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set forth in SEQ ID NO:2 and SEQ ID NO:4, respectively, and conservative sequence modifications thereof.

16. The antibody of any of the preceding claims 1-11 having human heavy chain and human kappa light chain variable regions which are at least 90% homologous, preferably at least 95% homologous, and more preferably at least 98%, or at least 99% homologous to the amino acid sequences as set forth in SEQ ID NO:2 and SEQ ID NO:4, respectively.

17. The antibody of any of the preceding claims 1-11 having a human heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set forth in SEQ ID NO:6 and SEQ ID NO:8, respectively, and conservative sequence modifications thereof.

18. The antibody of any of the preceding claims 1-11 having human heavy chain and human kappa light chain variable regions which are at least 90% homologous, preferably at least 95% homologous, and more preferably at least 98%, or at least 99% homologous to the amino acid sequences as set forth in SEQ ID NO:6 and SEQ ID NO:8, respectively.

19. The antibody of any of the preceding claims 1-11 having a human heavy chain and human kappa light chain variable regions comprising the amino acid sequences as set forth in SEQ ID NO:10 and SEQ ID NO:12, respectively, and conservative sequence modifications thereof.

20. The antibody of any of the preceding claims 1-11 having human heavy chain and human kappa light chain variable regions which are at least 90% homologous, preferably at least 95% homologous, and more preferably at least 98%, or at least 99% homologous to the amino acid sequences as set forth in SEQ ID NO:10 and SEQ ID NO:12, respectively.

Samsung Bioepis Exhibit No. 1002
Page 12298

21. The antibody of any of the preceding claims 1-11 comprising at least one human variable region selected from the group consisting of:

(i) SEQ ID NOs:2, 4, 6, 8, 10, or 12; and

(ii) a sequence which is at least 90% homologous, preferably at least 95% homologous, and more preferably at least 98%, or at least 99% homologous to any one of the amino acid sequences as set forth in (i) above.

22. An isolated human monoclonal antibody which binds to an epitope on human CD20 defined by the antibody of any one of claims 12-21.

23. An isolated human monoclonal antibody which binds to an epitope on CD20

(i) which does not comprise or require the amino acid residue proline at position 172;

(ii) which does not comprise or require the amino acid residues alanine at position 170 or proline at position 172;

(iii) which comprises or requires the amino acid residues asparagine at position 163 and asparagine at position 166;

(iv) which does not comprise or require the amino acid residue proline at position 172, but which comprises or requires the amino acid residues asparagine at position 163 and asparagine at position 166; or

(v) which does not comprise or require the amino acid residues alanine at position 170 or proline at position 172, but which comprises or requires the amino acid residues asparagine at position 163 and asparagine at position 166.

Samsung Bioepis Exhibit No. 1002
Page 12299

24. An isolated human monoclonal antibody which binds to CD20, wherein the antibody has one or more of the following characteristics:

(i) binds to mutant P172S CD20 (proline at position 172 mutated to serine) with at least the same affinity as to human CD20;

(ii) binds to mutant AxP (alanine at position 170 mutated to serine, and proline at position 172 mutated to serine) with at least the same affinity as to human CD20;

(iii) shows a reduced binding of 50% or more to mutant N166D (asparagine at position 166 mutated to aspartic acid) compared to human CD20 at an antibody concentration of 10 μg/ml; or

(iv) shows a reduced binding of 50% or more to mutant N163D (asparagine at position 163 mutated to aspartic acid) compared to human CD20 at an antibody concentration of 10 μg/ml.

25. An isolated human monoclonal antibody which binds to an epitope in the small first extracellular loop of human CD20.

26. An isolated human monoclonal antibody which binds to a discontinuous epitope on CD20.

27. An isolated human monoclonal antibody which binds to a discontinuous epitope on CD20, wherein the epitope comprises part of the first small extracellular loop and part of the second extracellular loop.

28. An isolated human monoclonal antibody which binds to a discontinuous epitope on CD20, wherein the epitope has residues AGIYAP of the small first extracellular loop and residues MESLNFIRAHTPYI of the second extracellular loop.

29. An isolated human monoclonal antibody which has the binding characteristics of the antibody of any one of claims 11-28.

30. An isolated human monoclonal antibody which binds to human CD20 comprising at least one CDR sequence selected from the group consisting of:

(i) SEQ ID NOs: 13, 14, 15, 16, 17, or 18;

(ii) conservative sequence modifications of the sequences listed in (i); and

Samsung Bioepis Exhibit No. 1002
Page 12300

(iii) fragments of any one of the sequences defined in (i) or (ii) which retain the ability to bind to human CD20.

31. The antibody of claim 30, comprising SEQ ID NO:15.

32. The antibody of claim 30, comprising at least four CDR sequences selected from the group consisting of:

(i) SEQ ID NOs: 13, 14, 15, 16, 17, or 18;

(ii) conservative sequence modifications of the sequences listed in (i); and

(iii) fragments of any one of the sequences defined in (i) or (ii) which retain the ability to bind to human CD20.

33. The antibody of claim 30, comprising SEQ ID NOs: 13, 14, 15, 16, 17, and 18.

34. An isolated human monoclonal antibody which binds to human CD20 comprising at least one CDR sequence selected from the group consisting of:

(i) SEQ ID NOs: 19, 20, 21, 22, 23, or 24;

(ii) conservative sequence modifications of the sequences listed in (i); and

(iii) fragments of any one of the sequences defined in (i) or (ii) which retain the ability to bind to human CD20.

35. The antibody of claim 34, comprising at least four CDR sequences selected from the group consisting of:

(i) SEQ ID NOs: 19, 20, 21, 22, 23, or 24;

(ii) conservative sequence modifications of the sequences listed in (i); and

(iii) fragments of any one of the sequences defined in (i) or (ii) which retain the ability to bind to human CD20.

36. The antibody of claim 34, comprising SEQ ID NOs: 19, 20, 21, 22, 23, and 24.

37. An isolated human monoclonal antibody which binds to human CD20 comprising at least one CDR sequence selected from the group consisting of:

(i) SEQ ID NOs: 25, 26, 27, 28, 29, or 30;

Samsung Bioepis Exhibit No. 1002
Page 12301

(ii) conservative sequence modifications of the sequences listed in (i); and

(iii) fragments of any one of the sequences defined in (i) or (ii) which retain the ability to bind to human CD20.

38. The antibody of claim 37, comprising SEQ ID NO:27.

39. The antibody of claim 37, comprising at least four CDR sequences selected from the group consisting of:

(i) SEQ ID NOs: 25, 26, 27, 28, 29, or 30;

(ii) conservative sequence modifications of the sequences listed in (i); and

(iii) fragments of any one of the sequences defined in (i) or (ii) which retain the ability to bind to human CD20.

40. The antibody of claim 39, comprising SEQ ID NOs: 25, 26, 27, 28, 29, and 30.

41. The antibody of any of the preceding claims 1-11 comprising at least one CDR selected from the group consisting of

(i) SEQ ID NOs:13, 19, or 25, or a sequence having 1 amino acid substitution, deletion or addition of the sequence of SEQ ID NOs:13, 19 or 25;

(ii) SEQ ID NOs:14, 20, or 26, or a sequence having 1-4 amino acid substitutions, deletions or additions of the sequence of SEQ ID NOs:14, 20, or 26;

(iii) SEQ ID NOs:15, or 27, or a sequence having 1-4 amino acid substitutions, deletions or additions of the sequence of SEQ ID NOs:15, or 27;

(iv) SEQ ID NO: 16, or a sequence having 1-2 amino acid substitutions, deletions or additions of the sequence of SEQ ID NO:16;

(v) SEQ ID NO: 17, or a sequence having 1-2 amino acid substitutions, deletions or additions of the sequence of SEQ ID NO:17; and

(vi) SEQ ID NOs: 18, or 30, or a sequence having 1-2 amino acid substitutions, deletions or additions of the sequence of SEQ ID NOs: 18, or 30.

Samsung Bioepis Exhibit No. 1002
Page 12302

42. The antibody of claim 41 comprising at least four CDRs selected from the group consisting of

(i) SEQ ID NOs:13, 19, or 25, or a sequence having 1 amino acid substitution, deletion or addition of the sequence of SEQ ID NOs:13, 19 or 25;

(ii) SEQ ID NOs:14, 20, or 26, or a sequence having 1-4 amino acid substitutions, deletions or additions of the sequence of SEQ ID NOs:14, 20, or 26;

(iii) SEQ ID NOs:15, or 27, or a sequence having 1-4 amino acid substitutions, deletions or additions of the sequence of SEQ ID NOs:15, or 27;

(iv) SEQ ID NO: 16, or a sequence having 1-2 amino acid substitutions, deletions or additions of the sequence of SEQ ID NO:16;

(v) SEQ ID NO: 17, or a sequence having 1-2 amino acid substitutions, deletions or additions of the sequence of SEQ ID NO:17; and

(vi) SEQ ID NOs: 18, or 30, or a sequence having 1-2 amino acid substitutions, deletions or additions of the sequence of SEQ ID NOs: 18, or 30.

43. The antibody of claim 41 comprising one CDR selected from the group consisting of

SEQ ID NOs:15, or 27, and a sequence having 1-4 amino acid substitutions, deletions or additions of the sequence of SEQ ID NOs:15, or 27.

44. The antibody of any one of the preceding claims which is an intact antibody selected from the group consisting of: an intact IgG1 antibody, an intact IgG2 antibody, an intact IgG3 antibody, an intact IgG4 antibody, an intact IgM antibody, an intact IgA1 antibody, an intact IgA2 antibody, an intact secretory IgA antibody, an intact IgD antibody, and an intact IgE antibody, wherein the antibody is glycosylated in a eukaryotic cell.

45. The antibody of any one of the preceding claims which is an antibody fragment or a single chain antibody.

46. The antibody of any one of the preceding claims which is a binding-domain immunoglobulin fusion protein comprising (i) a binding domain polypeptide in the form of a heavy chain variable region or a light chain variable region as defined in claim 24 that is fused to an immunoglobulin hinge region polypeptide, (ii) an immunoglobulin heavy chain CH2 constant region fused to the hinge region, and (iii) an immunoglobulin heavy chain CH3 constant region fused to the CH2 constant region.

Samsung Bioepis Exhibit No. 1002
Page 12303

47. The antibody of any one of the preceding claims produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, in which V-(D)-J gene segment rearrangements have resulted in the formation of a functional human heavy chain transgene and a functional human light chain transgene, fused to an immortalized cell.

48. A hybridoma comprising a B cell obtained from a transgenic non-human animal in which V-(D)-J gene segment rearrangements have resulted in the formation of a functional human heavy chain transgene and a functional light chain transgene fused to an immortalized cell, wherein the hybridoma produces a detectable amount of the monoclonal antibody of any one of the preceding claims.

49. A hybridoma which produces a human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NOs:1, 5, or 9 and SEQ ID NOs:3, 7, or 11, respectively, and conservative sequence modifications thereof.

50. A hybridoma which produces a human monoclonal having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences as set forth in SEQ ID NOs:2, 6, or 10 and SEQ ID NOs: 4, 8, or 12, respectively, and conservative sequence modifications thereof.

51. The antibody of any one of claims 1-45 produced by a transfectoma comprising nucleic acids encoding a human heavy chain and a human light chain.

52. A transfectoma comprising nucleic acids encoding a human heavy chain and a human light chain, wherein the transfectoma produces a detectable amount of the antibody of any one of claims 1-45.

53. A transfectoma which produces a human monoclonal antibody encoded by human IgG heavy chain and human kappa light chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID NOs:1, 5, or 9 and SEQ ID NOs:3, 7, or 11, respectively, and conservative sequence modifications thereof.

Samsung Bioepis Exhibit No. 1002
Page 12304

54. A transfectoma which produces a human monoclonal antibody having IgG heavy chain and kappa light chain variable regions which comprise the amino acid sequences as set forth in SEQ ID NOs:2, 6, or 10 and SEQ ID NOs:4, 8, or 12, respectively, and conservative sequence modifications thereof.

55. A eukaryotic or prokaryotic host cell which produces a human monoclonal antibody having heavy chain and light chain variable regions which comprise the amino acid sequences as set forth in SEQ ID NOs:2, 6, or 10 and SEQ ID NOs:4, 8, or 12, respectively, and conservative sequence modifications thereof.

56. A transgenic non-human animal or plant which produces a human monoclonal antibody having heavy chain and light chain variable regions which comprise the amino acid sequences as set forth in SEQ ID NOs:2, 6, or 10 and SEQ ID NOs:4, 8, or 12, respectively, and conservative sequence modifications thereof.

57. A method of producing a human monoclonal antibody which binds to human CD20, comprising:

immunizing a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene with human CD20 or a cell expressing human CD20, such that antibodies are produced by B cells of the animal;

isolating B cells of the animal;

fusing the B cells with myeloma cells to form immortal, hybridoma cells that secrete human monoclonal antibodies specific for human CD20; and

isolating the human monoclonal antibodies specific for CD20 from the culture supernatant of the hybridoma, or the transfectoma derived from such hybridoma.

58. A method according to claim 57, wherein the immunization is performed with cells which have been transfected with human CD20.

59. An isolated human monoclonal antibody which binds to human CD20 obtained by:

immunizing a transgenic non-human animal having a genome comprising a human heavy chain transgene and a human light chain transgene with a cell which has been transfected with human CD20, such that antibodies are produced by B cells of the animal;

isolating B cells of the animal;

Samsung Bioepis Exhibit No. 1002
Page 12305

fusing the B cells with myeloma cells to form immortal, hybridoma cells that secrete human monoclonal antibodies specific for human CD20; and

isolating the human monoclonal antibodies specific for CD20 from the culture supernatant of the hybridoma, or the transfectoma derived from such hybridoma.

60. An isolated human antibody comprising a heavy chain variable region amino acid sequence derived from a human V_H3-13/DP-44 germline sequence (SEQ ID NO:54) and a light chain variable region amino acid sequence derived from a human L6/JK4-CK (SEQ ID NO:55) germline sequence, wherein the human antibody binds to human CD20.

61. An isolated human antibody comprising a heavy chain variable region amino acid sequence derived from a human V_H3-09/JH6b germline sequence (SEQ ID NO:56) and a light chain variable region amino acid sequence derived from a human V_L-L6/JK5 germline sequence (SEQ ID NO:57), wherein the human antibody binds to human CD20.

62. A composition comprising the human antibody of any one of claims 1-45 and a pharmaceutically acceptable carrier.

63. A composition comprising a combination of two or more human antibodies according to any one of claims 1-45, which have complementary functional activities.

64. A composition according to claim 61 comprising a first antibody according to claim 15 and a second antibody according to claim 19.

65. A composition according to any of claims 62-64 further comprising a therapeutic agent.

66. The antibody according to any one of claims 1-45, further comprising a chelator linker for attaching a radioisotope.

67. An immunoconjugate comprising an antibody according to any one of claims 1-45 linked to a cytotoxic agent, a radioisotope, or a drug.

68. A bispecific molecule comprising an antibody according to any one of claims 1-45 and a binding specificity for a human effector cell.

Samsung Bioepis Exhibit No. 1002
Page 12306

69. A bispecific molecule comprising an antibody according to any one of claims 1-45 and a binding specificity for a human Fc receptor or a binding specificity for a T cell receptor, such as CD3.

70. A method of inhibiting growth of a cell expressing CD20, comprising contacting the cell with an effective amount of an antibody according to any one of claims 1-45 such that the growth of the cell is inhibited.

71. A method of killing a cell expressing CD20, comprising contacting the cell with the antibody of any one of claims 1-45, such that killing of the cell expressing CD20 occurs.

72. The method of any one of claims 70 or 71, wherein the cell is a B lymphocyte or a tumor cell.

73. A method of treating or preventing a disease or disorder involving cells expressing CD20, comprising administering to a subject a human antibody, composition, immunoconjugate, or bispecific molecule according to any one of claims 1-45 or 60-69, an expression vector according to any one of the claims 94-97, in an amount effective to treat or prevent the disease.

74. The method of claim 73, wherein the disease is a B cell lymphoma.

75. The method of claim 73, wherein the disease is B cell non-Hodgkin's lymphoma.

76. The method of claim 73, wherein the disease is selected from the group consisting of precursor B cell lymphoblastic leukemia/lymphoma and mature B cell neoplasms, such as B cell chronic lymhocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, mantle cell lymphoma (MCL), follicular lymphoma (FL), cutaneous follicle center lymphoma, marginal zone B cell lymphoma (MALT type, nodal and splenic type), hairy cell leukemia, diffuse large B cell lymphoma, Burkitt's lymphoma, plasmacytoma, plasma cell myeloma, post-transplant lymphoproliferative disorder, Waldenström's macroglobulinemia, and anaplastic large-cell lymphoma (ALCL).

Samsung Bioepis Exhibit No. 1002
Page 12307

77. The method of claim 76, wherein the disease is follicular lymphoma (FL).

78. The method of claim 76, wherein the disease is B cell chronic lymhocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

79. The method of claim 73, wherein the disease is selected from the group consisting of lymphomatoid granulomatosis, primary effusion lymphoma, intravascular large B cell lymphoma, mediastinal large B cell lymphoma, heavy chain diseases (including γ, μ, and α disease), lymphomas induced by therapy with immunosuppressive agents, such as cyclosporine-induced lymphoma, and methotrexate-induced lymphoma.

80. A method of treating or preventing an immune disease involving CD20 expressing immune cells, comprising administering to a subject the antibody, composition, immunoconjugate, or bispecific molecule according to any one of claims 1-45 or 60-67 or an expression vector according to any one of the claims 94-97, in an amount effective to treat or prevent the immune disease.

81. The method of claim 80, wherein treatment includes the killing of B cells which produce antibodies against autoantigens.

82. The method of claim 73, wherein the disease or disorder is selected from the group consisting of psoriasis, psoriatic arthritis, dermatitis, systemic scleroderma and sclerosis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, respiratory distress syndrome, meningitis, encephalitis, uveitis, glomerulonephritis, eczema, asthma, atherosclerosis, leukocyte adhesion deficiency, multiple sclerosis, Raynaud's syndrome, Sjögren's syndrome, juvenile onset diabetes, Reiter's disease, Behçet's disease, immune complex nephritis, IgA nephropathy, IgM polyneuropathies, immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, hemolytic anemia, myasthenia gravis, lupus nephritis, systemic lupus erythematosus, rheumatoid arthritis (RA), atopic dermatitis, pemphigus, Graves' disease, Hashimoto's thyroiditis, Wegener's granulomatosis, Omenn's syndrome, chronic renal failure, acute infectious mononucleosis, HIV, and herpes virus associated diseases.

83. The method of claim 82, wherein the autoimmune disease is rheumatoid arthritis (RA).

Samsung Bioepis Exhibit No. 1002
Page 12308

84. The method of claim 73, wherein the disease is an inflammatory, immune and/or autoimmune disorder selected from ulcerative colitis, Crohn's disease, juvenile onset diabetes, multiple sclerosis, immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, hemolytic anemia, myasthenia gravis, systemic sclerosis, and pemphigus vulgaris.

85. The method of claim 73, wherein the disease is an inflammatory, immune and/or autoimmune disorder selected from inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, and multiple sclerosis.

86. The method of any one of claims 70-85, further comprising separately administering another therapeutic agent to the subject.

87. The method of claim 86, wherein the therapeutic agent is a cytotoxic agent or a radiotoxic agent.

88. The method of claim 86, wherein the therapeutic agent is an immunosuppressant.

89. The method of claim 86, wherein the therapeutic agent is an immunological modulating agent, such as a cytokine or a chemokine.

90. The method of claim 86, wherein the therapeutic agent is selected from the group consisting of doxorubicin, cisplatin, bleomycin, carmustine, chlorambucil, and cyclophosphamide.

91. The method of claim 86, wherein the therapeutic agent is selected from the group consisting of anti-CD25 antibodies, anti-CD19 antibodies, anti-CD21 antibodies, anti-CD22 antibodies, anti-CD37 antibodies, anti-CD38 antibodies, anti-IL6R antibodies, anti-IL8 antibodies, anti-IL15 antibodies, anti-IL15R antibodies, anti-CD4 antibodies, anti-CD11a antibodies, anti-alpha-4/beta-1 integrin (VLA4) antibodies, CTLA4-Ig, and anti-C3b(i) antibodies.

Samsung Bioepis Exhibit No. 1002
Page 12309

92. An *in vitro* method for detecting the presence of CD20 antigen, or a cell expressing CD20, in a sample comprising:

contacting the sample with the antibody of any one of claims 1-45 under conditions that allow for formation of a complex between the antibody and CD20; and

detecting the formation of a complex.

93. A kit for detecting the presence of CD20 antigen , or a cell expressing CD20, in a sample comprising the antibody of any one of claims 1-45.

94. An *in vivo* method for detecting CD20 antigen, or a cell expressing CD20, in an subject comprising:

administering the antibody of any one of claims 1-45 under conditions that allow for formation of a complex between the antibody and CD20; and

detecting the formed complex.

95. An expression vector comprising a nucleotide sequence encoding the variable region of a light chain, heavy chain or both light and heavy chains of a human antibody which binds human CD20.

96. The expression vector of claim 95, further comprising a nucleotide sequence encoding the constant region of a light chain, heavy chain or both light and heavy chains of a human antibody which binds human CD20.

97. An expression vector comprising a nucleotide sequence encoding a heavy chain variable region comprising a nucleotide selected from the group consisting of the nucleotide sequences as set forth in SEQ ID NOs: 1, 5, and 9, and a light variable region comprising a nucleotide sequence selected from the group consisting of the nucleotide sequences as set forth in SEQ ID NOs: 3, 7, and 11, and conservative modifications thereof.

98. An expression vector comprising a nucleotide sequence encoding a heavy chain variable region comprising an amino acid sequence selected from the group consisting of the amino acid sequences as set forth in SEQ ID NOs:2, 6, and 10, and a light chain variable region comprising the amino acid sequence selected from the group consisting of the amino acid sequences as set forth in shown in SEQ ID NOs: 4, 8, and 12, and conservative sequence modifications thereof.

Samsung Bioepis Exhibit No. 1002
Page 12310

99. A pharmaceutical composition comprising the expression vector of any one of claims 95-98 and a pharmaceutically acceptable carrier.

100. An anti-idiotypic antibody binding to an antibody of any one of claims 1-45.

101. An anti-idiotypic antibody binding to 2F2, 11B8 or 7D8.

102. Use of an anti-idiotypic antibody of claim 100 or 101 for detecting the level of human monoclonal antibody against CD20 in a sample.

Samsung Bioepis Exhibit No. 1002
Page 12311

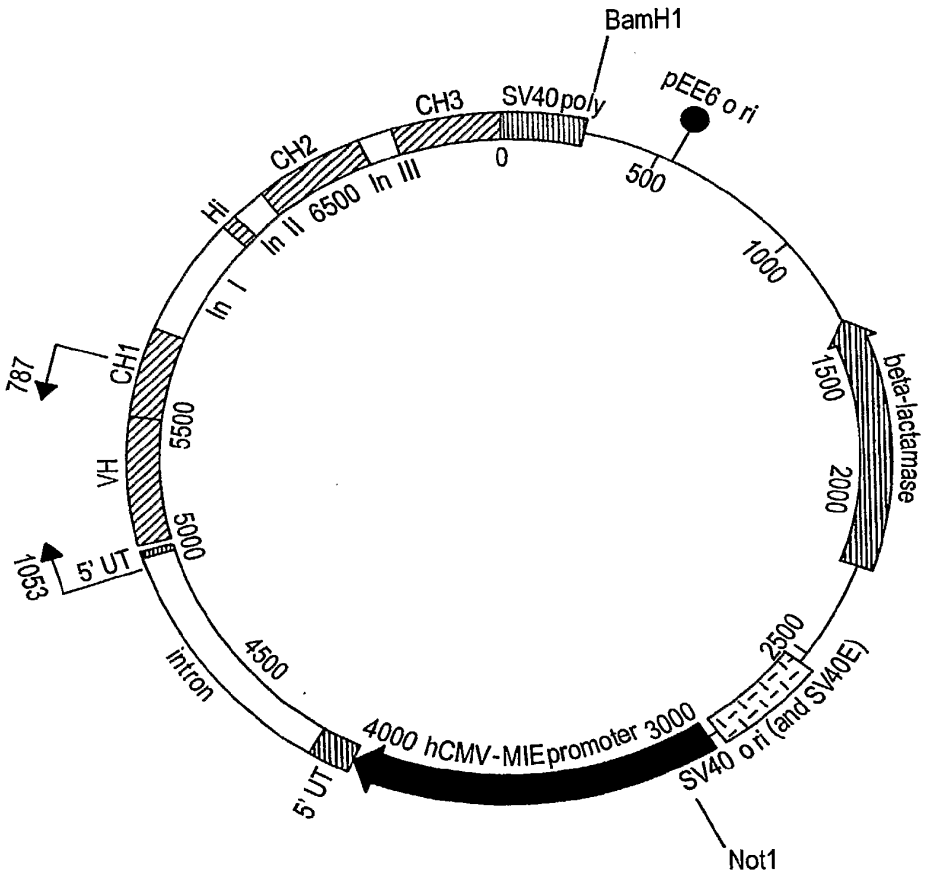

BamH1
pEE6 o ri
SV40 poly
CH3
CH2
Hi
In III
In II
6500
In I
0
500
1000
1500
2000
2500
beta-lactamase
787
CH1
VH
5500
5000
1053
5' UT
intron
4500
4000 hCMV-MIEpromoter 3000
5' UT
SV40 ori (and SV40E)
Not1

Fig. 1

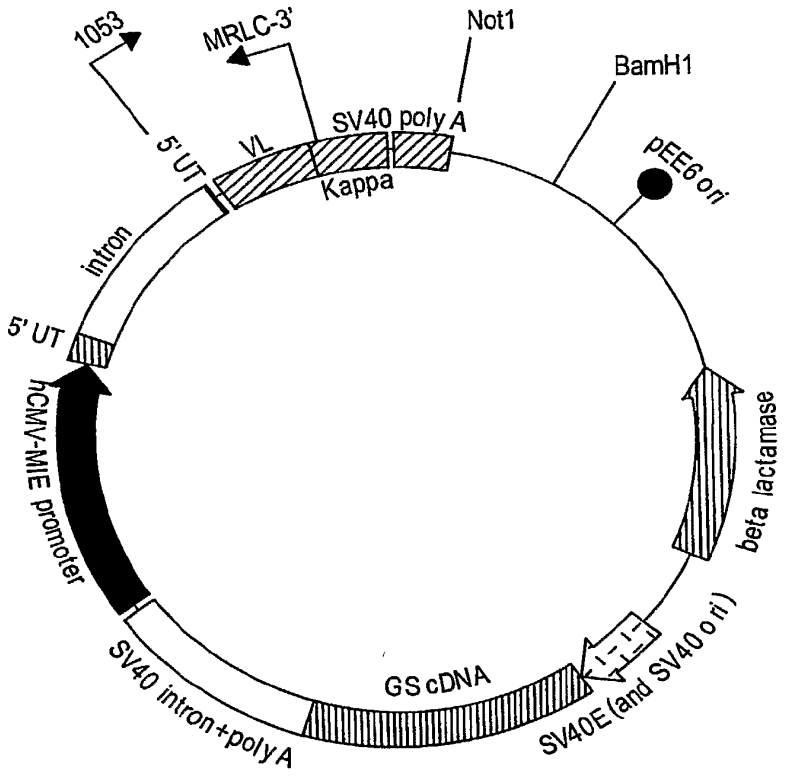


Fig. 2

Samsung Bioepis Exhibit No. 1002
Page 12313

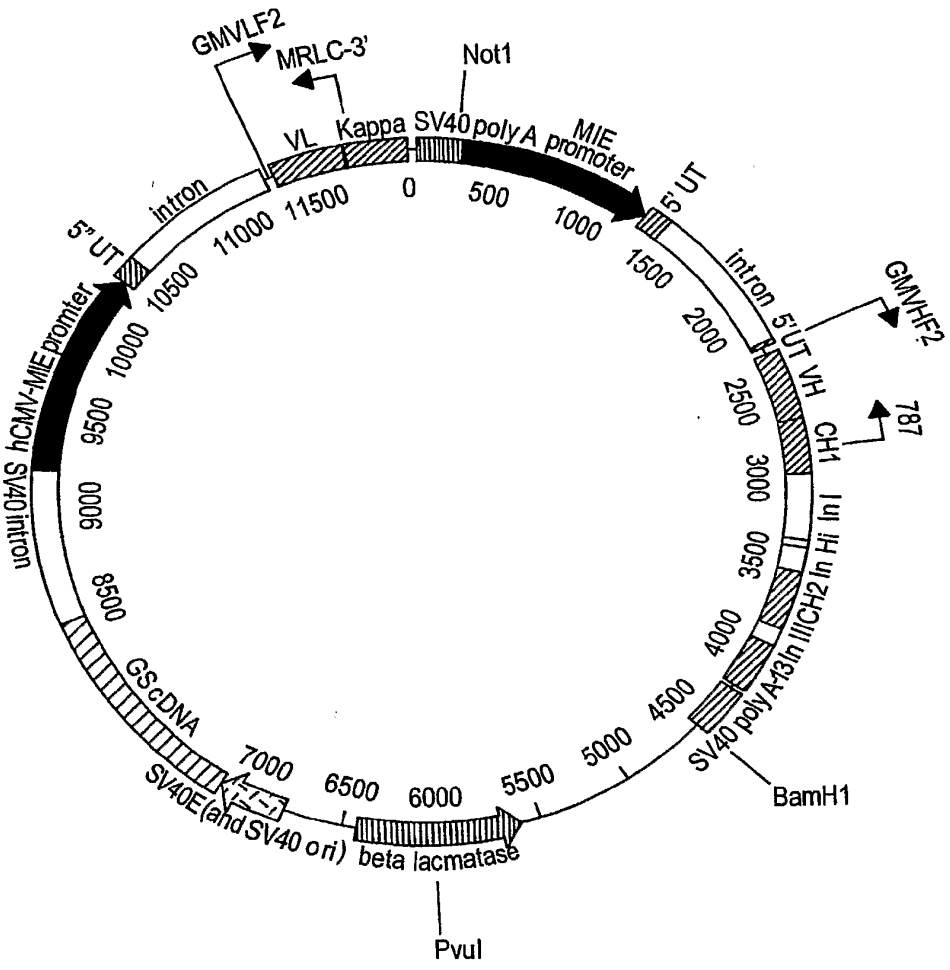


Fig. 3

Samsung Bioepis Exhibit No. 1002
Page 12314

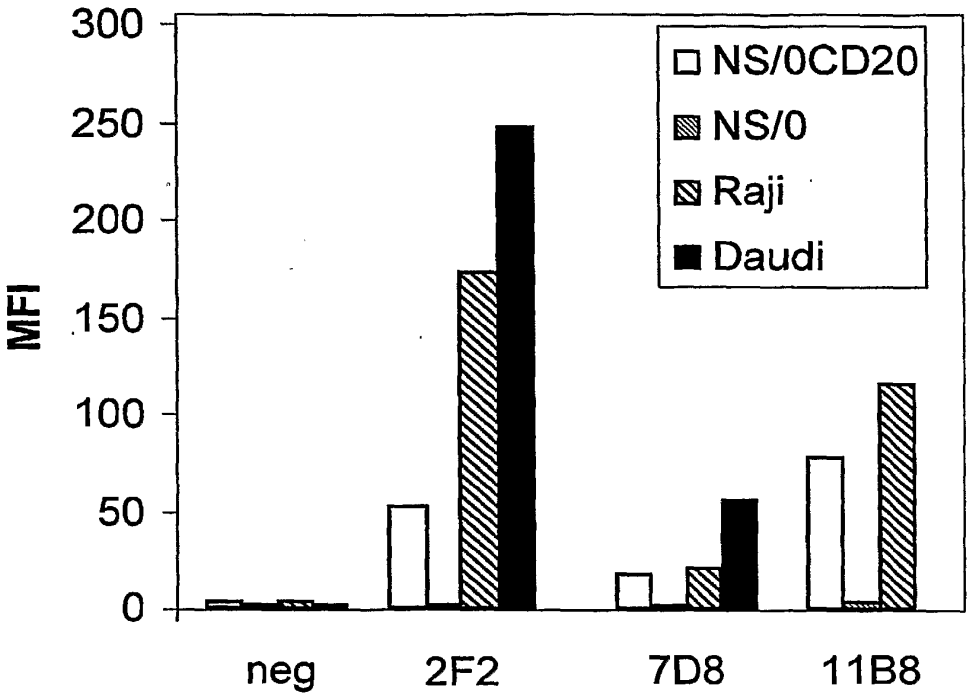

300
250
200
150
100
50
0
MFI
NS/0CD20
NS/0
Raji
Daudi
neg
2F2
7D8
11B8

Fig. 4

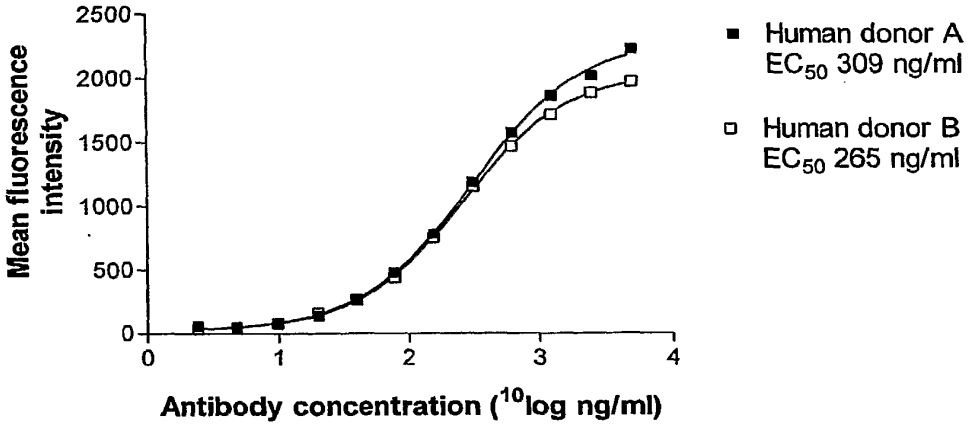

Mean fluorescence intensity
2500
2000
1500
1000
500
0
0
1
2
3
4
Antibody concentration (^{10}log ng/ml)
Human donor A
EC50 309 ng/ml
Human donor B
EC50 265 ng/ml

Fig. 5A

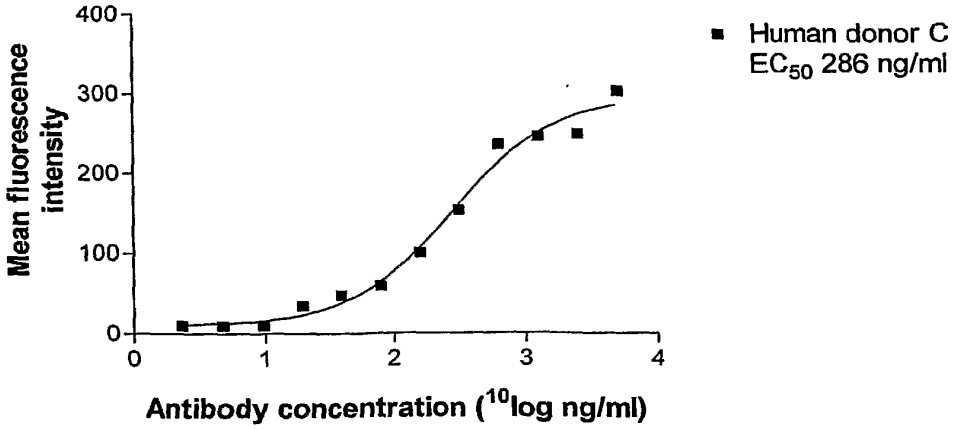

Mean fluorescence intensity
400
300
200
100
0
0
1
2
3
4
Antibody concentration (^{10}log ng/ml)
Human donor C
EC50 286 ng/ml

Fig. 5B

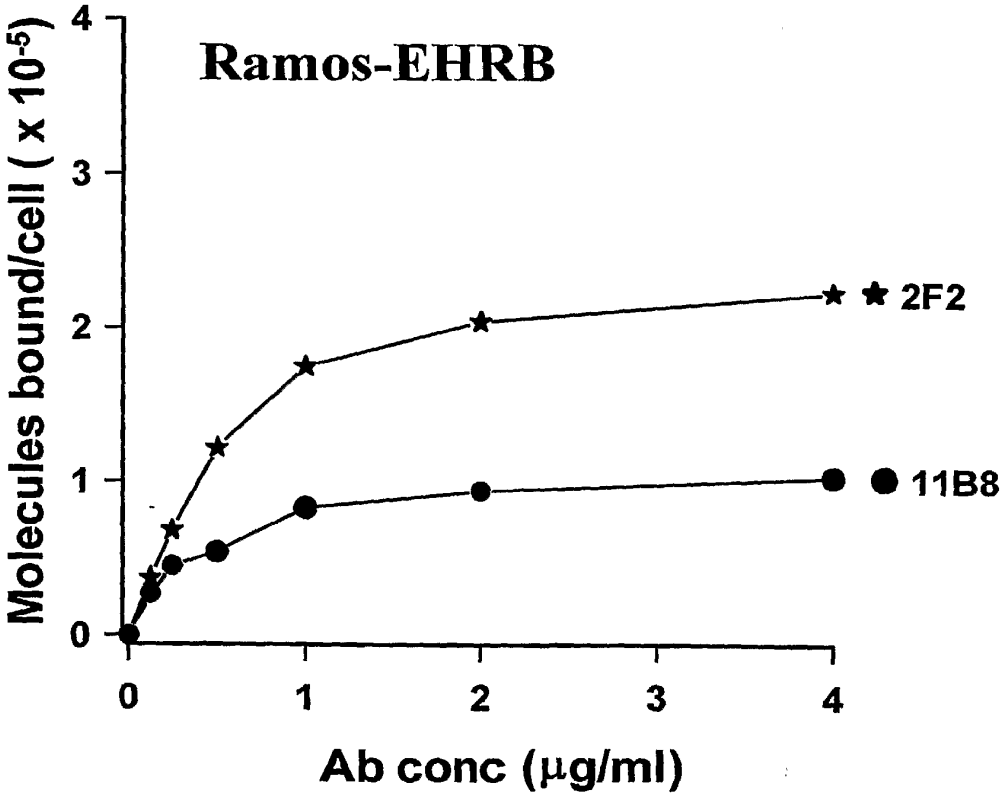

Ramos-EHRB
Molecules bound/cell (x 10-5)
4
3
2
1
0
0
1
2
3
4
Ab conc (µg/ml)
2F2
11B8

Fig 6

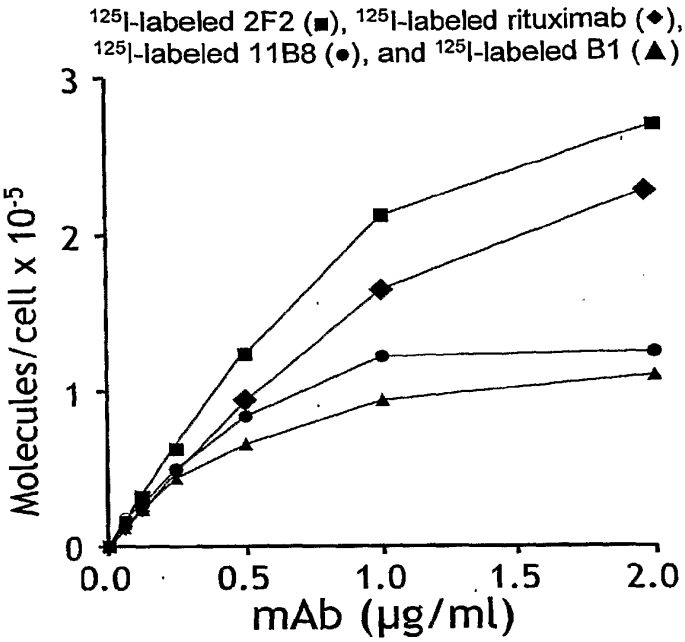

^{125}I-labeled 2F2 (■), ^{125}I-labeled rituximab (◆),
^{125}I-labeled 11B8 (●), and ^{125}I-labeled B1 (▲)
Molecules/cell x 10^{-5}
0
1
2
3
0.0
0.5
1.0
1.5
2.0
mAb (µg/ml)

Fig. 7A

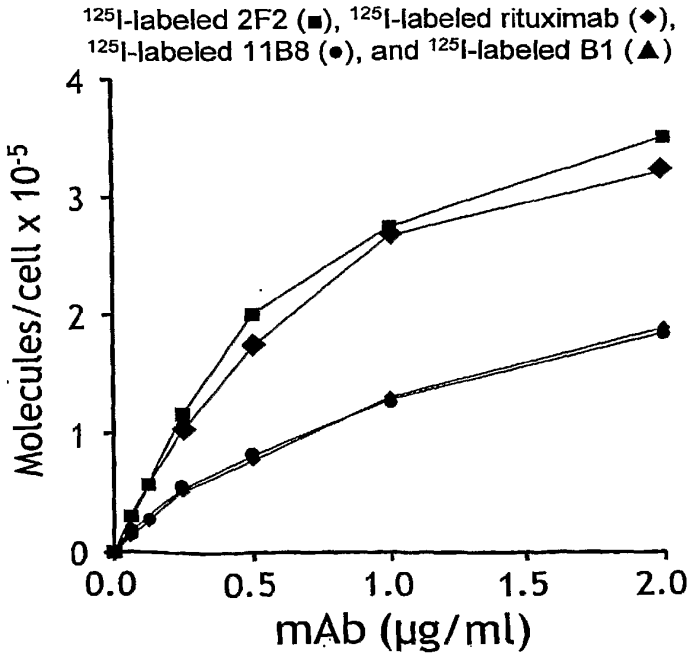

^{125}I-labeled 2F2 (■), ^{125}I-labeled rituximab (◆),
^{125}I-labeled 11B8 (●), and ^{125}I-labeled B1 (▲)
Molecules/cell x 10^{-5}
0
1
2
3
4
0.0
0.5
1.0
1.5
2.0
mAb (µg/ml)

Fig. 7B

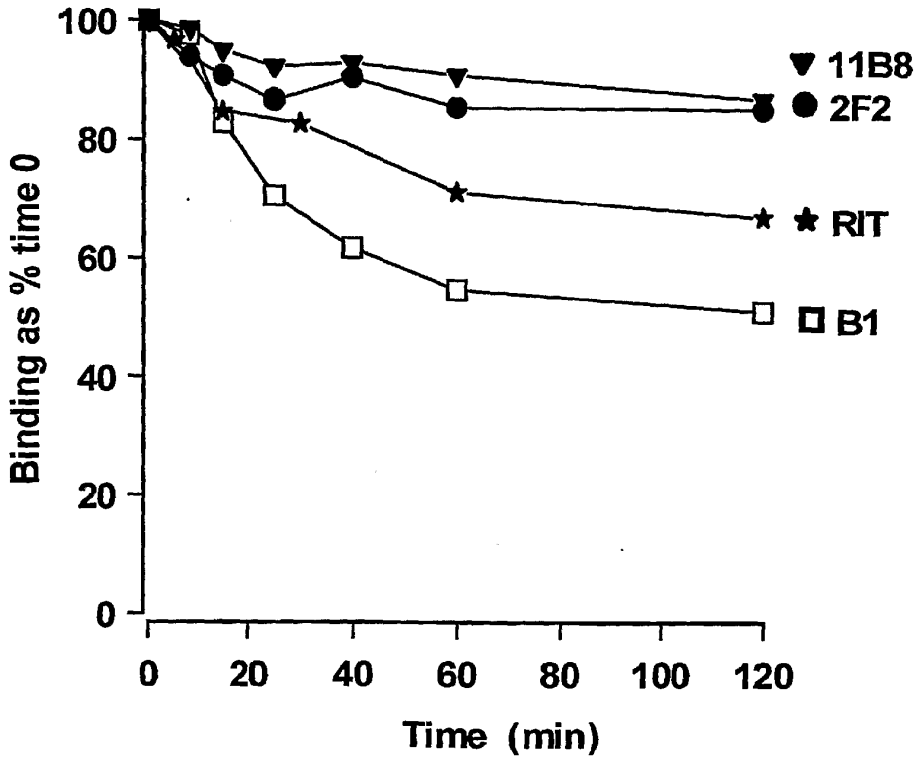


Fig. 8

Samsung Bioepis Exhibit No. 1002
Page 12319

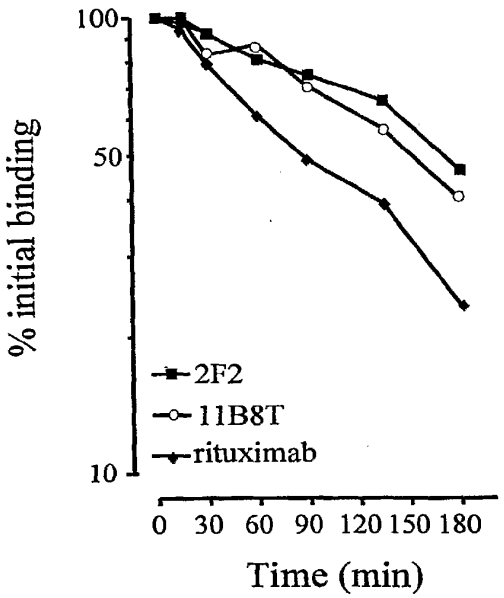


Fig. 9

Samsung Bioepis Exhibit No. 1002
Page 12320

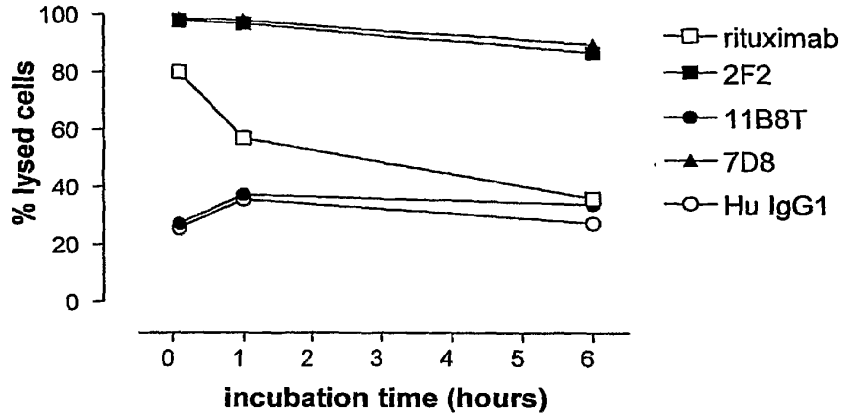


Fig. 10A

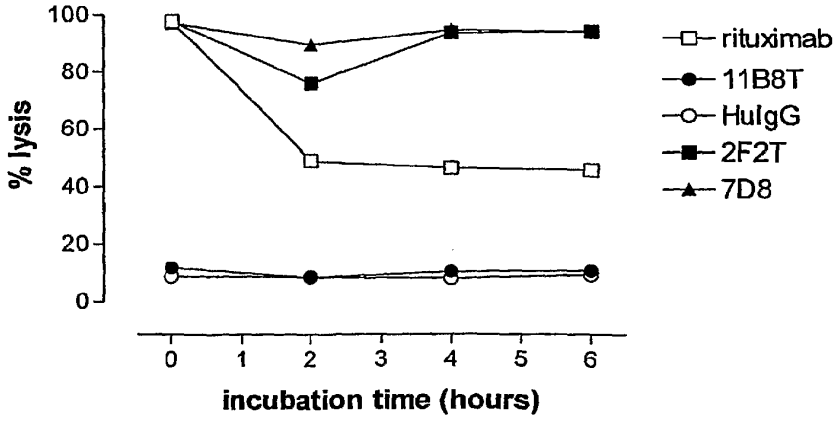


Fig. 10B

Samsung Bioepis Exhibit No. 1002
Page 12321

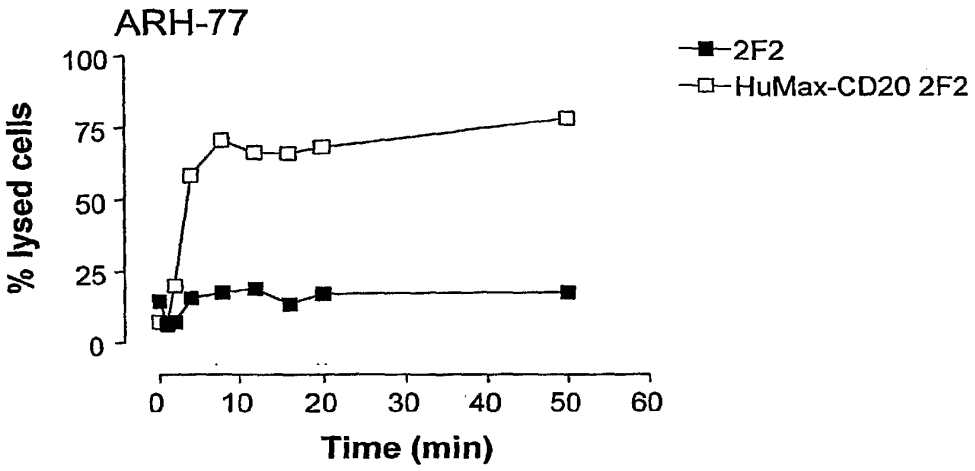


Fig. 11A

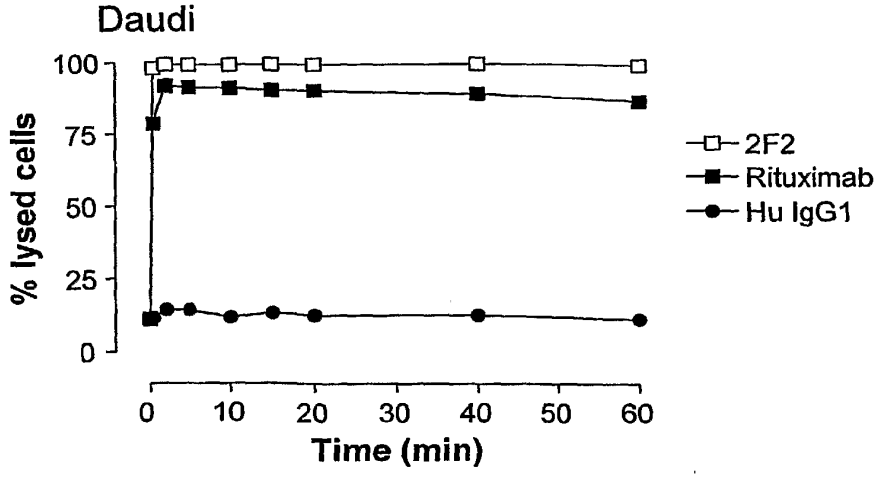


Fig. 11A

Samsung Bioepis Exhibit No. 1002
Page 12322

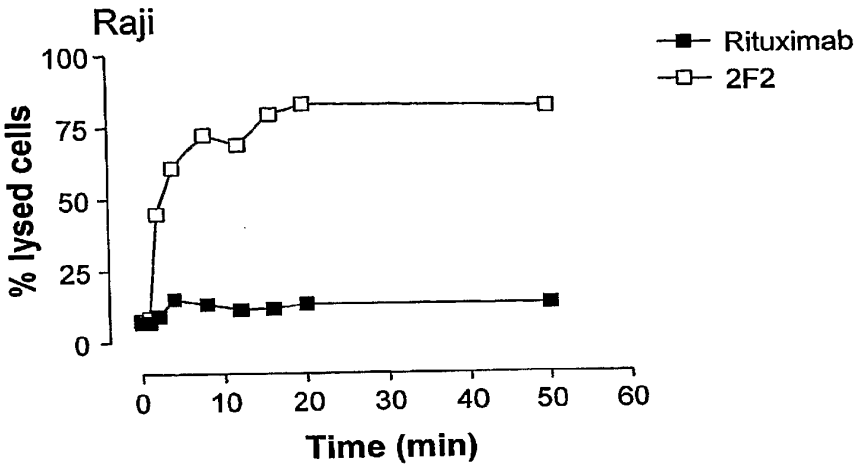


Fig. 11C

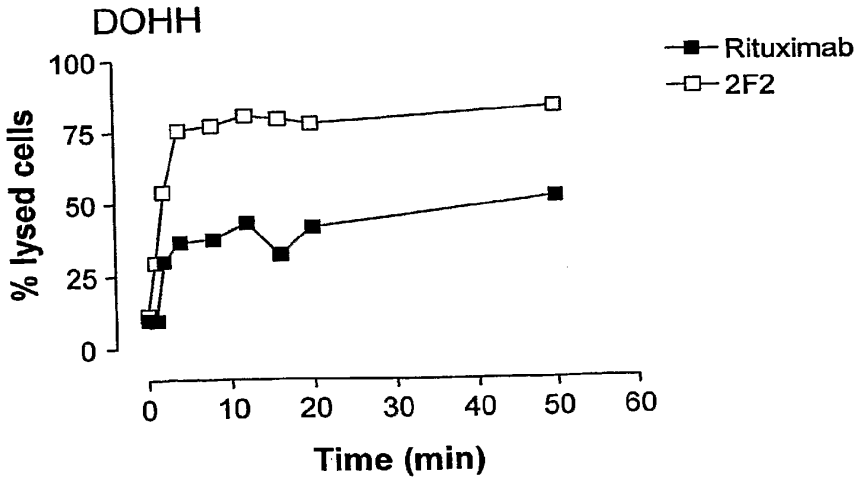


Fig. 11D

Samsung Bioepis Exhibit No. 1002
Page 12323

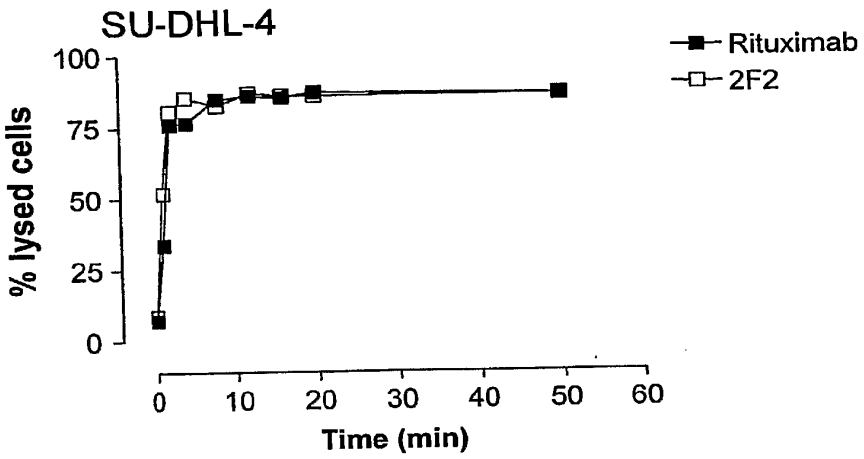


Fig. 11E

Samsung Bioepis Exhibit No. 1002
Page 12324

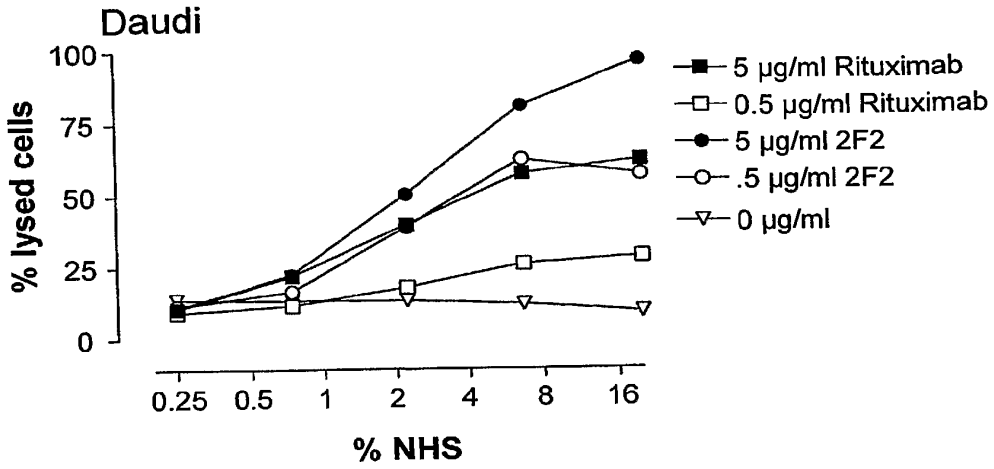


Fig. 12A

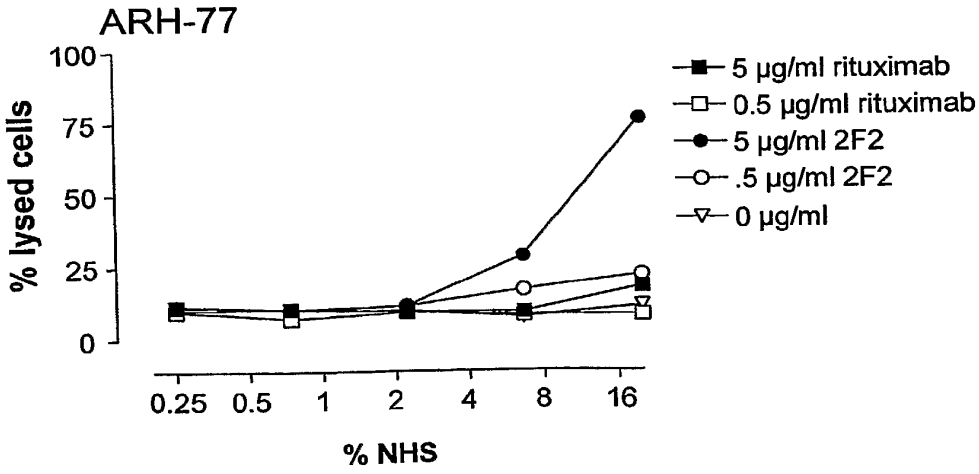


Fig. 12B

Samsung Bioepis Exhibit No. 1002
Page 12325

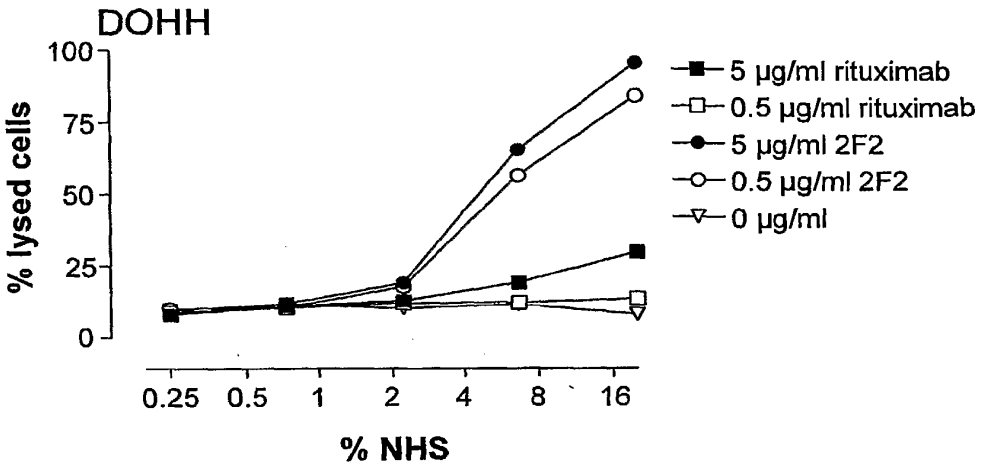


Fig. 12C

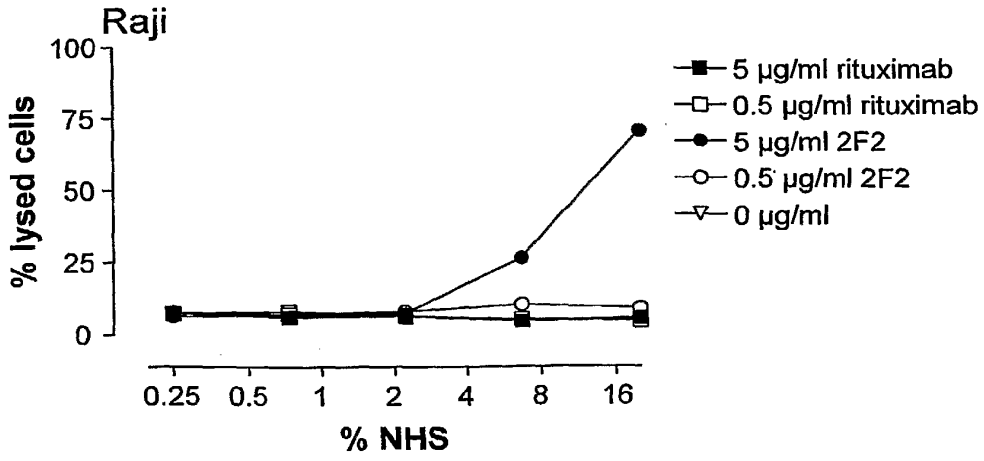


Fig. 12D

Samsung Bioepis Exhibit No. 1002
Page 12326

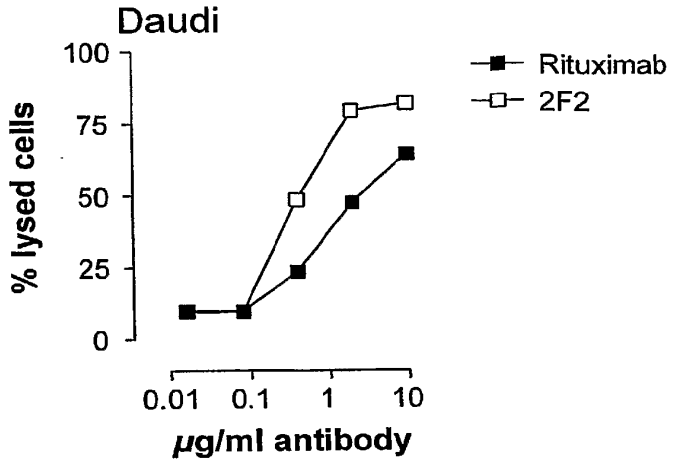


Fig. 13A

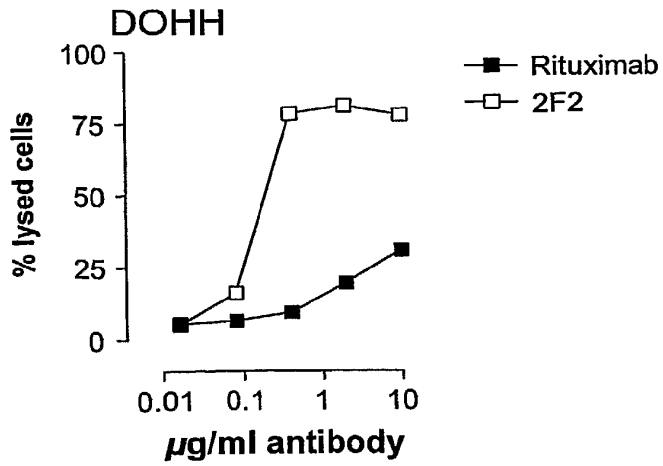


Fig. 13B

Samsung Bioepis Exhibit No. 1002
Page 12327

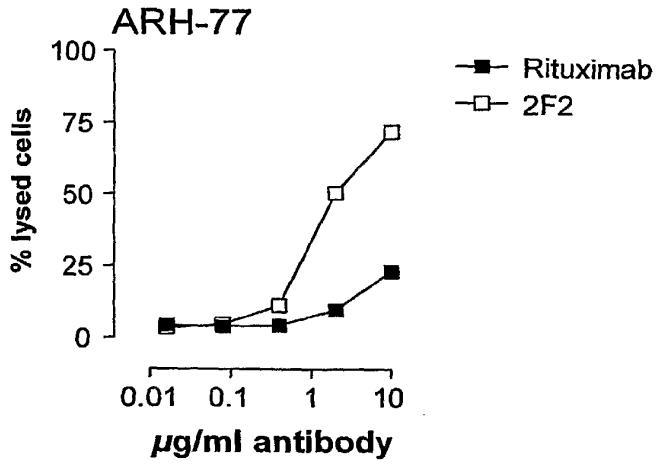


Fig. 13C

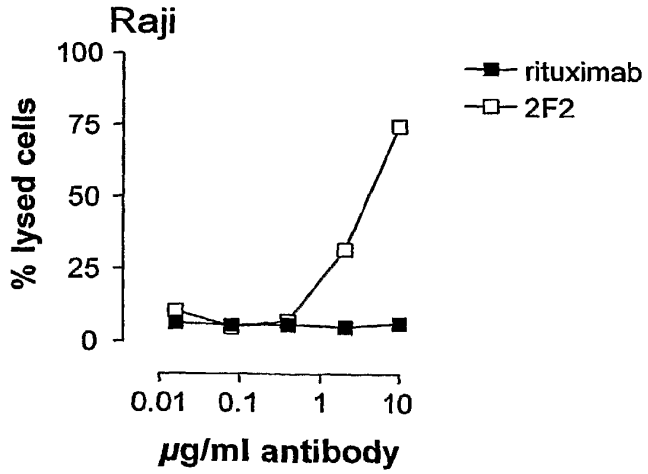


Fig. 13D

Samsung Bioepis Exhibit No. 1002
Page 12328

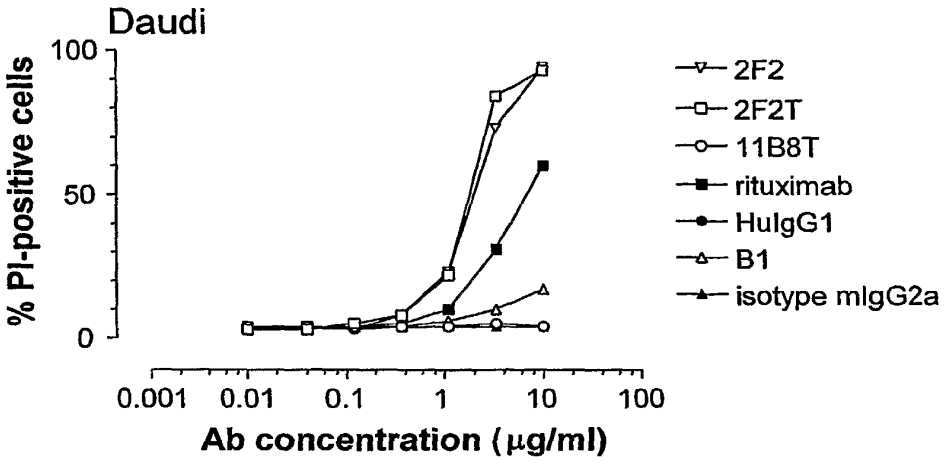


Fig. 14A

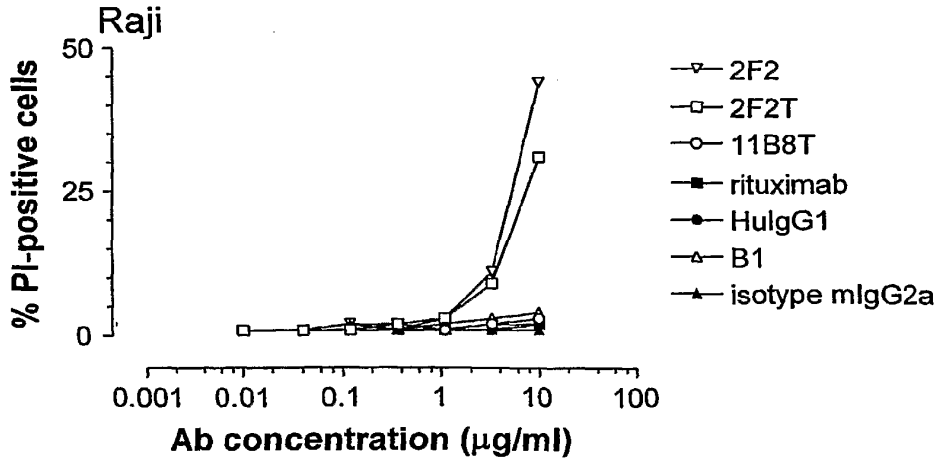


Fig. 14B

Samsung Bioepis Exhibit No. 1002
Page 12329

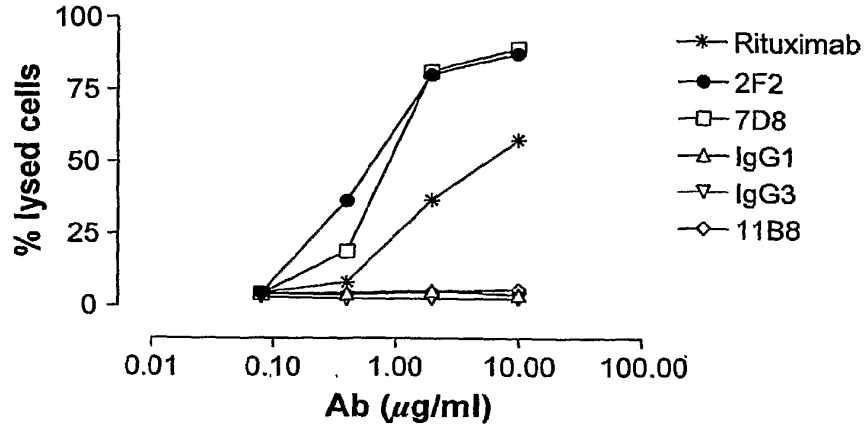


Fig. 15A

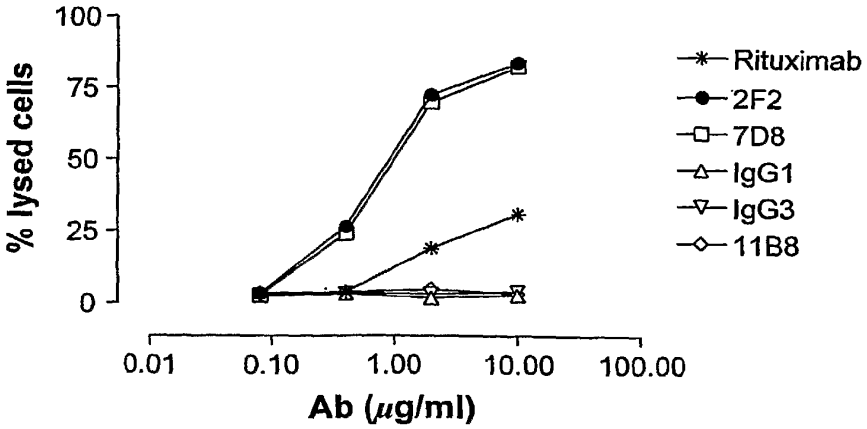


Fig. 15B

Samsung Bioepis Exhibit No. 1002
Page 12330

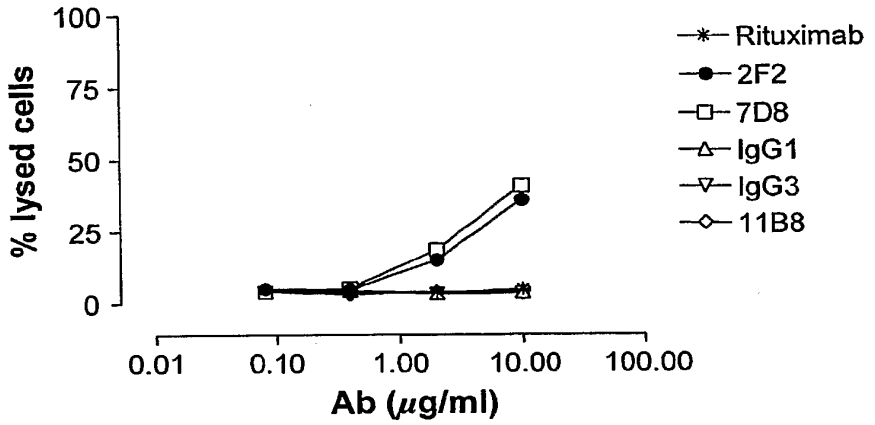


Fig. 16A

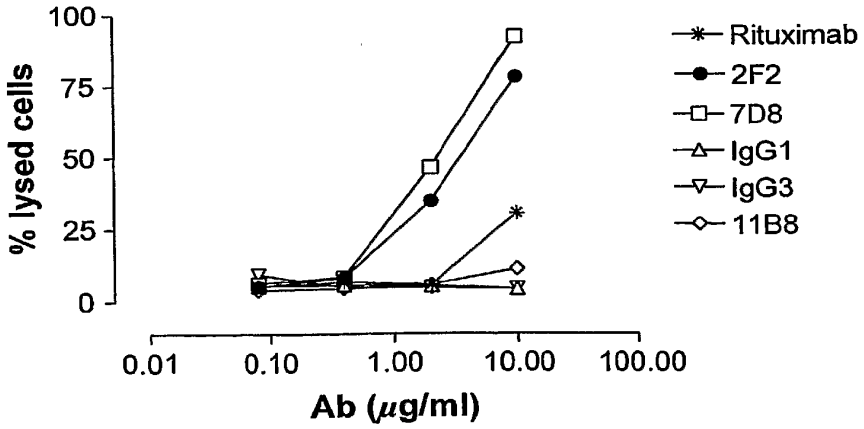


Fig. 16B

Samsung Bioepis Exhibit No. 1002
Page 12331

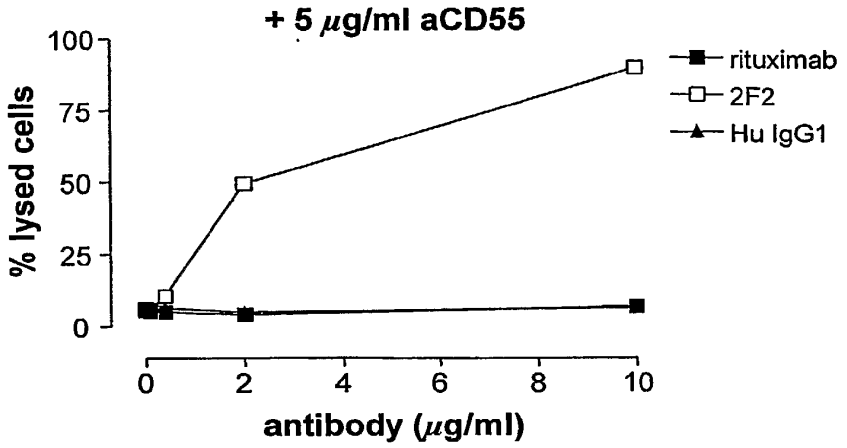


Fig. 17A

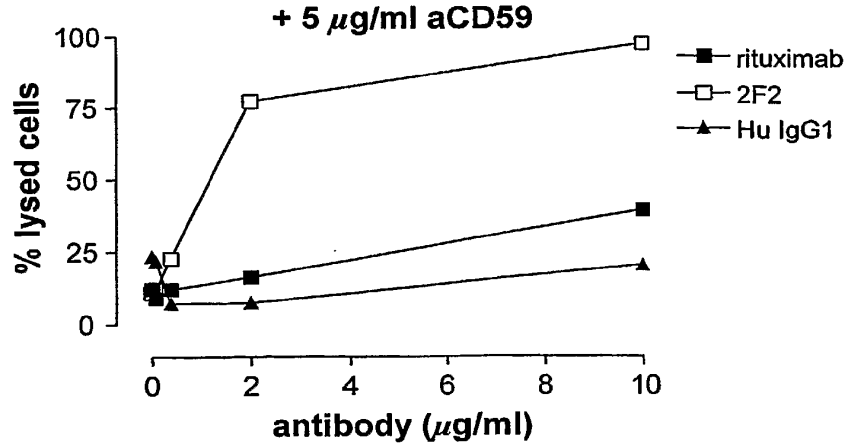


Fig. 17B

Samsung Bioepis Exhibit No. 1002
Page 12332

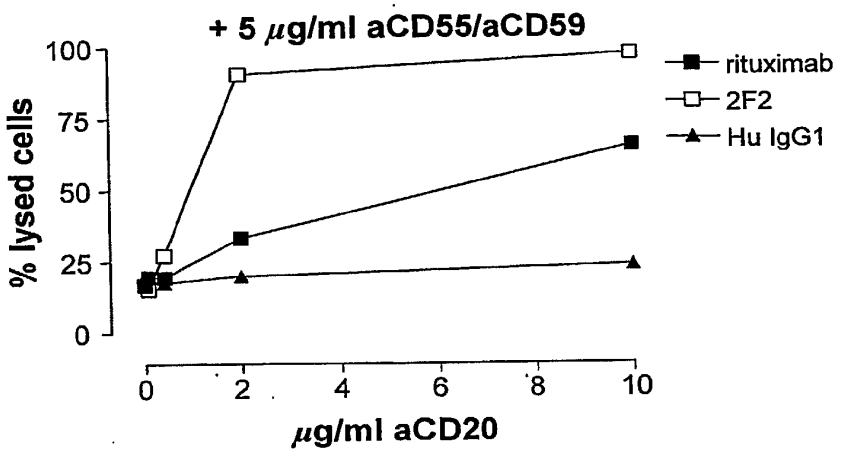


Fig. 17C

Samsung Bioepis Exhibit No. 1002
Page 12333

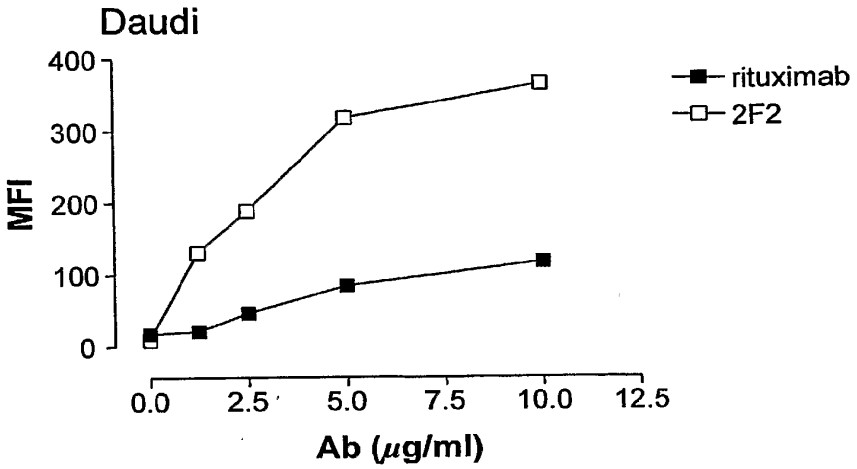


Fig. 18A

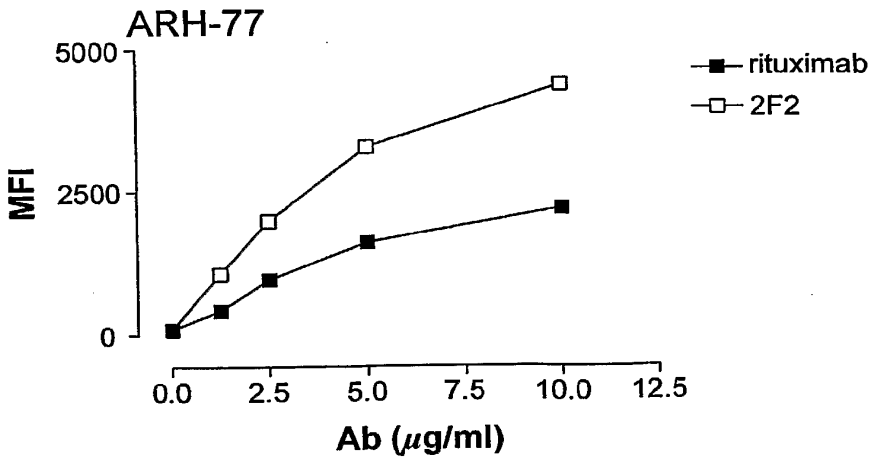


Fig. 18B

Samsung Bioepis Exhibit No. 1002
Page 12334

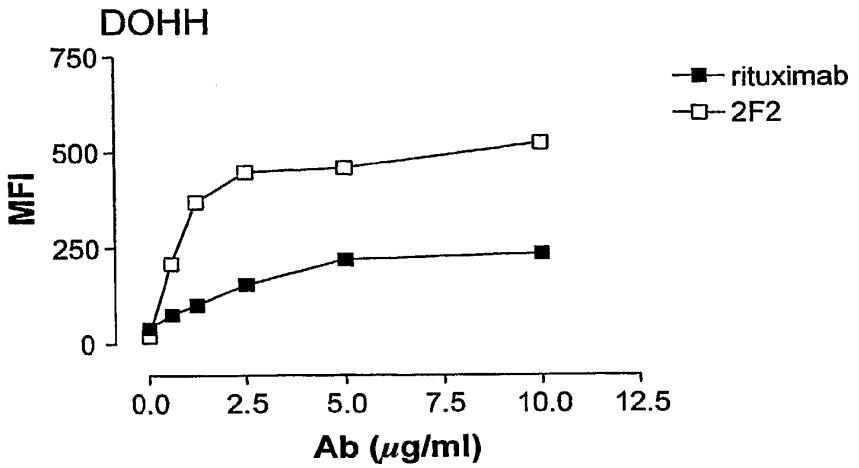


Fig. 18C

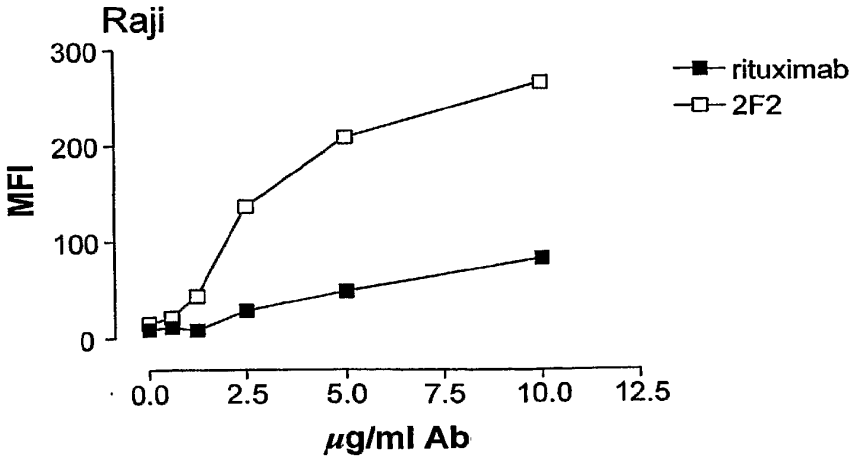


Fig. 18D

Samsung Bioepis Exhibit No. 1002
Page 12335

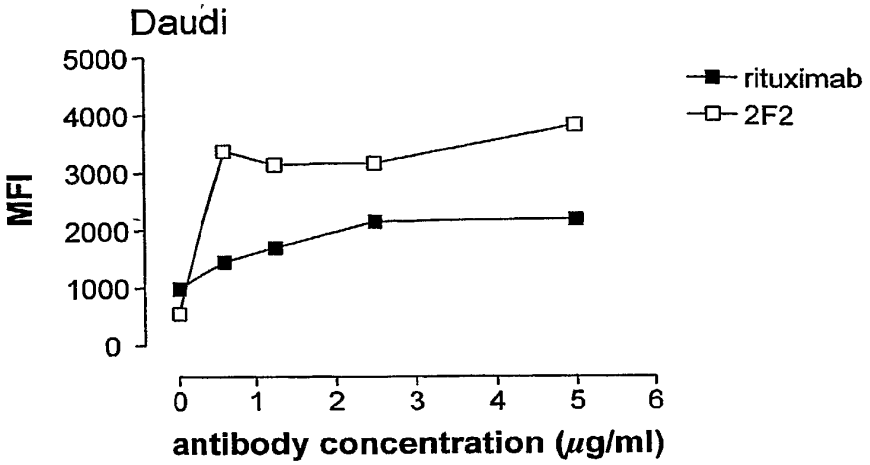


Fig. 19A

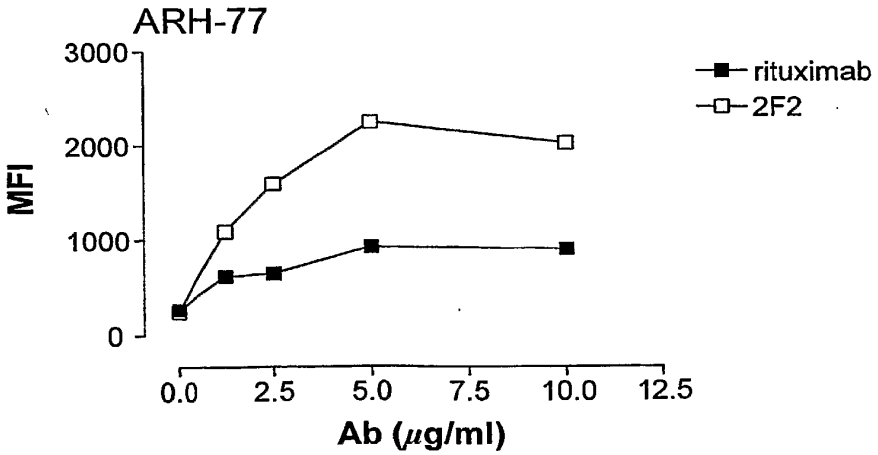


Fig. 19B

Samsung Bioepis Exhibit No. 1002
Page 12336

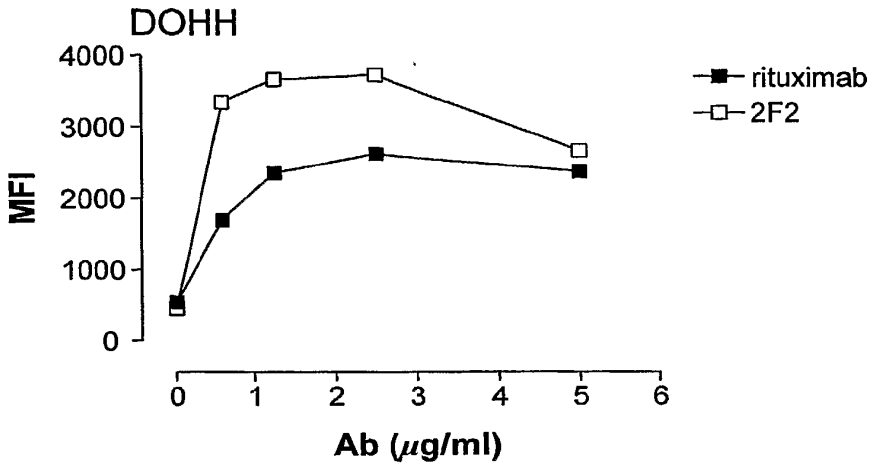


Fig. 19C

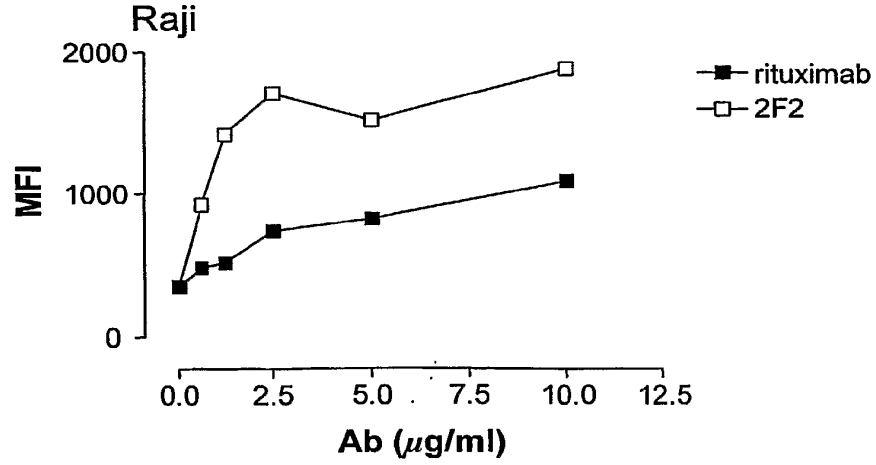


Fig. 19D

Samsung Bioepis Exhibit No. 1002
Page 12337

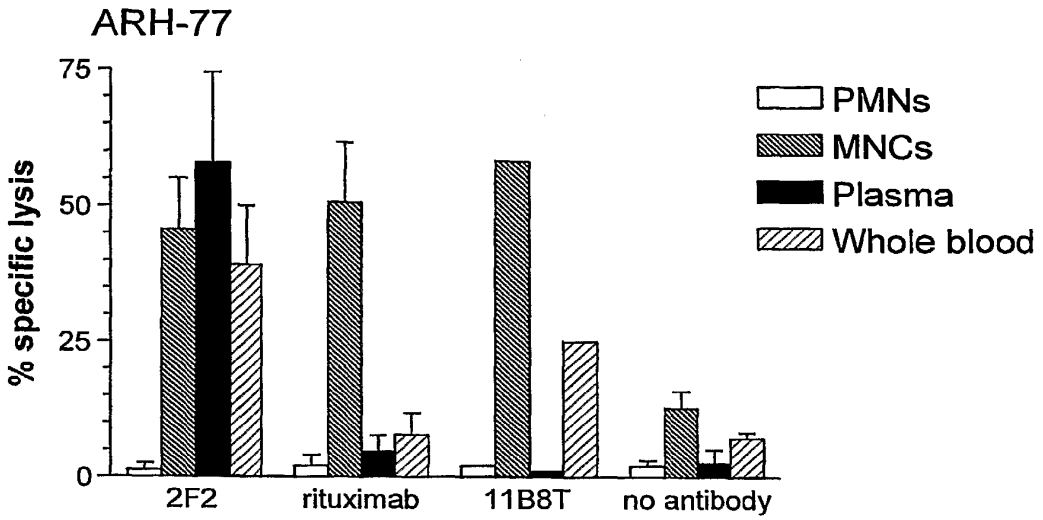


Fig. 20

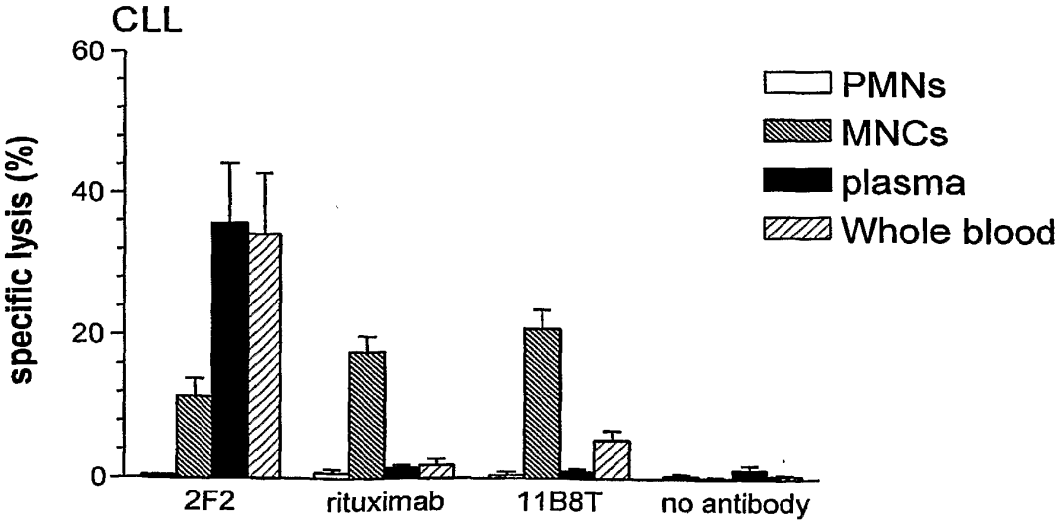


Fig. 21

Samsung Bioepis Exhibit No. 1002
Page 12338

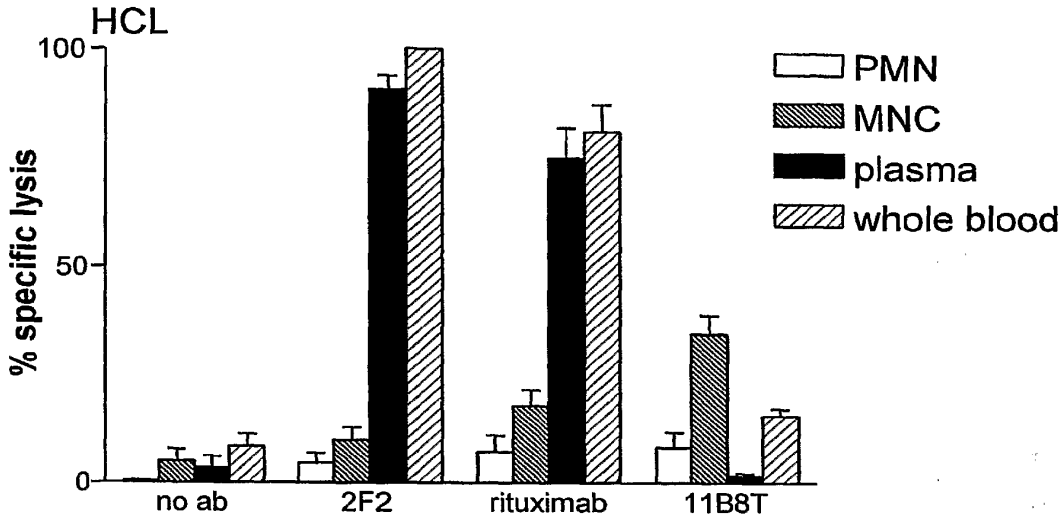


Fig. 22

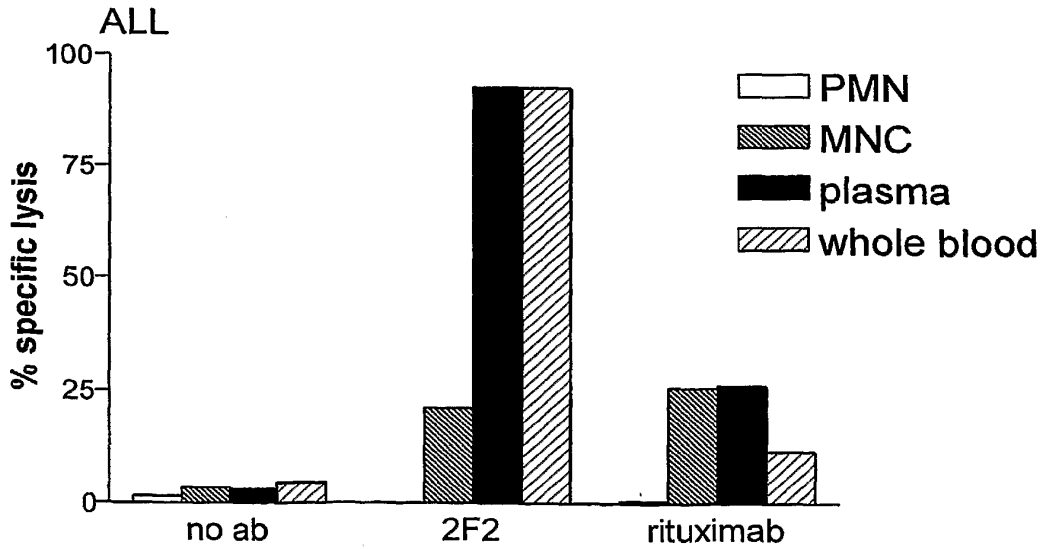


Fig. 23

Samsung Bioepis Exhibit No. 1002
Page 12339

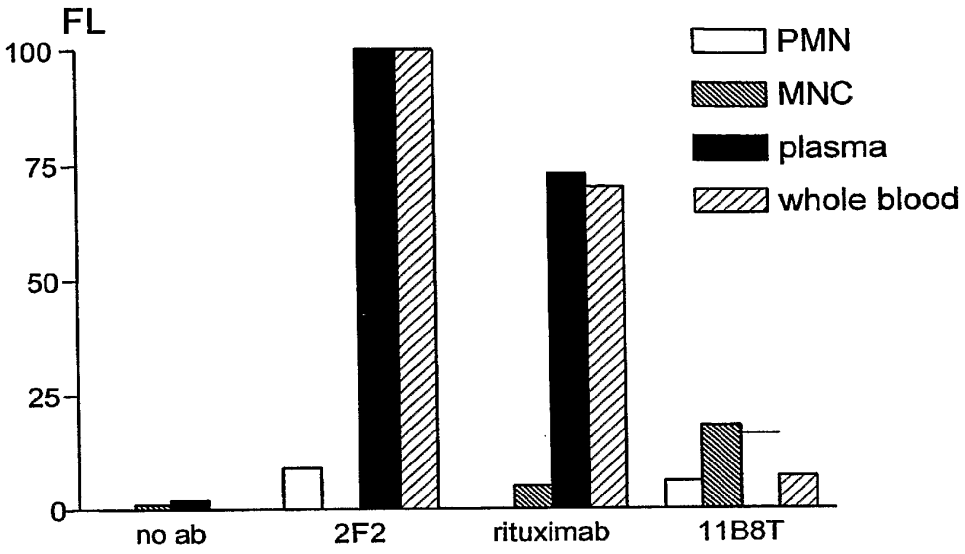


Fig. 24

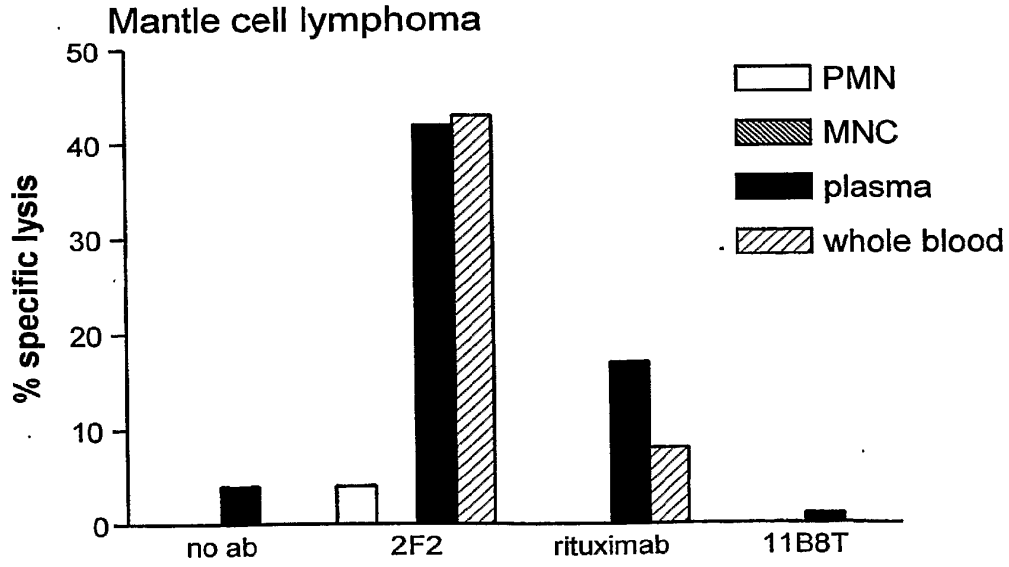


Fig. 25

Samsung Bioepis Exhibit No. 1002
Page 12340

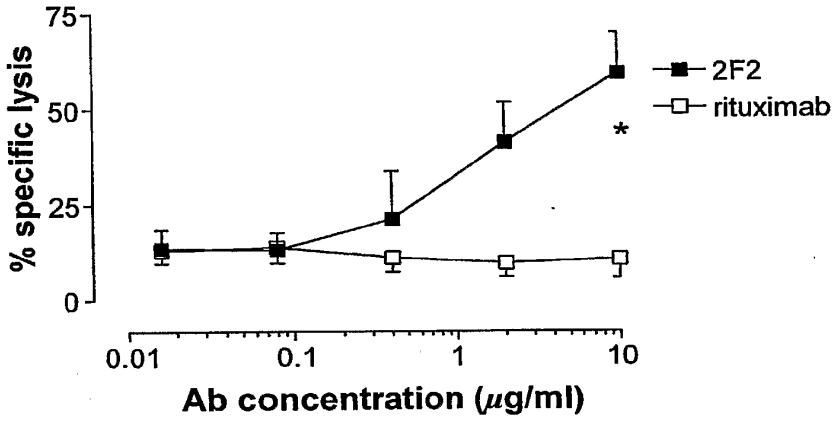

75
50
25
0
% specific lysis
0.01
0.1
1
10
Ab concentration (μg/ml)
2F2
rituximab
*

Fig. 26

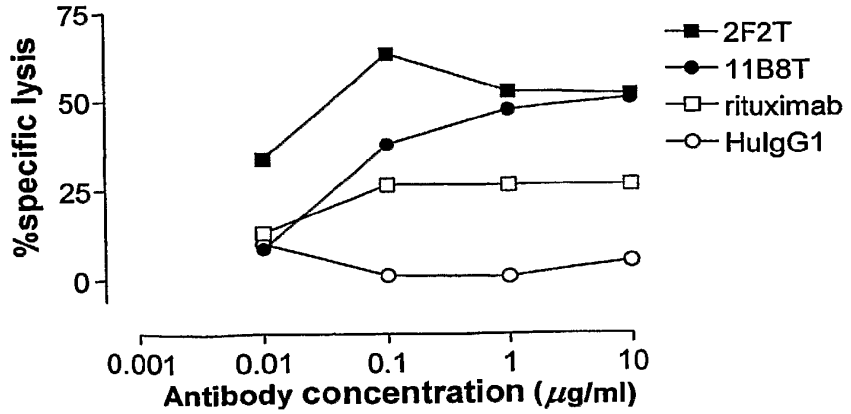

75
50
25
0
%specific lysis
0.001
0.01
0.1
1
10
Antibody concentration (μg/ml)
2F2T
11B8T
rituximab
HulgG1

Fig. 27

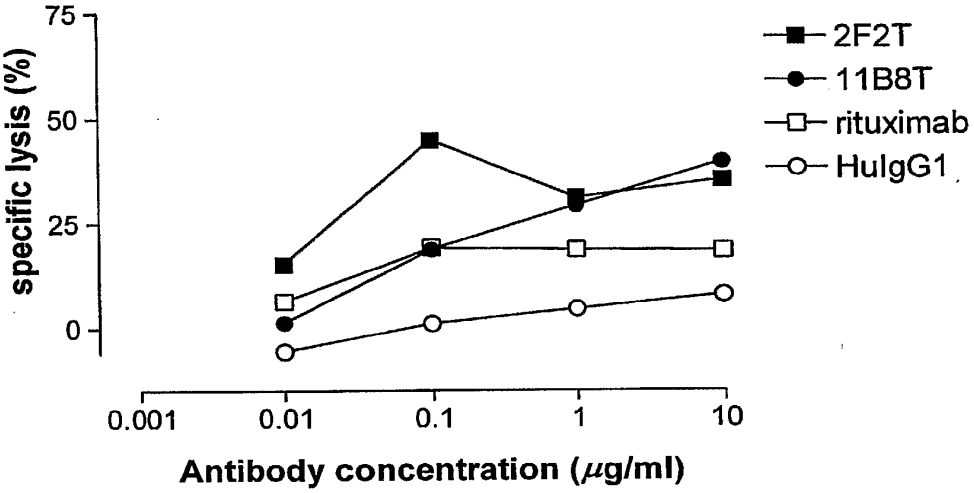


Fig. 28

Samsung Bioepis Exhibit No. 1002
Page 12342

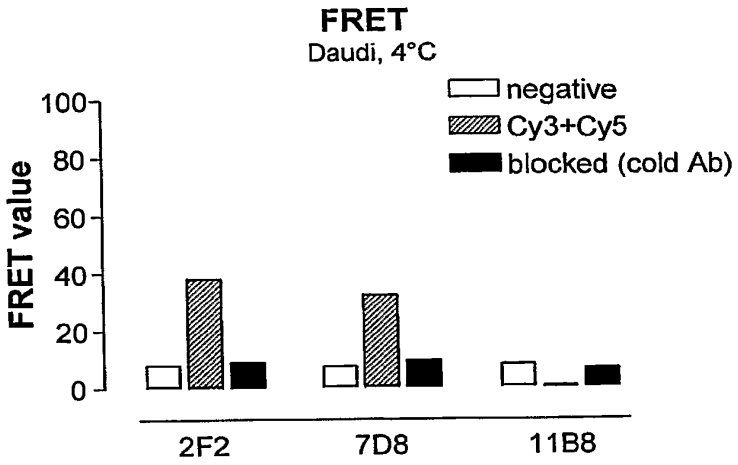


Fig. 29A

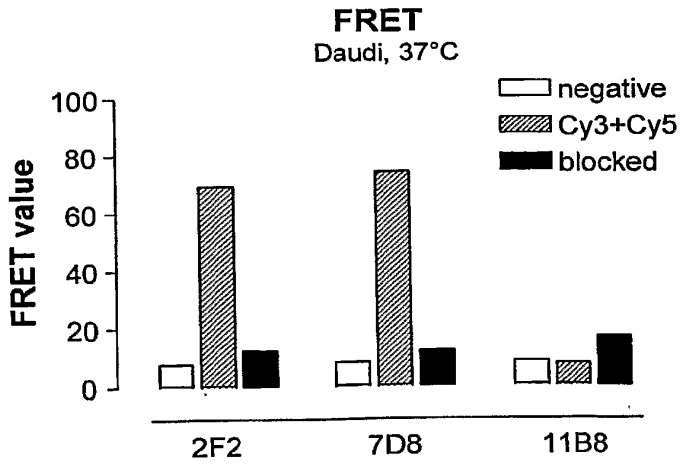


Fig. 29B

Samsung Bioepis Exhibit No. 1002
Page 12343

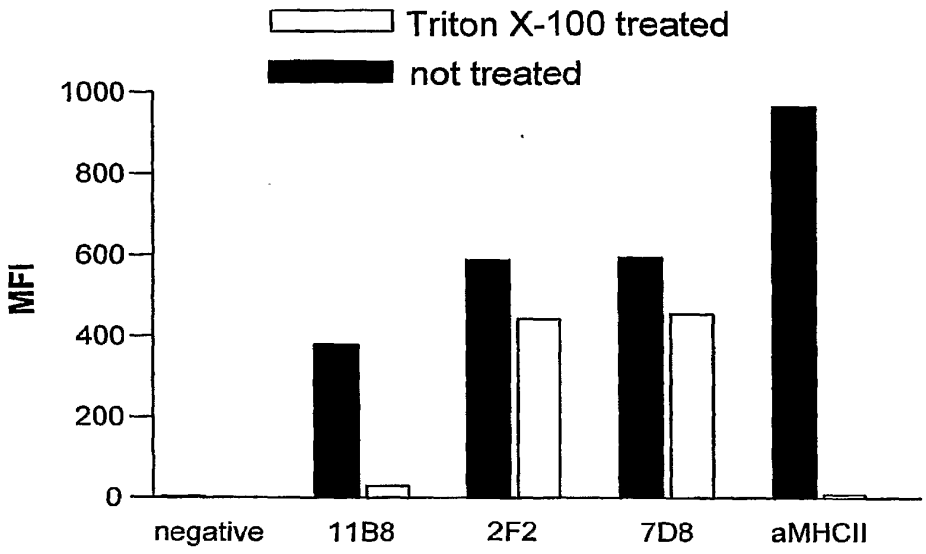


Fig. 29C

Samsung Bioepis Exhibit No. 1002
Page 12344

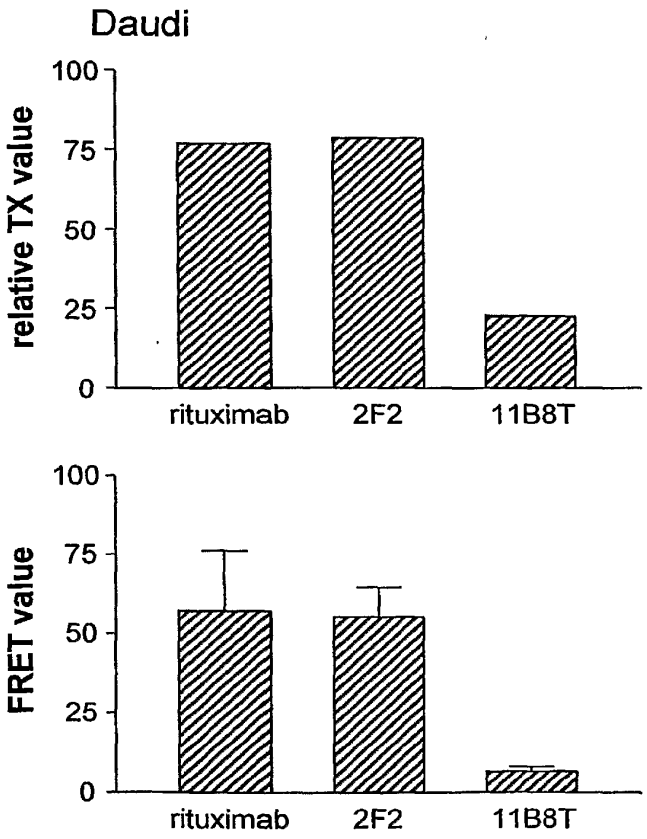


Fig. 30

Samsung Bioepis Exhibit No. 1002
Page 12345

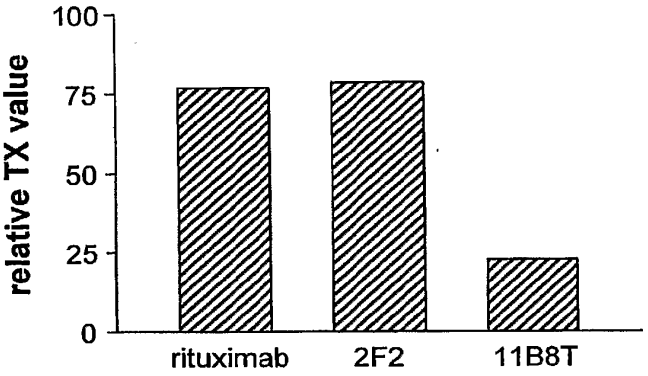


Fig. 31

Samsung Bioepis Exhibit No. 1002
Page 12346

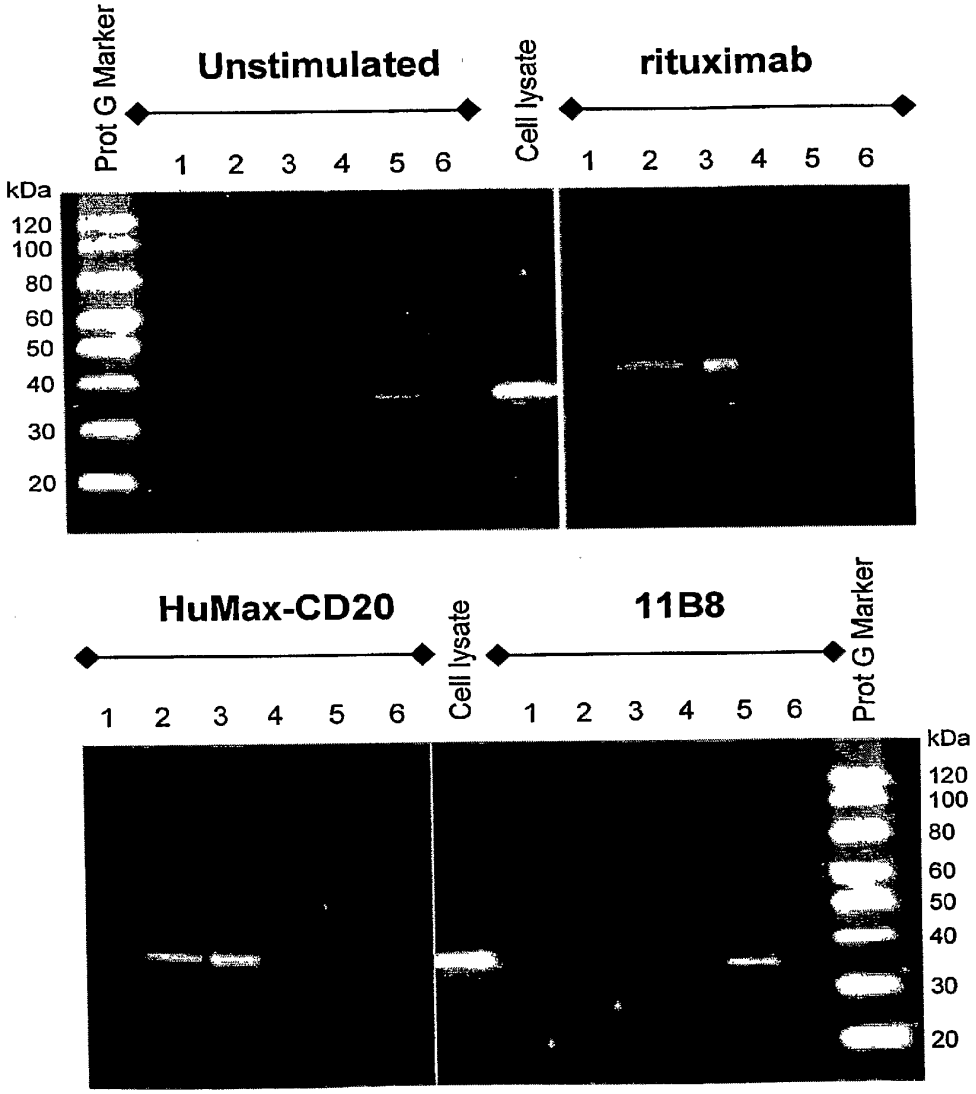

Prot G Marker
Unstimulated
Cell lysate
rituximab
1 2 3 4 5 6
1 2 3 4 5 6
kDa
120
100
80
60
50
40
30
20
HuMax-CD20
Cell lysate
11B8
Prot G Marker
1 2 3 4 5 6
1 2 3 4 5 6
kDa
120
100
80
60
50
40
30
20

Fig. 32

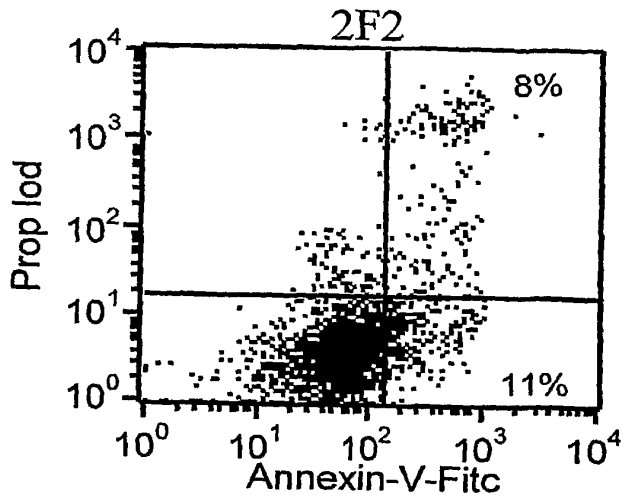


Fig. 33A

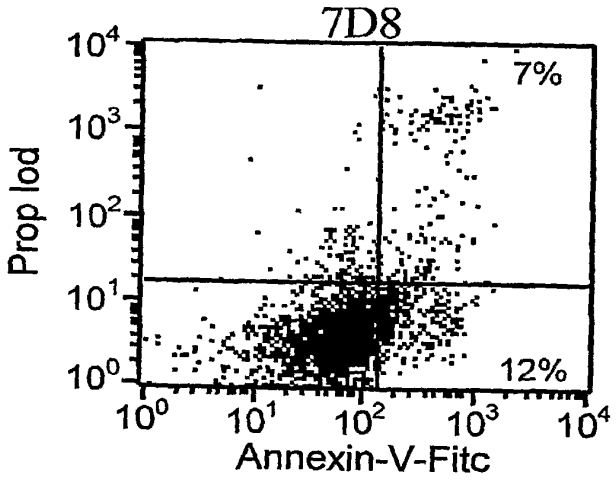


Fig. 33B

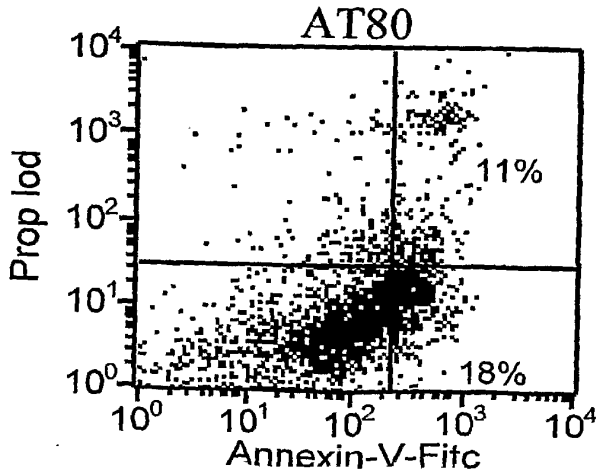


Fig. 33C

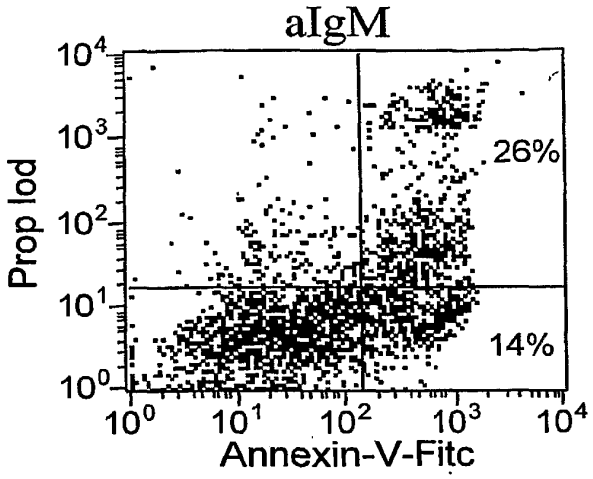


Fig. 33D

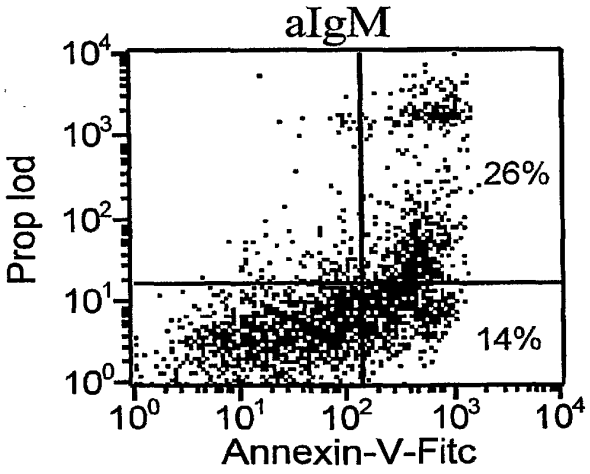


Fig. 33E

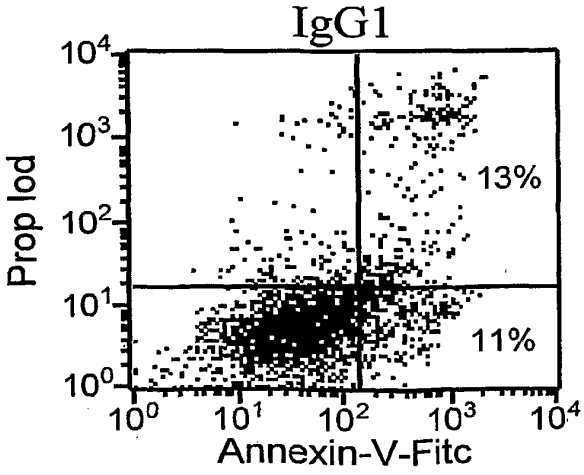


Fig. 33F

Samsung Bioepis Exhibit No. 1002
Page 12349

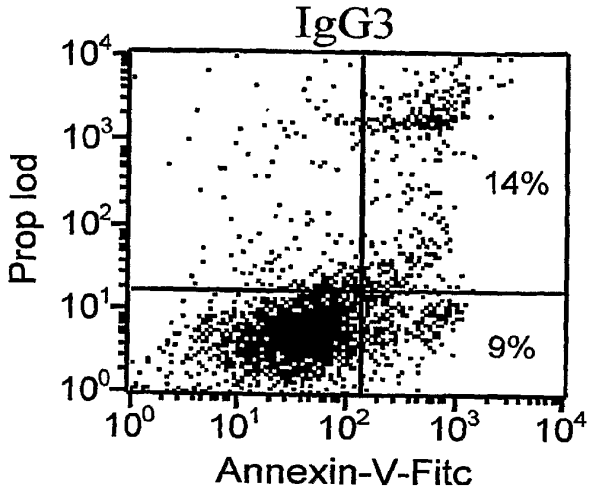


Fig. 33G

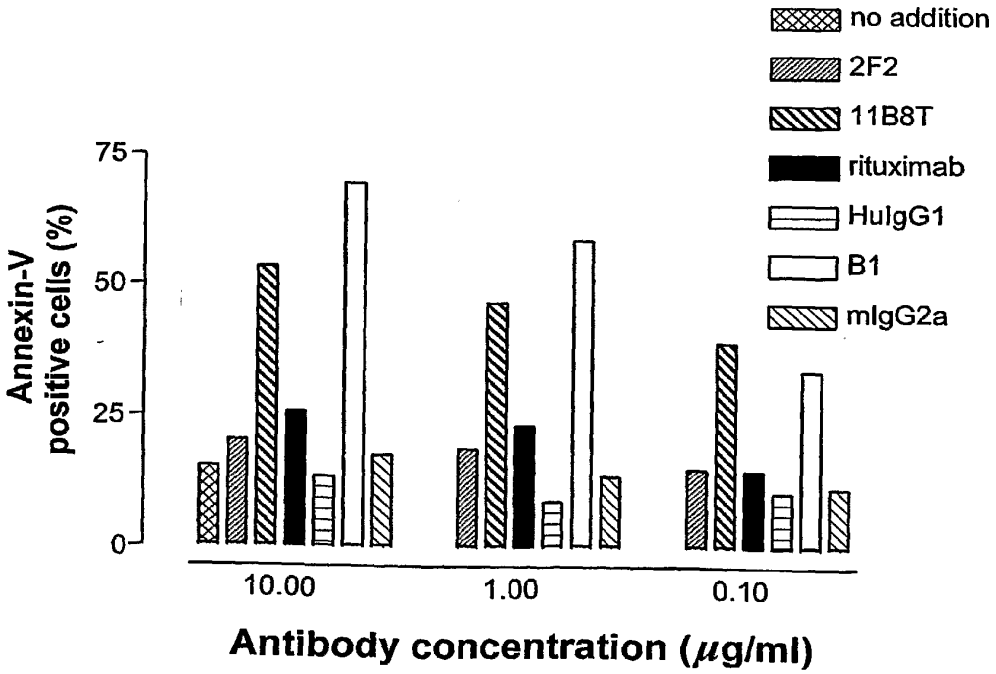


Fig. 34

Samsung Bioepis Exhibit No. 1002
Page 12350

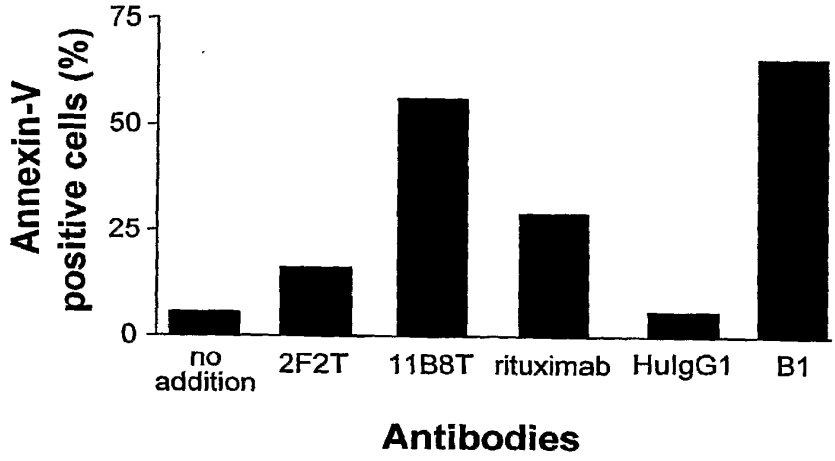


Fig. 35A

Samsung Bioepis Exhibit No. 1002
Page 12351

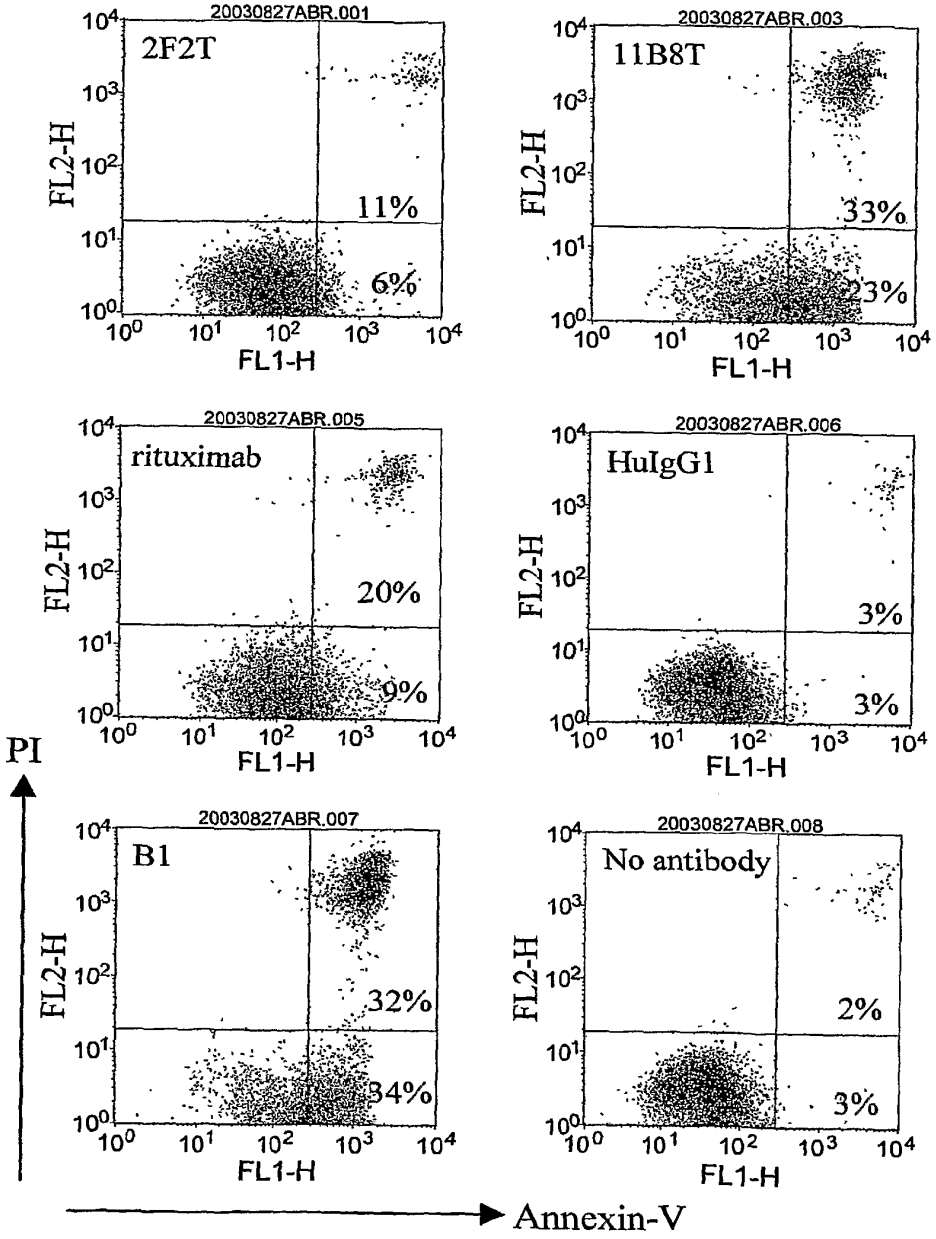


Fig. 35B

Samsung Bioepis Exhibit No. 1002
Page 12352

Homotypic adhesion of Ramos cells.

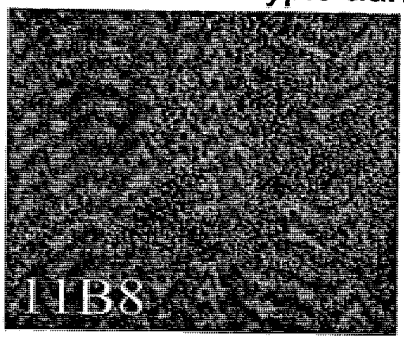


Fig. 36A

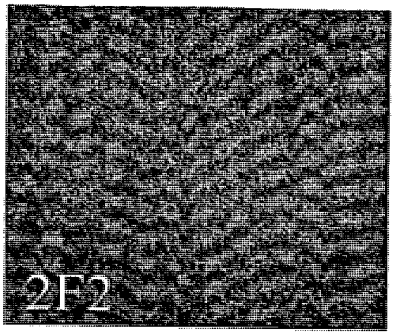


Fig. 36B

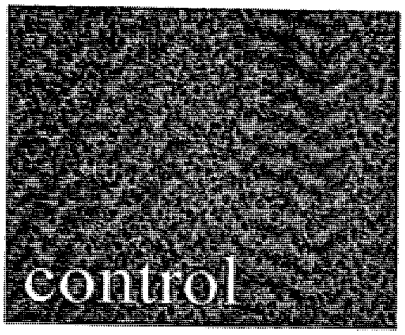


Fig. 36C

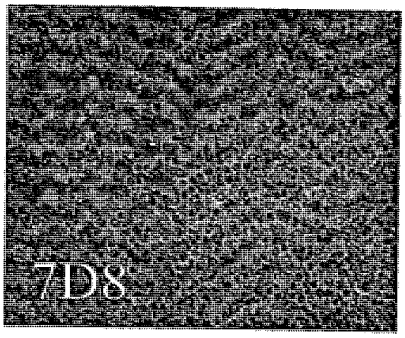


Fig. 36D

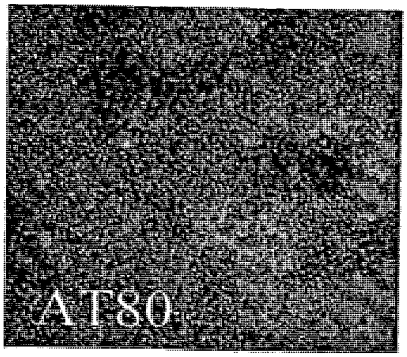


Fig. 36E

Samsung Bioepis Exhibit No. 1002
Page 12353

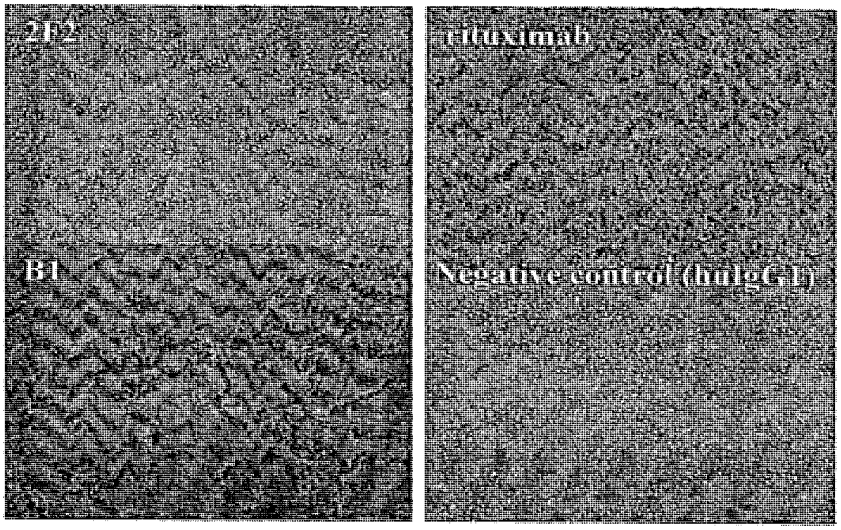


Fig. 37

Samsung Bioepis Exhibit No. 1002
Page 12354

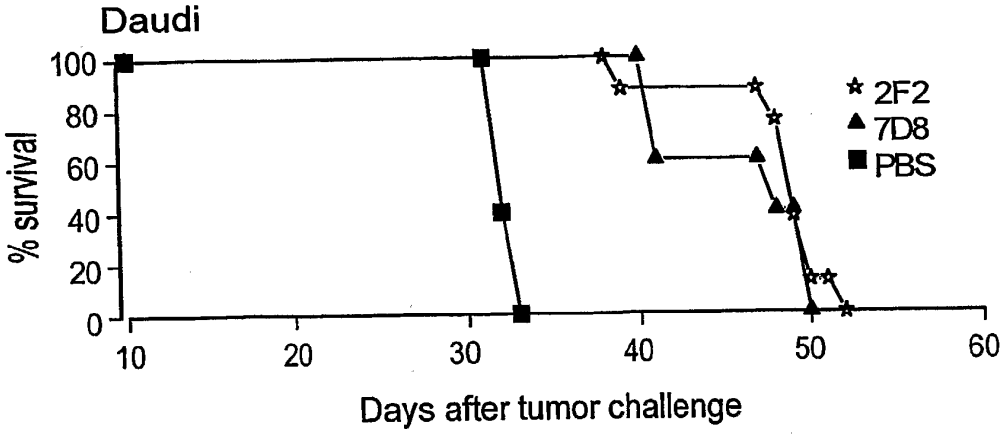


Fig. 38

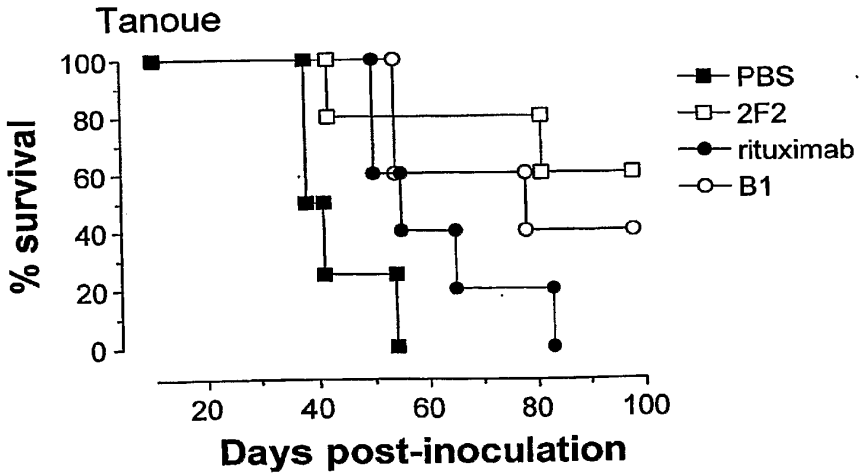


Fig. 39

Samsung Bioepis Exhibit No. 1002
Page 12355

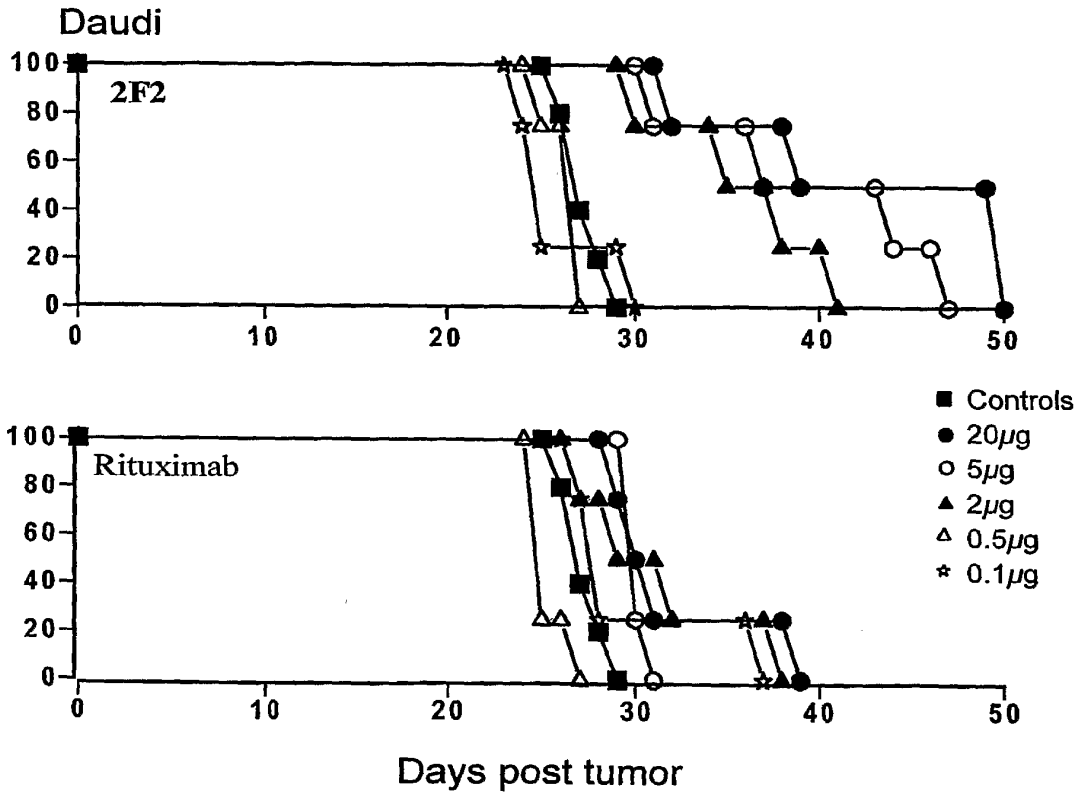

Daudi
2F2
Rituximab
100
80
60
40
20
0
0
10
20
30
40
50
Controls
20μg
5μg
2μg
0.5μg
0.1μg
Days post tumor

Fig. 40

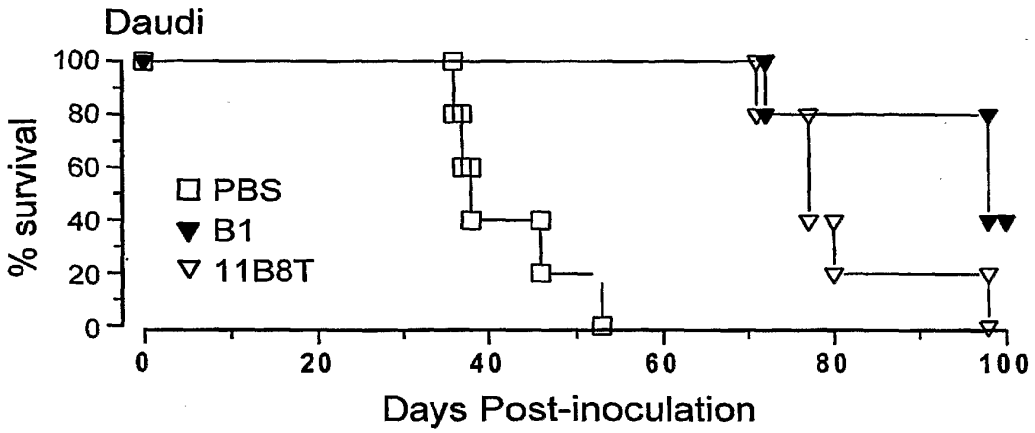


Fig. 41

Samsung Bioepis Exhibit No. 1002
Page 12357

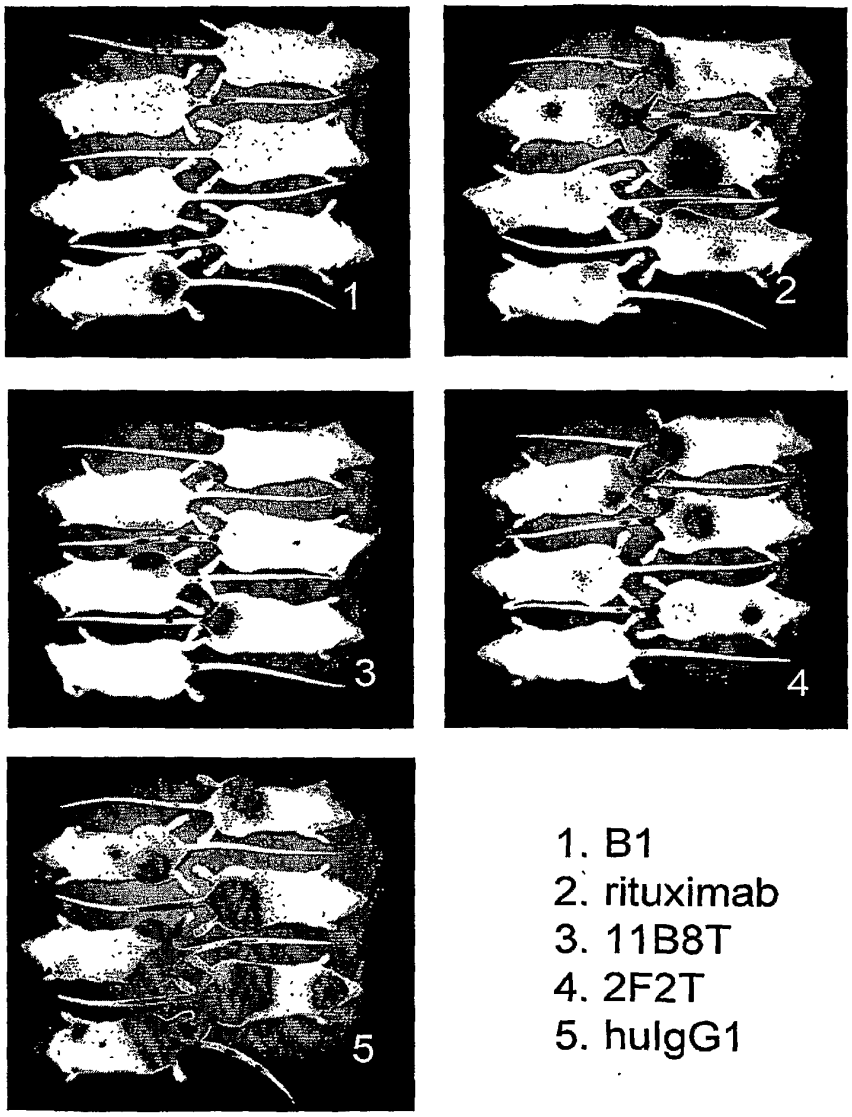


Fig. 42

Samsung Bioepis Exhibit No. 1002
Page 12358

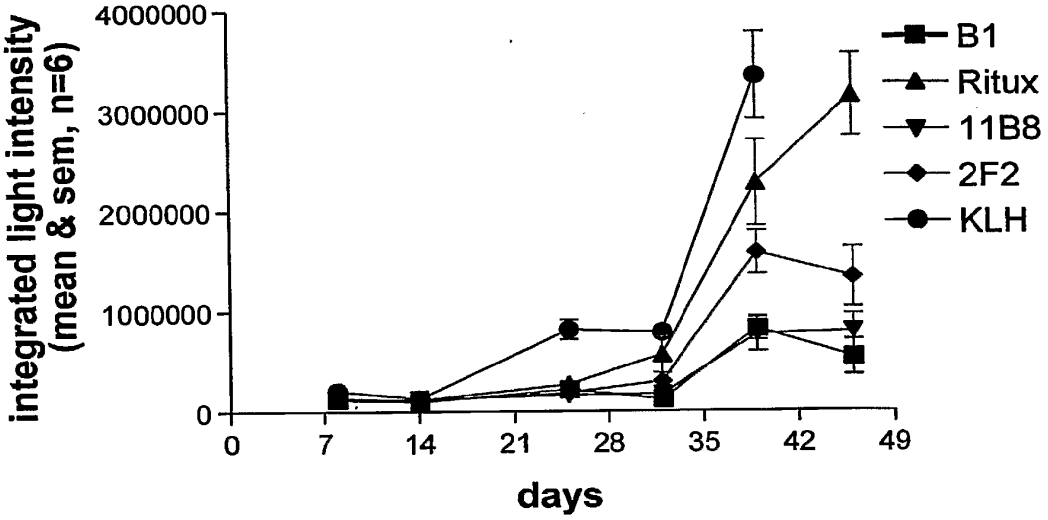

integrated light intensity
(mean & sem, n=6)
4000000
3000000
2000000
1000000
0
0
7
14
21
28
35
42
49
days
B1
Ritux
11B8
2F2
KLH

Fig. 43

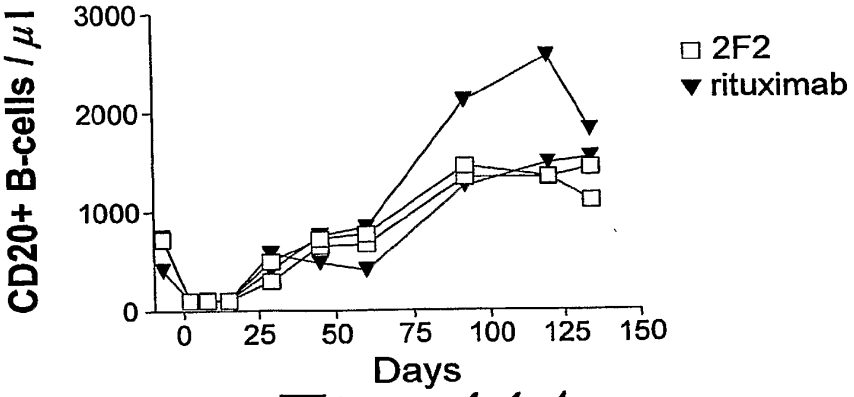


Fig. 44A

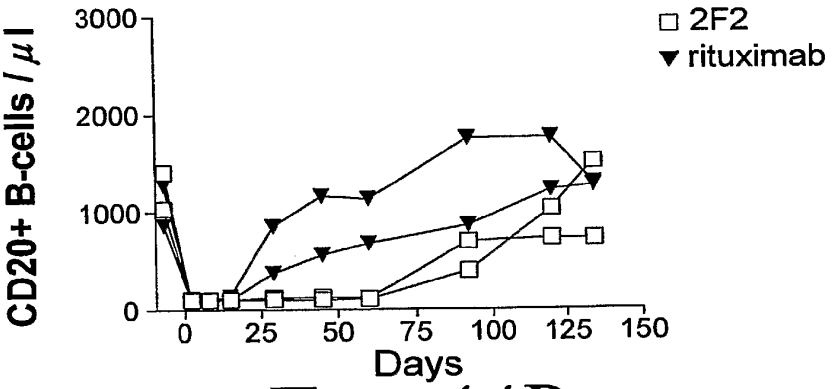


Fig. 44B

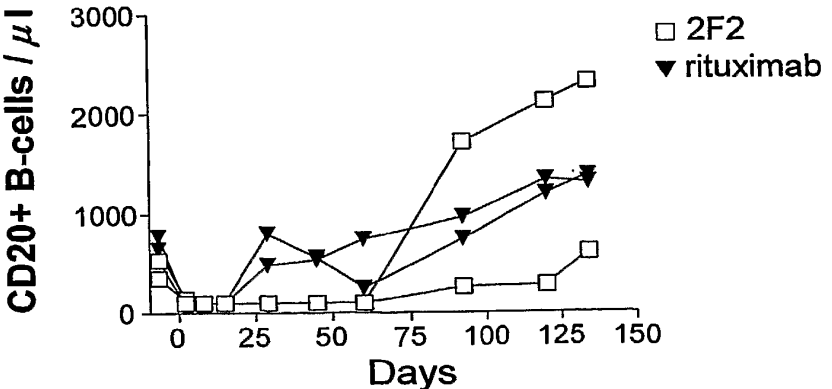


Fig. 44C

Samsung Bioepis Exhibit No. 1002
Page 12360

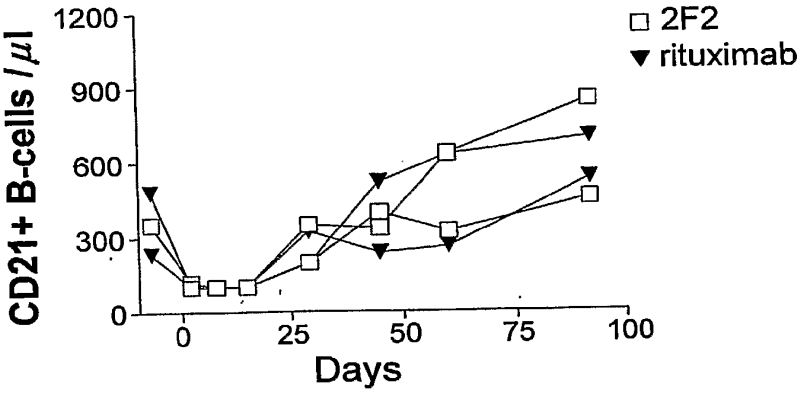


Fig. 45A

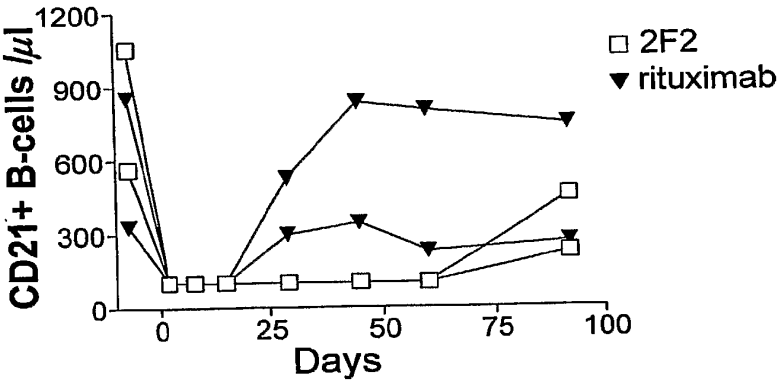


Fig. 45B

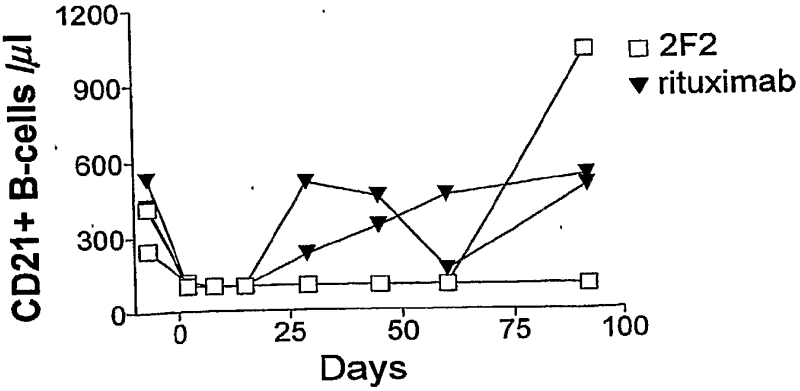


Fig. 45C

Samsung Bioepis Exhibit No. 1002
Page 12361

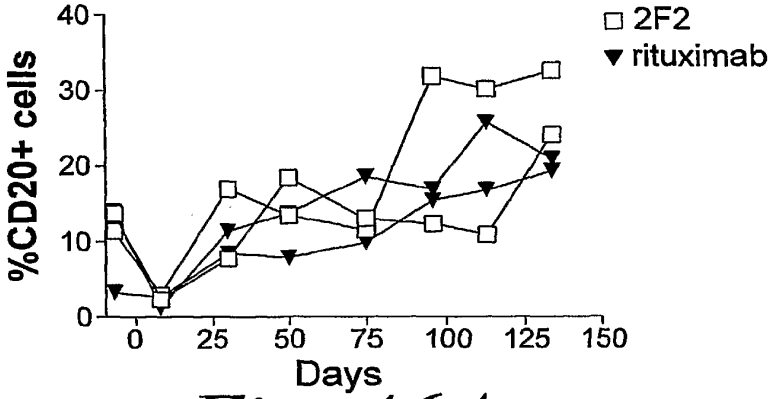


Fig. 46A

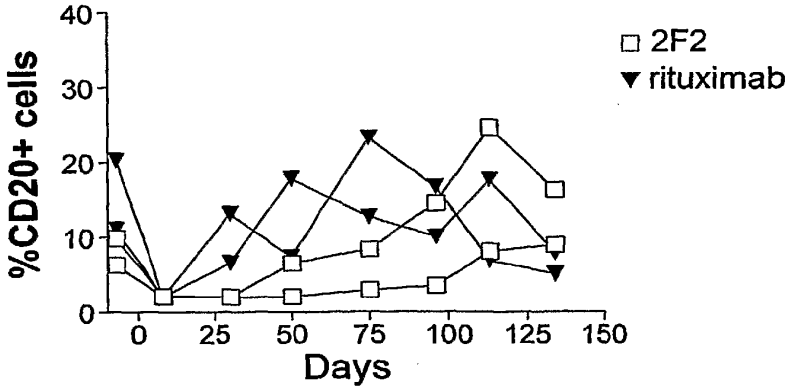


Fig. 46B

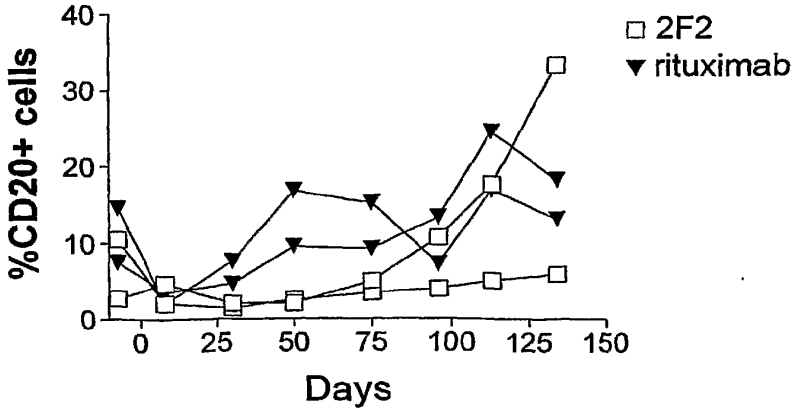


Fig. 46C

Samsung Bioepis Exhibit No. 1002
Page 12362

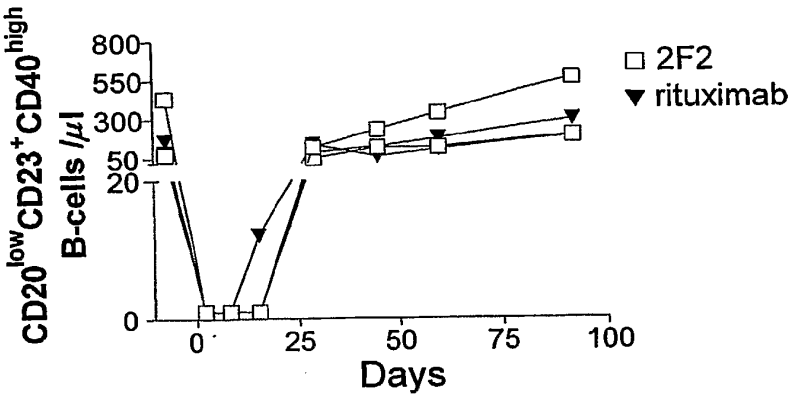


Fig. 47B

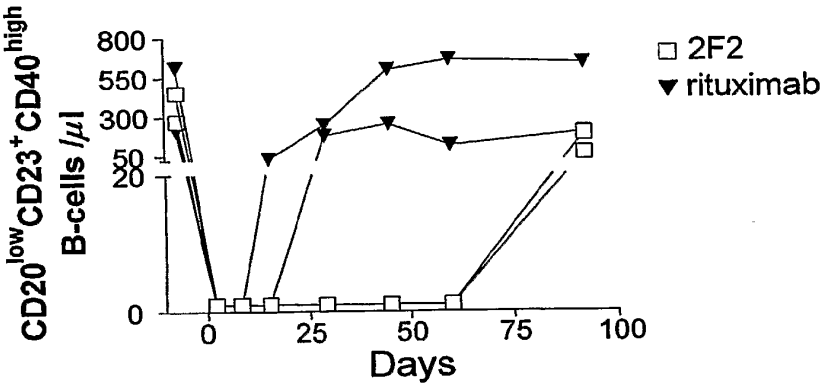


Fig. 47B

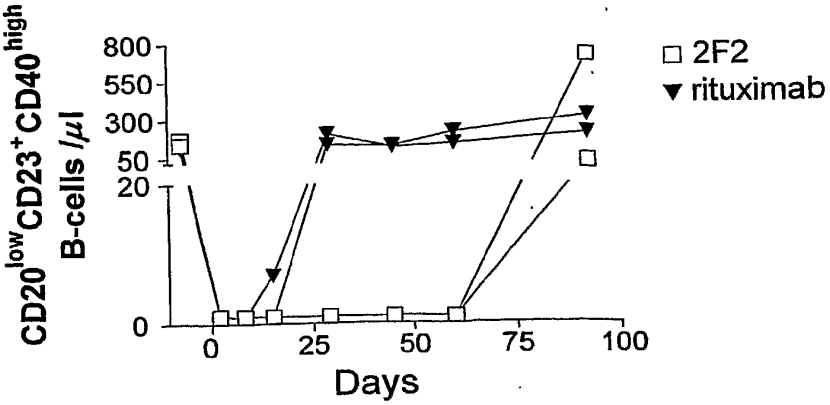


Fig. 47C

Samsung Bioepis Exhibit No. 1002
Page 12363

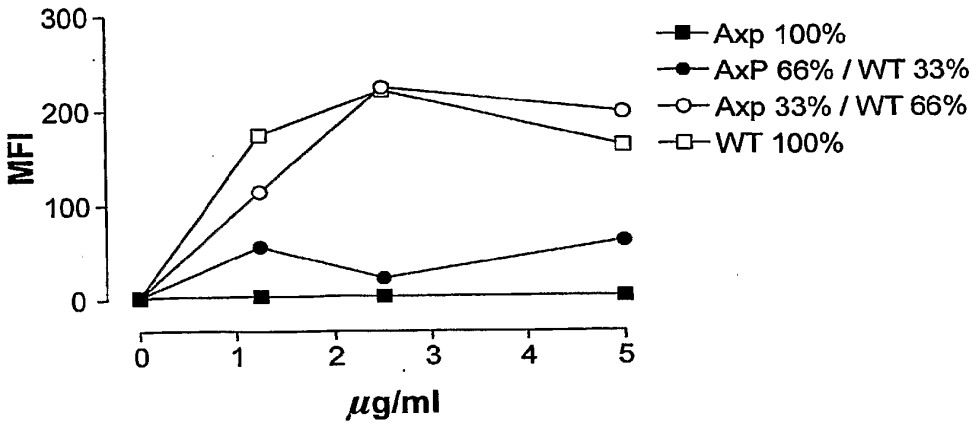


Fig. 48A

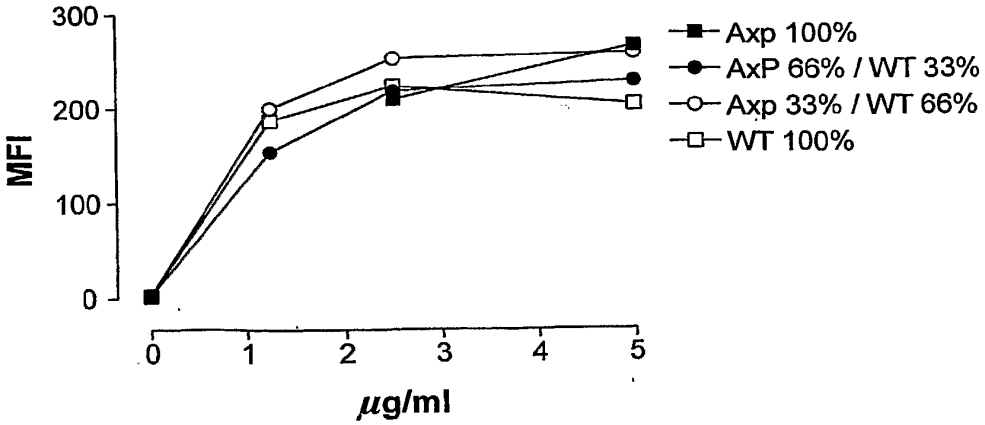


Fig. 48B

Samsung Bioepis Exhibit No. 1002
Page 12364

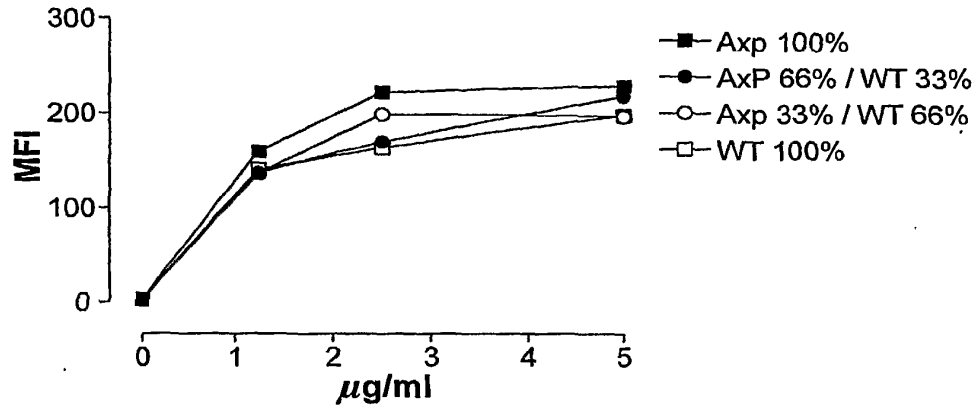


Fig. 48C

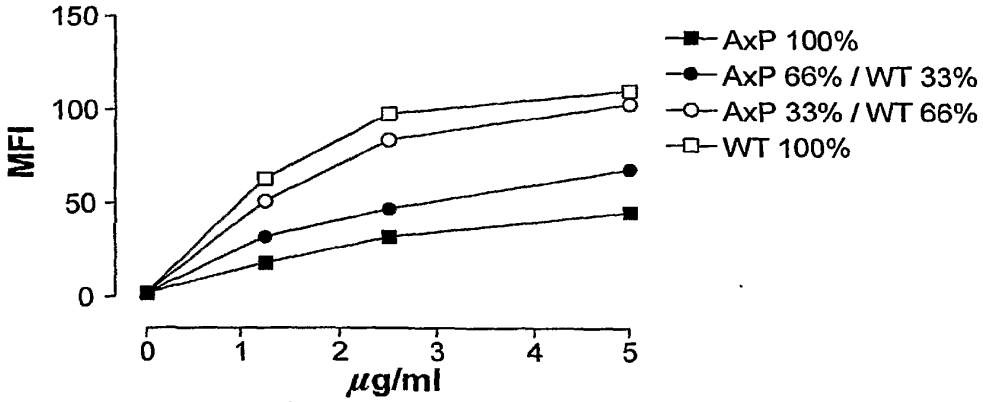


Fig. 48D

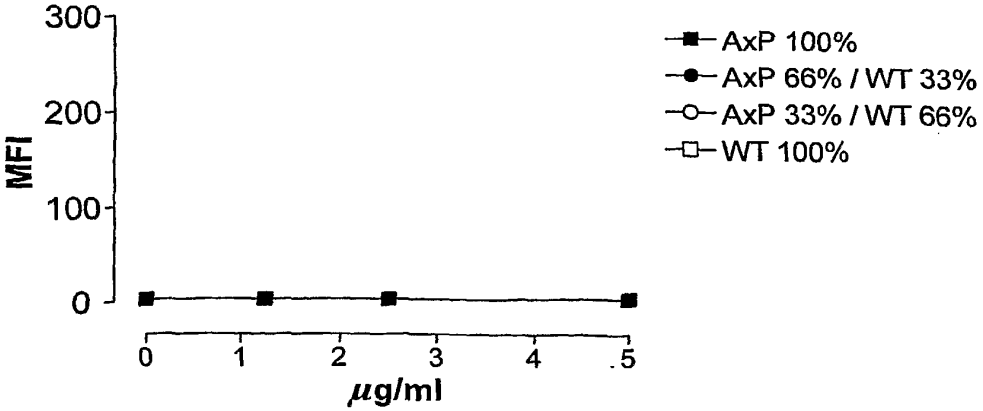


Fig. 48E

Samsung Bioepis Exhibit No. 1002
Page 12365

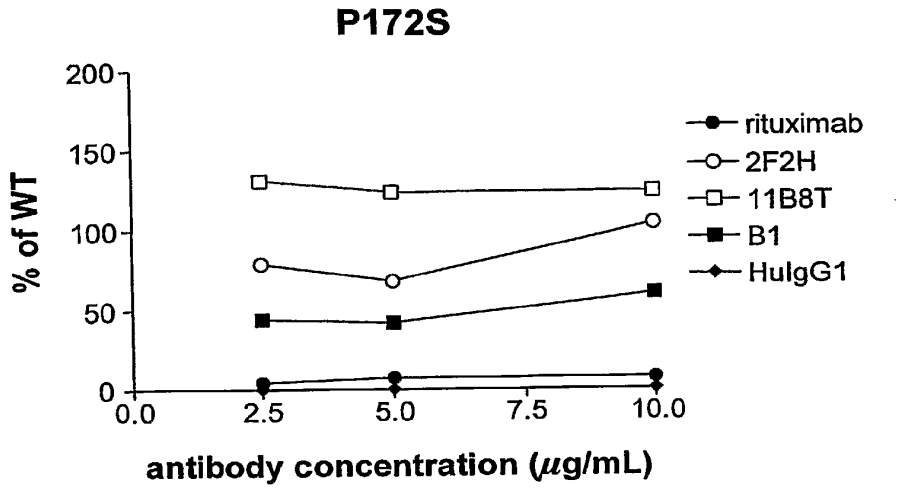


Fig. 49A

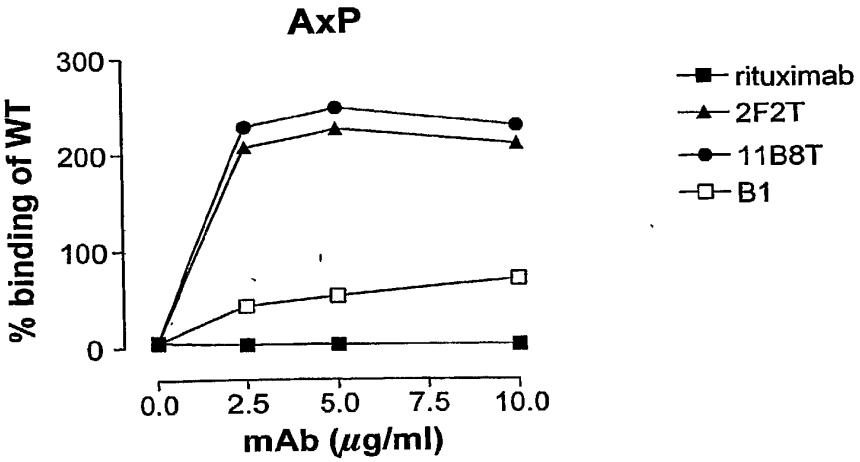


Fig. 49B

Samsung Bioepis Exhibit No. 1002
Page 12366

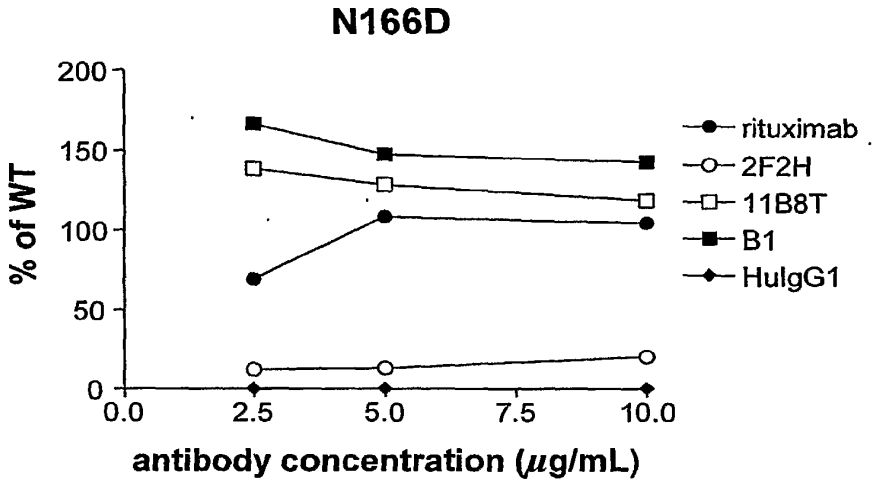


Fig. 49C

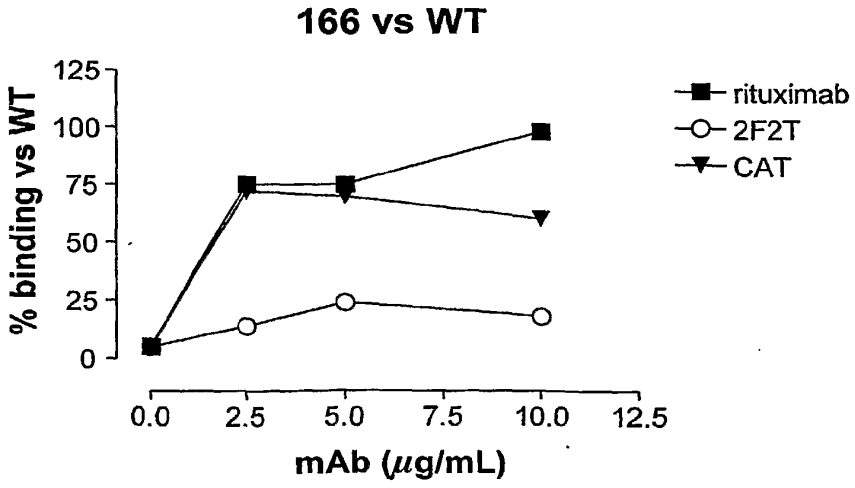


Fig. 49D

Samsung Bioepis Exhibit No. 1002
Page 12367

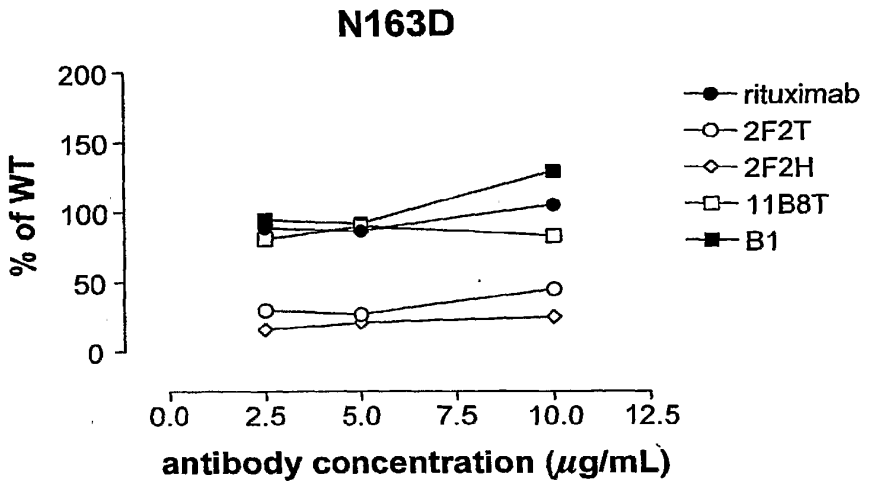


Fig. 49E

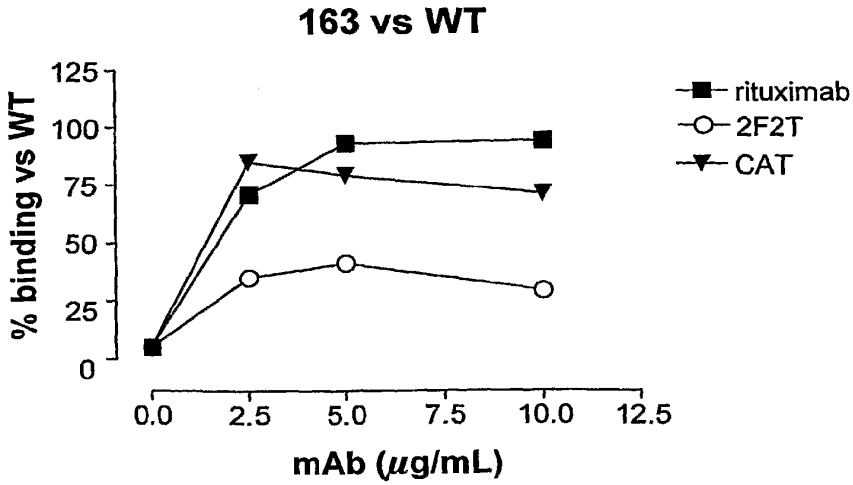


Fig. 49F

Samsung Bioepis Exhibit No. 1002
Page 12368

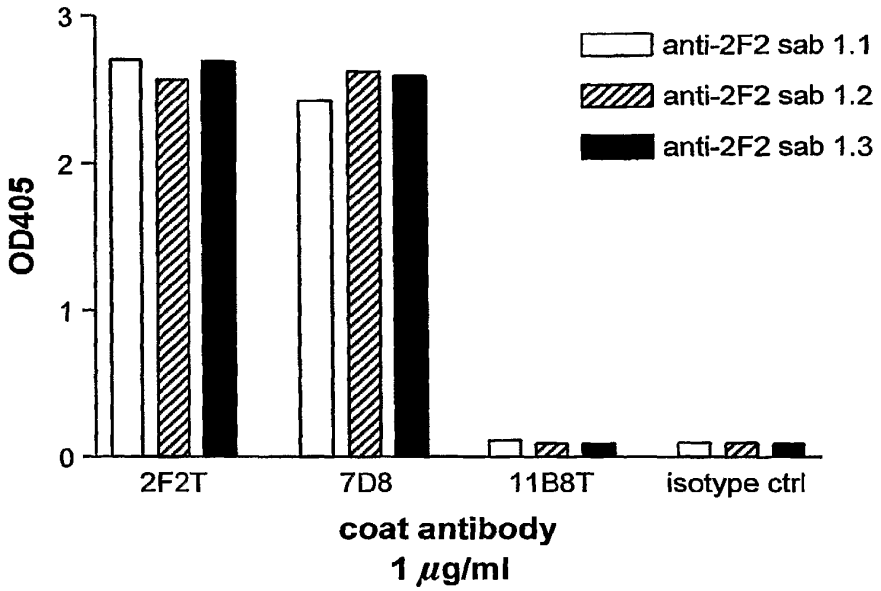


Fig. 50

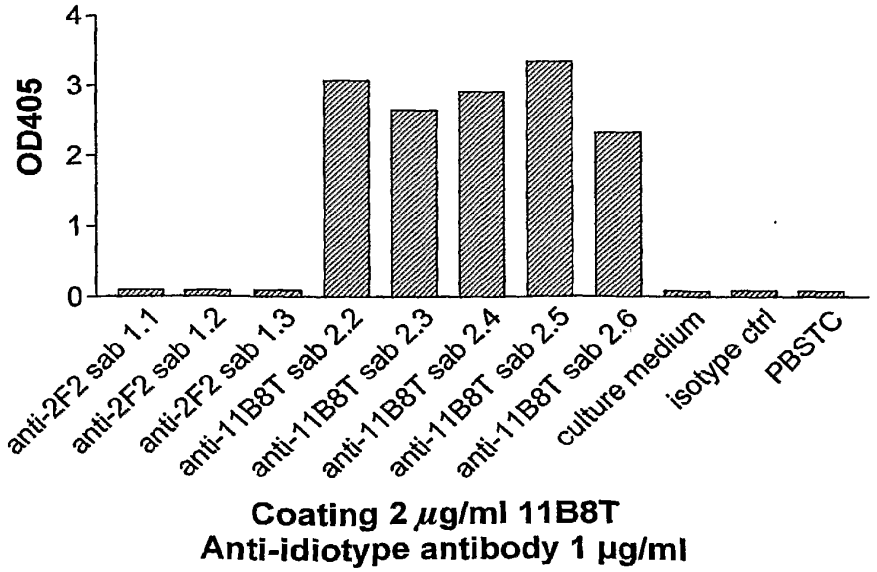


Fig. 51

Samsung Bioepis Exhibit No. 1002
Page 12369

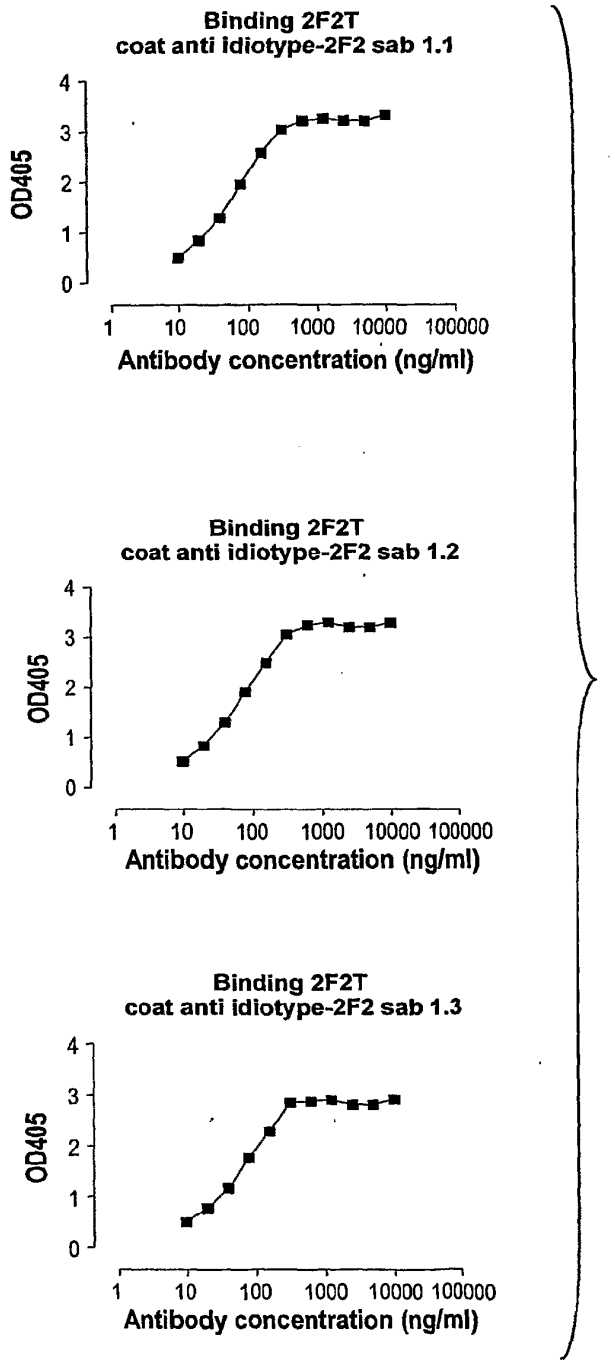


Fig. 52

Samsung Bioepis Exhibit No. 1002
Page 12370

Translation of 2F2 VH

```
  1  MFLGLSWIFL LAILKGVQCE VQLVESGGGL VQPGRSLRLS CAASGFTFND
 51  YAMHWVRQAP GKGLEWVSTI SWNSGSIGYA DSVKGRFTIS RDNAKKSLYL
101  QMNSLRAEDT ALYYCAKDTQ YGNYYYGMDV WGQGTTVTVS S
```

Translation of 2F2VL

```
  1  MEAPAQLLFL LLLWLPDTTG EIVLTQSPAT LSLSPGERAT LSCRASQSVS
 51  SYLAWYQQKP GQAPRLLIYD ASNRATGIPA RFSGSGSGTD FTLTISSLEP
101  EDFAVYYCQQ RSNWPPTFGQ GTRLEIK
```

CDR1

CDR2

CDR3

Fig. 53

Samsung Bioepis Exhibit No. 1002
Page 12371

2F2 VH

```
   1   ATGGAG TTGGGA CTGAGC TGGATT TTCCTT TTGGCT ATTTTA AAAGGT GTCCAG
  55   TGTGAA GTGCAG CTGGTG GAGTCT GGGGGA GGCTTG GTACAG CCTGGC AGGTCC
 109   CTGAGA CTCTCC TGTGCA GCCTCT GGATTC ACCTTT AATGAT TATGCC ATGCAC
 163   TGGGTC CGGCAA GCTCCA GGGAAG GGCCTG GAGTGG GTCTCA ACTATT AGTTGG
 217   AATAGT GGTTCC ATAGGC TATGCG GACTCT GTGAAG GGCCGA TTCACC ATCTCC
 271   AGAGAC AACGCC AAGAAG TCCCTG TATCTG CAAATG AACAGT CTGAGA GCTGAG
 325   GACACG GCCTTG TATTAC TGTGCA AAAGAT ATACAG TACGGC AACTAC TACTAC
 379   GGTATG GACGTC TGGGGC CAAGGG ACCACG GTCACC GTCTCC TCAG
```

2F2VL

```
   1   ATGGAA GCCCCA GCTCAG CTTCTC TTCCTC CTGCTA CTCTGG CTCCCA GATACC
  55   ACCGGA GAAATT GTGTTG ACACAG TCTCCA GCCACC CTGTCT TTGTCT CCAGGG
 109   GAAAGA GCCACC CTCTCC TGCAGG GCCAGT CAGAGT GTTAGC AGCTAC TTAGCC
 163   TGGTAC CAACAG AAACCT GGCCAG GCTCCC AGGCTC CTCATC TATGAT GCATCC
 217   AACAGG GCCACT GGCATC CCAGCC AGGTTC CGTGGC AGTGGG TCTGGG ACAGAC
 271   TTCACT CTCACC ATCAGC AGCCTA GAGCCT GAAGAT TTTGCA GTTTAT TACTGT
 325   CAGCAG CGTAGC AACTGG CCGATC ACCTTC GGCCAA GGGACA CGACTG GAGATT
 379   AAAC
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Fig. 54

Samsung Bioepis Exhibit No. 1002
Page 12372

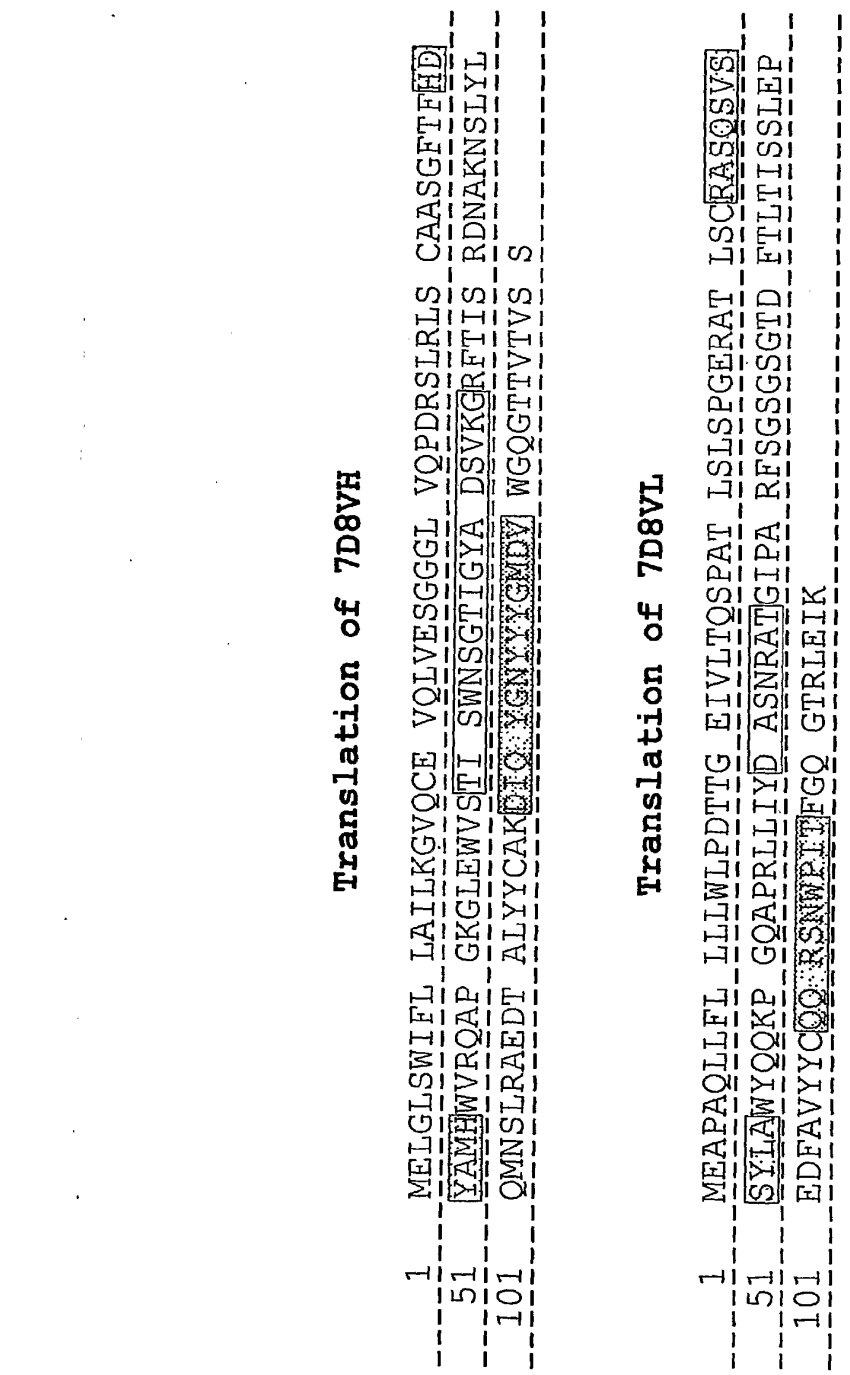


Fig. 55

Samsung Bioepis Exhibit No. 1002
Page 12373

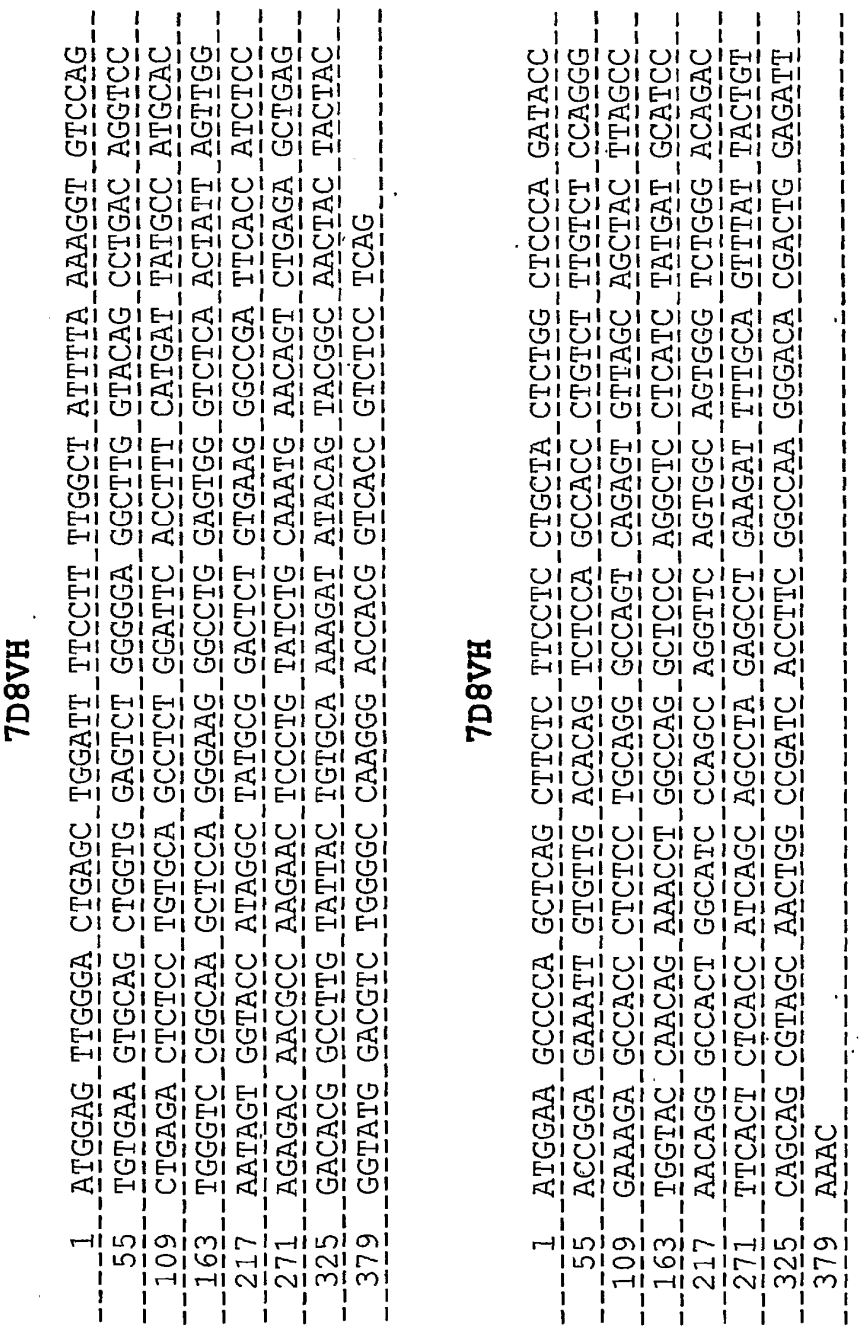


Fig. 56

Samsung Bioepis Exhibit No. 1002
Page 12374

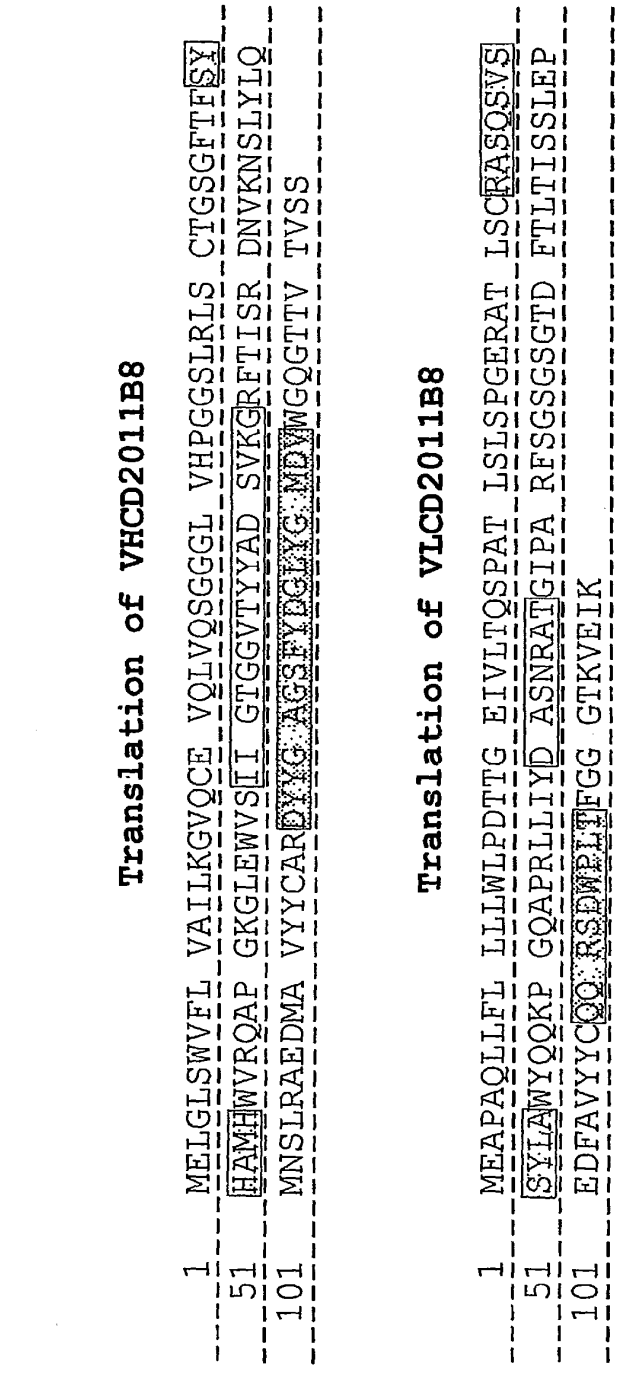


Fig. 57

Samsung Bioepis Exhibit No. 1002
Page 12375

VHCD2011B8

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  55  TGTGAG GTTCAG CTGGTG CAGTCT GGGGGA GGCTTG GTACAT CCTGGG GGGTCC
 109  CTGAGA CTCTCC TGTACA GGCTCT GGATTC ACCTTC AGTTAC CATGCT ATGCAT
 163  TGGGTT CGCCAG GCTCCA GGAAAA GGTCTG GAATGG GTATCA ATTATT GGGACT
 217  GGTGGT GTCACA TACTAT GCAGAC TCCGTG AAGGGC CGATTC ACCATC TCCAGA
 271  GACAAT GTCAAG AACTCC TTGTAT CTTCAA ATGAAC AGCCTG AGAGCC GAGGAC
 325  ATGGCT GTGTAT TACTGT GCAAGA GATTAC TATGGT GCGGGG AGTTTT TATGAC
 379  GGCCTC TACGGT ATGGAC GTCTGG GGCCAA GGGACC ACGGTC ACCGTC TCCTCA
 433  G
```

VLCD2011B8

```
   1  ATGGAA GCCCCA GCACAG CTTCTC TTCCTC CTGCTA CTCTGG CTCCCA GATACC
  55  ACCGGA GAAATT GTGTTG ACACAG TCTCCA GCCACC CTGTCT TTGTCT CCAGGG
 109  GAAAGA GCCACC CTCTCC TGCAGG GCCAGT CAGAGT GTTAGC AGCTAC TTAGCC
 163  TGGTAC CAACAG AAACCT GGCCAG GCTCCC AGGCTC CTCATC TATGAT GCATCC
 217  AACAGG GCCACT GGCATC CCAGCC AGGTTC AGTGGC AGTGGG TCTGGG ACAGAC
 271  TTCACT CTCACC ATCAGC AGCCTA GAGCCT GAAGAT TTTGCA GTTTAT TACTGT
 325  CAGCAG CGTAGC GACTGG CCGCTC ACTTTC GGCGGA GGGACC AAGGTG GAGATC
 379  AAAC
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Fig. 58

Samsung Bioepis Exhibit No. 1002
Page 12376

GMI-055PC

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<160> 57

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tgtgcagcct ctggattcac ctttaatgat tatgccatgc actgggtccg gcaagctcca 180
gggaagggcc tggagtgggt ctcaactatt agttggaata gtggttccat aggctatgcg 240
gactctgtga agggccgatt caccatctcc agagacaacg ccaagaagtc cctgtatctg 300
caaatgaaca gtctgagagc tgaggacacg gccttgtatt actgtgcaaa agatatacag 360
tacggcaact actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 420
tcag 424

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<212> PRT
<213> Homo sapiens

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 20 25 30
Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
 35 40 45
Asn Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
 50 55 60
Glu Trp Val Ser Thr Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala
65 70 75 80
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Lys
 85 90 95
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu
 100 105 110
Tyr Tyr Cys Ala Lys Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met
 115 120 125
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 130 135 140

Samsung Bioepis Exhibit No. 1002
Page 12377

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<213> Homo sapiens

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ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct 180
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 240
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 300
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<213> Homo sapiens

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Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45
Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
85 90 95
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100 105 110
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115 120 125

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tgtgcagcct ctggattcac ctttcatgat tatgccatgc actgggtccg gcaagctcca 180
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caaatgaaca gtctgagagc tgaggacacg gccttgtatt actgtgcaaa agatatacag 360
tacggcaact actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 420
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Samsung Bioepis Exhibit No. 1002
Page 12378

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<211> 141
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<213> Homo sapiens

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Pro Asp Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45
His Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60
Glu Trp Val Ser Thr Ile Ser Trp Asn Ser Gly Thr Ile Gly Tyr Ala
65 70 75 80
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu
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aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 300
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gggacacgac tggagattaa ac 382

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20 25 30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45
Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
50 55 60
Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65 70 75 80

Samsung Bioepis Exhibit No. 1002
Page 12379

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser
            100                 105                 110
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        115                 120                 125
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            20                  25                  30
Pro Gly Gly Ser Leu Arg Leu Ser Cys Thr Gly Ser Gly Phe Thr Phe
        35                  40                  45
Ser Tyr His Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60
Glu Trp Val Ser Ile Ile Gly Thr Gly Gly Val Thr Tyr Tyr Ala Asp
65                  70                  75                  80
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Val Lys Asn Ser
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Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Met Ala Val Tyr
            100                 105                 110
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Samsung Bioepis Exhibit No. 1002
Page 12380

ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct 180
ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 240
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 300
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Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45
Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
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Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65 70 75 80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
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<210> 15
<211> 13
<212> PRT
<213> Homo sapiens

Samsung Bioepis Exhibit No. 1002
Page 12381

<400> 15
Asp Ile Gln Tyr Gly Asn Tyr Tyr Tyr Gly Met Asp Val
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<210> 16
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<212> PRT
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<400> 16
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<213> Homo sapiens

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Samsung Bioepis Exhibit No. 1002
Page 12382

GMI-055PC

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1 5

<210> 25
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<400> 25
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1 5

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Samsung Bioepis Exhibit No. 1002
Page 12383

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<212> PRT
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1 5 10 15
Val

<210> 28
<211> 11
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<400> 28
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1 5 10

<210> 29
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<400> 29
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1 5

<210> 30
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1 5

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<211> 32
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<220>
<223> primer

Samsung Bioepis Exhibit No. 1002
Page 12384

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<400> 32
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Samsung Bioepis Exhibit No. 1002
Page 12385

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Samsung Bioepis Exhibit No. 1002
Page 12386

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Samsung Bioepis Exhibit No. 1002
Page 12387

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Samsung Bioepis Exhibit No. 1002
Page 12388

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20 25 30
Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Gly Ser Gly Phe Thr Phe
35 40 45
Ser Ser Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60
Glu Trp Val Ser Ala Ile Gly Thr Gly Gly Gly Thr Tyr Tyr Ala Asp
65 70 75 80
Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
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100 105 110
Tyr Cys Ala Arg
115

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1 5 10 15
Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
20 25 30

Samsung Bioepis Exhibit No. 1002
Page 12389

```
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45
Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60
Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65                  70                  75                  80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser
            100                 105                 110
Asn Trp Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
        115                 120                 125
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
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<213> Homo sapiens

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            20                  25                  30
Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45
Asp Asp Tyr Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60
Glu Trp Val Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala
65                  70                  75                  80
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
                85                  90                  95
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu
            100                 105                 110
Tyr Tyr Cys Ala Lys Asp Ile Asp Tyr Tyr Tyr Tyr Tyr Tyr Gly Met
        115                 120                 125
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
    130                 135                 140
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<213> Homo sapiens

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            20                  25                  30
Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
        35                  40                  45
Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
    50                  55                  60
```


Samsung Bioepis Exhibit No. 1002
Page 12390

```
Arg Leu Leu Ile Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala
65                  70                  75                  80
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95
Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser
            100                 105                 110
Asn Trp Pro Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
        115                 120                 125
```

The authorized list of established names
for drugs in the United States of America

2007

USP DICTIONARY

Of USAN and International Drug Names

Published in accordance with the directions of the Expert Committee
on Nomenclature of the USP Council of Experts, with the cooperation of the
United States Adopted Names Council

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"Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in the *USAN and the USP Dictionary of Drug Names."* [21 CFR299.4]

A compilation of the United States Adopted Names (USAN) selected and released from June 15, 1961, through January 31, 2007, current USP and NF names for drugs, and other nonproprietary drug names, the *USP Dictionary* incorporates the text previously published under the title *USAN and the USP Dictionary of Drug Names*.

Executive Vice President / Roger L. Williams

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Contents

PAGE

How to Use This Book 7

Preface 9

- USP Expert Committee on Nomenclature 9
- USAN Council 10
- USAN Review Board 10
- USAN Program 10
- USAN Procedure 11
- Pronunciation 12
- FDA Established Names 12
- International Nonproprietary Names 12
- International Cooperation 13
- Pharmacy Equivalent Names 13
- FDA Orphan Drugs 13
- Chemical Nomenclature 13
- Identification of Names by Number 14
- Graphic Formulas 15
- Molecular Weights 15
- Radioactive Pharmaceuticals 15
- Brand Names 15
- Code Designations 15
- Summary of Types of Information Provided 15
- Acknowledgments 16

Pronunciation Guide 17

- for Drug Names 17
- of Other Words (Secondary Words) 18

Abbreviations 21

New Nonproprietary Names 23

PAGE

Main List

United States Adopted Names (USAN), Compendial (USP and NF) Names, and Other Names for Drugs 25

Appendices

I—Brand Names for USAN and Other Nonproprietary Names 937

II—USAN and USP and NF Names Listed by Categories 969

III—Molecular Formulas 1007

IV—Code Designations for USAN and Other Nonproprietary Names 1077

V—CAS Registry Numbers and NSC Numbers 1113

VI—Veterans Administration Classification System 1199

VII—Guiding Principles for Coining U.S. Adopted Names for Drugs 1207

VIII—Guiding Principles for Coining U.S. Adopted Names for Contact Lens Materials 1223

IX—USAN Submission Forms 1229

Historical Note 1239

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Samsung Bioepis Exhibit No. 1002
Page 12395

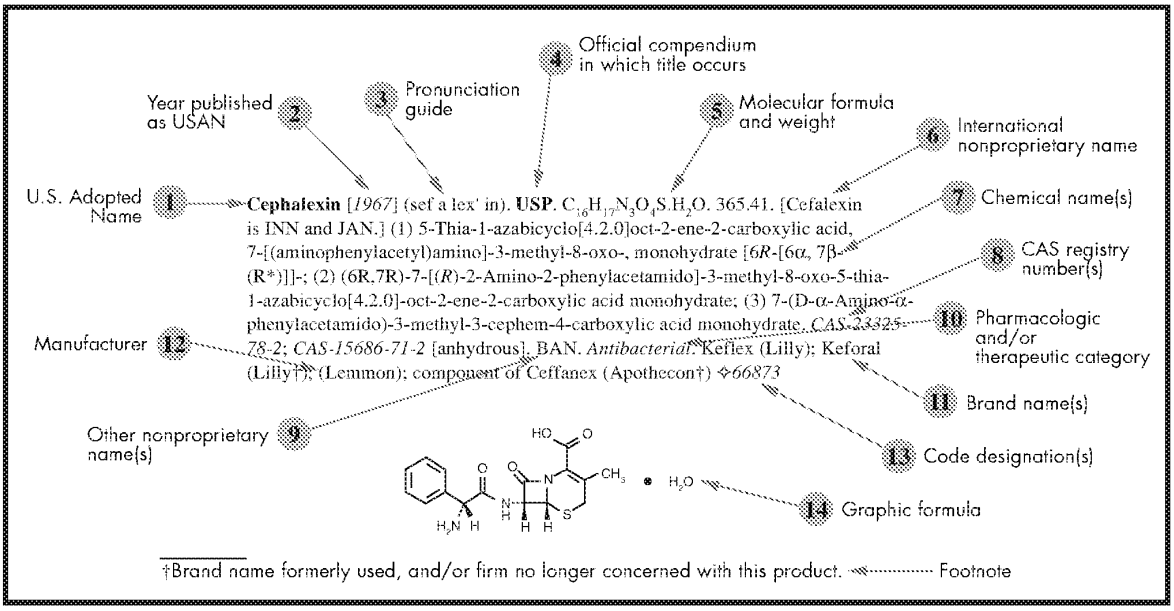
HOW TO USE THIS BOOK

For the most effective use of this book, the reader is urged to read the Preface and to consult the list of Abbreviations as needed. In addition, the following notes and examples are provided as pointers on how to use the book.

Each U.S. Adopted Name is shown in **boldface** type. The USAN entry typically includes:

1. U.S. Adopted Name (USAN)
2. Year of publication as a USAN, in brackets and italicized
3. Pronunciation guide
4. Designation of official compendium in which title occurs; e.g., boldface **USP** or **NF** if current, or specific edition in lightface type if not current
5. Molecular formula and weight
6. International nonproprietary name (INN)
7. Chemical name(s)
8. CAS registry number(s)
9. Other nonproprietary name(s)
10. Pharmacologic and/or therapeutic activity (italicized), based largely on representations from the sponsor of the USAN and subject to possible change as additional information becomes available
11. Brand name(s)
12. Name(s) of manufacturer(s) [a † symbol appears if the firm is no longer associated with the product]
13. Code designation(s) (italicized), preceded by the symbol ✧
14. Graphic formula

ILLUSTRATIVE USAN ENTRY



TYPES OF ENTRIES IN THE BOOK

USAN (in **boldface** type and accompanied by [date])

Current USP and NF titles followed by USP or NF (in **boldface** type)

International and other nonproprietary names

Brand names

Code designations

Cross-references

USAN APPENDICES

I Brand Names for USAN and Other Nonproprietary Names
II USAN and USP and NF Names Listed by Categories
III Molecular Formulas
IV Code Designations for USAN and Other Nonproprietary Names
V CAS Registry Numbers and NSC Numbers
VI VA Classification System
VII Guiding Principles for Coining U.S. Adopted Names for Drugs
VIII Guiding Principles for Coining U.S. Adopted Names for Contact Lens Materials
IX USAN Submission Forms

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Samsung Bioepis Exhibit No. 1002
Page 12396

Preface

The text of this dictionary of nonproprietary names, brand names, code designations, and Chemical Abstracts Service registry numbers for drugs has been published continually since 1963 by the United States Pharmacopeial Convention, Inc. (USP), as a public service and particularly to support the United States Adopted Names (USAN) program which began in 1961. It is prepared under the aegis of the USP Nomenclature Expert Committee.

43rd Edition

This Dictionary, now in its forty-third edition, is the annual compilation of United States Adopted Names (for which the abbreviation, USAN, generally is used). It is cumulative from June 15, 1961, when the U.S. Adopted Names program began. It incorporates the text of the publication previously known as *USAN and the USP Dictionary of Drug Names* and supersedes the 2006 edition and all earlier editions of the dictionary.

Supplements to the Dictionary are published bimonthly in the *Nomenclature* section of *Pharmacopeial Forum* (*PF*), USP's Journal of Standards Development and Official Compendia Revision. The new names and revisions of existing names in supplements are cumulatively included in the next published edition of the Dictionary.

The Federal Food and Drug Administration (FDA) has stated that interested persons may, in the absence of the designation of an official name, rely on *USAN and the USP Dictionary of Drug Names* (now known as the *USP Dictionary of USAN and International Drug Names*) for the established name for any drug in the U.S.A. (see *FDA Established Names*). The FDA has indicated also that it will not routinely designate official names and will do so only under certain specific conditions.

The USAN and the current compendial—*United States Pharmacopeia* (*USP*) and *National Formulary* (*NF*)—names are printed in **boldface** type. The International Nonproprietary Names (INN), British Approved Names (BAN) and Japanese Accepted Names (JAN), along with other miscellaneous names, appear in regular lightface type.

Included herein are 169 new U.S. Adopted Names released since publication of the previous edition of this book, as well as additions of other names for drugs. This edition reflects also hundreds of changes affecting information given in previously published entries.

The need for such compilations grows ever greater as the lists lengthen. The body of compounds in active use as drugs does not increase greatly, because new and better drugs tend to displace older drugs intended for the same purposes. On the other hand, new brand names may appear long after a drug is first marketed. The number of nonproprietary names increases steadily because, once assigned, a name remains on record and may not be reassigned even though the compound that it designates has been abandoned. Although rarely done, a brand name may be recycled and applied to another drug. Notable, too, are changes in the ingredients of combination drug products, while retaining the same brand name.

This book lists 10,193 nonproprietary drug name entries. These entries contain more than 3,584 brand names; 4,697 code designations (including 399 NSC numbers); and more than 11,103 CAS registry numbers. There are 8,059 graphic formulas depicted. The total number of USAN herein is 4,228.

All International Nonproprietary Names (INN) published by the World Health Organization from the start of the INN program in 1953 through 2006 are included in this book. Where an INN or other international name (BAN, JAN) exists for a drug that is covered by a **boldface** entry, the entry designates whether the INN, BAN, or JAN is the same as the corresponding USAN or *USP* or *NF* name or differs, in which case the difference is shown.

As is stated in this preface under *USAN Procedure*, there is increasing emphasis on the worldwide adoption of the same name for each therapeutic substance in view of the manifest advantages it offers to better communication and world trade. Thus the policy of including *all* INN in this Dictionary lends added perspective and serves to reinforce the aim for more uniformity.

Appendixes, which follow the main alphabetic list, are included on (I) brand names for USAN and other nonproprietary names; (II) USAN and USP and NF names listed by categories; (III) molecular formulas; (IV) code designations for USAN and other nonproprietary names; (V) CAS registry numbers and NSC numbers; (VI) VA classification system; (VII) guiding principles for coining U.S. Adopted Names for drugs; (VIII) guiding principles for coining U.S. Adopted Names for contact lens materials; and (IX) USAN submission forms.

With respect to the legal status of trademarks cited as brand names herein, inquiries should be directed to the U.S. Patent Office.

The database of this Dictionary is maintained on a computer with storage and retrieval capabilities designed to facilitate future revisions and additions to the text as needed. Completeness and accuracy are of course paramount objectives in a compilation such as this. Suggestions of corrections or additions to the text will be welcomed for future consideration.

USP Nomenclature Expert Committee

A USP Drug Nomenclature Committee was established in 1985. The designation was changed subsequently to the USP Nomenclature Committee, the term Drug being removed when it became necessary for the Committee to address the nomenclature of articles other than drugs (e.g., dietary supplements and devices) that were introduced into the official compendia. The designation was changed again to the Nomenclature Expert Committee and Labeling. The responsibility for labeling was added to reflect the close interdependence of nomenclature and labeling that had become evident. Requiring certain information via labeling can afford an

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Samsung Bioepis Exhibit No. 1002
Page 12397

opportunity to leave it out of an article's name itself. However, since nomenclature is the essence of the Expert Committee's work, the name was simplified to the Nomenclature Expert Committee for the 2005–2010 revision cycle.

In accordance with the Rules and Procedures of the 2005–2010 Council of Experts as adopted pursuant to the USP Bylaws, this Dictionary is prepared under the aegis of the USP Nomenclature Expert Committee for 2005–2010, which currently comprises:

Loyd V. Allen, Jr., Ph.D.
Mary B. Baker, Pharm.D.
Dawn M. Boothe, DVM, Ph.D.
Herbert S. Carlin, D.Sc.
Mrunal S. Chapekar, Ph.D.
Edward M. Cohen, Ph.D.
Stephanie Y. Crawford, Ph.D.
Everett Flanigan, Ph.D.
Thomas S. Foster, Pharm.D.
Michael J. Groves, Ph.D.
William M. Heller, Ph.D.
David F. Long, Ph.D.
Ginette A. Pepper, Ph.D., R.N.
Jerry Phillips, B.S., R.Ph.
Thomas P. Reinders, Pharm.D., *Chair*
Philip D. Walson, M.D.
Chao-Mei Yu, Ph.D.

The Nomenclature Expert Committee is responsible for promoting uniformity and consistency among official titles in the *USP* and the *NF*, coining suitable titles where such are needed because of the lack of public (nonproprietary) names or to improve the names already in use. The titles are designed to be in harmony with convenience in prescribing and with accepted tenets of general usage and are intended to be simple, useful, and clearly distinguishing and differentiating. The Nomenclature Expert Committee also determines the parameters of content, format, and style of the information contained in the Dictionary, and receives and rules upon all questions and appeals for reconsideration of text prepared by USP staff and appearing in the Dictionary. These responsibilities of the Nomenclature Expert Committee represent no change from the responsibilities relative to drug nomenclature that have resided with the Pharmacopeia since its founding in 1820. The appointment of the Nomenclature Expert Committee in no way alters the way in which the USP organization as a co-sponsor of the USAN Program, or the USP Council of Experts, works closely and cordially with the USAN Council. Indeed, the Nomenclature Expert Committee is concerned with several areas not within the scope of the USAN Council, e.g., nomenclature for dosage form monographs, applying the established policy of using the same terminology in both the monograph title and the strength expression for the article. The Expert Committee likewise deals with other aspects of the language used in the prescription, dispensing, sale, or manufacture of drugs.

The Nomenclature Expert Committee is supported by the U.S. Pharmacopeia. W. Larry Paul, Ph.D., is the USP Department of Healthcare Quality and Information's liaison to the Nomenclature Expert Committee.

USAN Council

The three organizations that sponsor the USAN Program, i.e., the American Medical Association, the American Pharmacists Association, and the U.S. Pharmacopeia, do so through representation on the USAN Council. Members are appointed by their sponsors, subject to acceptance by the other sponsors. In addition, the three organizations jointly select a member-at-large. Members are appointed for one-year terms and may serve no more than ten consecutive terms.

In 1967, negotiations were completed to provide for participation by the U.S. Food and Drug Administration in the program as a means of consolidating the work of selecting suitable nonproprietary names for drugs on the part of the federal government and the existing Council. Thus, a liaison representative of the FDA sits on the Council. The roster of the Council for 2007, with member appointment or designation shown parenthetically, includes:

William M. Heller, Ph.D. (at large)
David Lewis, Ph.D., (FDA)
Anthony Palmieri III, Ph.D. (APhA)
Peter Rheinstein, M.D., J.D. (AMA)
Darin J. Weber, Ph.D. (USP)

The USAN Council was formed January 2, 1964, to succeed the AMA–USP Nomenclature Committee. It works mainly by correspondence and e-mail, although Council meetings are held twice a year.

The USAN Council Secretariat is located at the American Medical Association, and is housed in the AMA headquarters. Inquiries and communications pertaining to USAN should be addressed to the USAN Council Secretary.[1]

USAN Review Board

The six-member USAN Review Board was established to provide an effective means of settling controversy stemming from irreconcilable differences of opinion regarding drug name selection. Two members are appointed by each sponsoring organization for one-year terms, subject to indefinite renewal.

Recourse to the Review Board in settling disputes over selection of the names has been relatively rare; in fact, its services have been employed in only five cases to date. Participants agree at the outset that the determination of the USAN Review Board is final and beyond appeal.

The USAN Review Board for 2007 comprises:

Donald R. Bennett, M.D., Ph.D. (AMA)
John E. Kasik, M.D., Ph.D. (AMA)
Stuart Feldman, Ph.D. (APhA)
Alice J. Matuszak, Ph.D. (APhA)
Jordan L. Cohen, Ph.D. (USP)
Gary L. Yingling, J.D., M.S. (USP)

The USAN Review Board secretariat is supported by the U.S. Pharmacopeia. Susan S. de Mars, J.D., serves the Board as Secretary.

USAN Program

The USAN Program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs and certain other related agents (e.g., pharmaceutic aids, contact lens plastics, surgical materials). The name-selection process should be initiated when the drug enters the clinical investigation stage. Indeed, USAN are often created for compounds that never come to be marketed as drugs.

The adoption of a name is independent of clinical evaluation or acceptance by the medical profession of the article to which the name applies. Nevertheless, the USAN Council chooses each U.S. Adopted Name with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official *United States Pharmacopeia* or *National Formulary*.

The USAN Program has earned a measure of prestige and world-wide recognition as an undertaking in the public interest. In addition to long-standing prejudices that work against instituting an orderly and effectual system of name selection, there also is widespread misunderstanding with respect to what constitutes

[1] Secretary, USAN Council, c/o American Medical Association, 515 North State Street, Chicago, Illinois 60610 [Telephone: (312) 464-4046].

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good nonproprietary names and what purposes they serve. The USAN Council is committed to following established principles for coining nonproprietary names (see Appendixes VII and VIII) and to enlisting the cooperation of the pharmaceutical industry in this country and of nomenclature groups abroad with a view to selecting a single, good nonproprietary name for each promising new drug. The most up-to-date copy of these principles, and specific nomenclature schemes for gene therapies, monoclonal antibodies, and cell therapies, are maintained at the USAN Program web site, www.ama-assn.org/go/usan.

The Purpose of USAN—A nonproprietary name of a drug serves numerous and varied purposes. Its principal functions are to identify the substance to which it applies and to serve as a designation that may be used without restriction by the public at large, both lay and professional. The importance of the latter function is enhanced by the restrictions necessarily imposed upon the nature and use of a trademark, particularly in the pharmaceutical field. Teaching in pharmacy and medicine requires a common designation, especially for a drug that is available from several sources or in a combination of two or more drugs. Nonproprietary names greatly facilitate communication between health professionals, and most journals demand their use. State formularies and hospital and managed care organization formularies generally use nonproprietary names as the titles of the articles recognized. A nonproprietary name is essential to the pharmaceutical manufacturer as a means of preserving trade mark rights to a brand name for the article concerned. Finally, federal law obliges the manufacturer to use the "established" nonproprietary name in advertising, labels, and brochures.

It is this wide variety of functions that makes difficult the task of expressing very exactly the criteria for judging simplicity and usefulness in drug names, attributes generally conceded to be desirable.

The Philosophy of the USAN Program—An examination of nonproprietary names for drugs currently in use is likely to result in an inaccurate evaluation of present nomenclature practices. Many of those names were coined prior to the adoption of current nomenclature procedures and principles. Indeed, many of those older names demonstrated the obvious need for an organized effort in the U.S. directed toward producing useful, simple and appropriate nonproprietary names for drugs. Existing names, then, reflect a mixture of old and new nomenclature practices and philosophy.

In many instances poor naming of drugs was due to the earlier practice of condensing the full chemical name into a chemically oriented nonproprietary name. At the time this practice came into being, the chemistry of most drugs was not too complex. With advancing chemical complexity of drug entities, however, nonproprietary names so derived became increasingly long and difficult to spell, pronounce, and remember.

In addition to the problems caused by the complexity of the word itself, chemically derived names have been criticized because they fail to provide useful information to anyone but a scientist involved in drug development. (Although the scientist's need is recognized, there exists more scientific and accurate chemical nomenclature to serve the purpose.)

Nonproprietary nomenclature is intended primarily for physicians, pharmacists, and those in related health professions concerned with the understanding of the drug's pharmacological and therapeutic properties. Therefore, it must be emphasized again that nonproprietary names should be coined in such a way as to be most useful to, and usable by, their primary users, i.e., those in the health professions.

USAN Procedure

A submission[2] for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America.

In the case of a substance that is regarded as an "Investigational New Drug" (IND) within the terms of the Federal Food, Drug, and Cosmetic Act of 1938, the process of selecting a USAN should be initiated preferably during the period of investigation when the substance is under clinical study so that the adoption of the USAN will be complete by the time the relevant New Drug Application is filed. The USAN Program requires submission of the IND number as part of the application.

A submission for a USAN is expected to conform to the established Guiding Principles (see Appendixes VII and VIII) and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. USAN and INN stems are building blocks of nonproprietary names. Nonproprietary names, by their very nature, are in the public domain. These USAN and INN stems will be utilized in creating USAN and INN for compounds manufactured by several pharmaceutical companies and are not available for ownership by an individual company or person. For these reasons, the USAN Council makes an effort to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks might act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs. Failure to recognize this is an impediment to the work of the USAN Council in establishing new USAN in a class of drugs and the freedom of both the USAN and INN programs in selecting further nonproprietary names in the same series of substances is seriously diminished. Where the initial screening of the application suggests that the name fails to conform, or that it appears to conflict with an existing name, the USAN Council Secretary may offer suggestions with a view to expediting the selection process.

A user's fee for each U.S. Adopted Name is to be submitted with the form, "Request for a United States Adopted Name (USAN)," copies of which are included in this Dictionary (see Appendix IX). An editable version of the USAN application form is available as a MS-Word document at the USAN Program web site, www.ama-assn.org/go/usan. Additional information about the application process is also available at that web site.

Each application should be accompanied by the appropriate form. This information, supplemented by the results of searches conducted by the Secretary, is referred to the Council members, whose views then are exchanged until a tentative decision can be submitted to the sponsor for comment. It should be emphasized that while the Council can ascertain the preferred chemical nomenclature for a structure claimed for any compound of definite composition, the Council is not in a position to confirm the structure or the claims for pharmacologic activity. The information given under the category Therapeutic Claim is based on the manufacturer's claims as submitted to FDA for investigational new drug approval or as approved by the firm for publication when the name is adopted. Adoption of a USAN does not imply endorse-ment of the claims or products by the USAN Council or its sponsoring organizations—the American Medical Association, the American Pharmacists Association, and the United States Pharmacopeia.

Suggested USAN are published on the USAN Program web site and are also sent to the World Health Organization (WHO) nomenclature secretariat. These publications and reviews serve as invita-

[2] Inquiries and submissions for USAN should be addressed to the Secretary, USAN Council, c/o American Medical Association, 515 North State Street, Chicago, Illinois 60610.

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tions for comments or protests. No disclosure of the name of the applicant or of the chemical nature of the substance appears in these statements.

Once the USAN Council and the applicant have agreed on a name, the tentatively adopted USAN is ordinarily submitted for consideration to the World Health Organization. If no objections are raised, adoption is considered final and newly approved USAN (updated monthly) are published electronically on the web site, www.ama-assn.org/go/usan. Soon thereafter the USAN is published in the USP bi-monthly publication *Pharmacopeial Forum*[3] as a Supplement to this Dictionary.

Despite the efforts to give notice of the proposed adoption of a USAN in the early stages and to exercise care in avoiding conflicts with established names, valid objections sometimes arise rather late. All such objections receive conscientious attention from the Council.

Occasionally, a USAN will be found unsuitable for adoption elsewhere, either internationally by the WHO or by one or more national bodies. Sometimes a closely similar name proves acceptable to one or more of these agencies, as in the case of the British Approved Name (BAN) "Cyclobarbitone" and its U.S. counterpart "Cyclobarbital." There is increasing emphasis, however, on the worldwide adoption of the same name for each therapeutic substance in view of the manifest advantages it offers to better communication and world trade.

Among the Guiding Principles for Coining U.S. Adopted Names for Drugs (see Appendix VII) is the principle that for most organic compounds, the designation for the pharmacologically active portion should appear first in the name; e.g., oxacillin sodium. This principle is applied generally in the entries herein.

Pronunciation

Responding to the continual introduction of new drug classes, the USAN Council develops common stems for which chemical and/or pharmacologic parameters are established (Appendix VII). In using such common stems for coining new nonproprietary names for drugs that belong to a series of related agents, the Council intends that they be pronounced consistently, thus bringing attention both orally and in writing to the presence of the stem and the prefixes or suffixes that distinguish one from another in the series.

Over the four decades of the USAN Program, inconsistencies in the Council's own suggested pronunciations became all too apparent. At its 10 June 2002 meeting, the Council adopted the Pronunciation Guide that follows (see page 17). The pronunciation of USANs adopted subsequently are to follow this Guide.

For over 3 years, culminating with 2,979 changes in the *2006 Dictionary*, the USP Expert Committees (Nomenclature and Labeling, 2000–2005, and Labeling, 2005–2010) reviewed the suggested pronunciations: first, to conform to the Pronunciation Guide in expressing the way the pronunciation is presented in the Dictionary; second, to standardize the pronunciations—"if it's spelled the same, it should be pronounced the same," applying particularly to the stems and to the first syllables; and third, to modify that standardization where a particular name had become pronounced differently in the popular culture.

Many of the changes involved adding a secondary accent, a feature which was rare in the original pronunciations. The stem syllable is generally the primary accent, and the secondary accent helps to differentiate the names within the class. In a few cases, suggested alternate pronunciations were provided. The Nomenclature Expert Committee continued to fine tune its review for the 2007 USP Dictionary. Revisions were made in 4,032 names.

For 2007, as a convenience to the reader, the pronunciation of each word within a bold-faced name is provided in every entry. This is in contrast to the usual dictionary style of providing the pronunciation of a word only on its first appearance. In addition, the pronunciations of those "Other Words"—secondary words—that are part of a name but do not appear alphabetically in the main entries, are provided in a list following the Pronunciation Guide. To save space, pronunciations have been deleted from names that were never USAN and are no longer USP or NF (exception: co-names created by USP for selected combination products, but never made official).

FDA Established Names

Under the terms of the Drug Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act, which became law October 10, 1962, the Secretary of Health and Human Services is authorized to designate an official name for any drug wherever deemed "necessary or desirable in the interest of usefulness and simplicity."[4]

The Commissioner of Food and Drugs and the Secretary of Health and Human Services published in the *Federal Register* regulations effective November 26, 1984, and elucidated February 16, 1988, which state, in part:

Sec.299.4 Established names of drugs.

(d) "...the Food and Drug Administration agrees with 'Guiding Principles for Coining U.S. Adopted Names for Drugs,' published in *USAN and the USP Dictionary of Drug Names....*"

(e) "The Food and Drug Administration will not routinely designate official names under subsection 508 of the act. As a result, the established name under subsection 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common and usual name of the drug. Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names....*"[5]

This Dictionary incorporates the text previously published under the title, *USAN and the USP Dictionary of Drug Names*. It is to make absolutely clear which names are compendial (*USP* or *NF*) or common or usual (USAN) that this Dictionary sets off the entries on these by showing them in **boldface** type.

International Nonproprietary Names

Under its charter, the World Health Organization (WHO) is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as proposals (PINN; i.e., "Proposed International Nonproprietary Names"). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confus-

[3] Published by the United States Pharmacopeia, 12601 Twinbrook Parkway, Rockville, Maryland 20852.

[4] F.D. & C. Act, Sec. 508 [358].

[5] 49 Fed. Reg. 37575 (1984) as amended by 53 Fed. Reg. 5369 (1988), amending 21 CFR 299.4.

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ingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the PINN as a RINN ("Recommended International Nonproprietary Name"), which almost all Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

International nonproprietary names selected during 1953–2006 are included herein. Some are identical to, and identified with, USAN, *USP*, or *NF* entries; others are independent entries designated as INN. Where an INN is given in this volume as an independent entry, the chemical name and any graphic formula shown are generally those provided by the WHO.

International Cooperation

The USAN Council functions primarily to serve the health professions in the U.S. However, in an age when drug manufacturers market their products in many countries, when international travel is increasing steadily, and medical and pharmaceutical literature is translated and read widely around the world, the need for cooperation regarding nomenclature activities among the major drug-producing countries clearly is evident.

In addition to the USAN Council, active nomenclature agencies exist for example in Great Britain, Japan, France, Spain, and Russia. These agencies operate at varying levels of authority and cooperate with pharmaceutical manufacturers within areas of jurisdiction in the selection of appropriate nonproprietary names.

The agencies maintain liaison with one another in an effort to secure the wide adoption of the most appropriate and universally acceptable designation for each drug. The natural concern of each of the groups is with the drugs that are being synthesized, isolated, investigated, produced, or marketed in its own national area.

To prevent the confusion that arises when several nonproprietary names are used for a single drug, either in the same country or in several different countries, the WHO has assumed the responsibility of coordinating existing nomenclature at the international level.

Through its Expert Group on International Nonproprietary Names, whose members are drawn primarily from representatives of the national nomenclature agencies, the WHO has developed a procedure and formulated guiding principles for the selection of International Nonproprietary Names (INN). Where national nomenclature agencies exist, they usually act as agents for manufacturers by referring mutually selected designations (usually prior to national adoption) to the WHO with the request that these be considered for selection as INNs.

A manufacturer located in a country without a nomenclature agency can make a direct request for a nonproprietary name to the WHO or, in some instances, to an existing agency in another country, preferably one in which the pharmaceutical preparation is likely to be marketed.

After the selection of INNs, the WHO proposes and, unless an objection is raised, recommends to all its member states that such names be adopted at the local level. Formal adoption in accordance with national practice is necessary to provide a review of the suitability of the INN for national use.

Pharmacy Equivalent Names

A Pharmacy Equivalent (PEN) name is a short and simple name that is offered by USP as a standardized and useful term that may be used for convenience by practitioners where it may be impractical to use the complete official monograph title of a compendial article.

The PEN name for a dosage form containing two or more therapeutic drug substances may be devised by combining portions of the official names of the component drug substances. A "Co-" prefix, not used elsewhere in compendial terminology, indicates that the article is a combination dosage form. For example, the PEN name Co-triamterzide is a representation of the *Co*mbination of *triamter*ene and hydrochlorothia*zide*.

PEN names are intended to be informative and to discourage the proliferation of trivial names and undefined abbreviations. Because a PEN name is not an official *USP* or *NF* title, it is not necessary that it appear on the label or in the labeling of a drug product.

FDA Orphan Drugs

Under the terms of the Orphan Drug Act[6] of 1983, the development and marketing of drug products expected to be of limited commercial appeal but potentially useful in relatively rare disease conditions are encouraged. When the FDA makes an orphan product designation, if the product has not already been approved for marketing for some other use, the name designated may not be the established or proper name approved by the FDA for the product if eventually approved or licensed for marketing.

The ultimate selection of a U.S. Adopted Name for an orphan drug may be based on special considerations that pertain to this rather select group of drugs. Therefore, where a USAN for an orphan drug appears to follow a more chemically oriented terminology than is customary for drug nomenclature generally, such instance is not to be regarded as a basis or a precedent for a future selection of a U.S. Adopted Name.

Chemical Nomenclature

A nonproprietary name (often referred to as a *generic* name) and a proprietary name (often referred to as a *brand name* or a *trademark*) serve different useful purposes, but neither is designed to provide precise information concerning the chemical structure of the drug substance. To describe the chemical structure, a third type of name, i.e., a *chemical name*, is needed.

Chemical names tend to be complex and cumbersome; thus, although they may provide, for scientific and technical personnel, a complete, precise, and unambiguous description of the substance, they fail to constitute a concise, convenient designation that meets the day-to-day needs of the pharmacist, the physician, the patient, the jurist, and others functioning in related activities that involve pharmaceuticals. These latter needs are more appropriately served by nonproprietary names, of which USAN are primary examples.

For USAN entries pertaining to drugs that are strictly definable chemical substances (and the vast majority of single-entity drugs are of this type), two *chemical names* are usually included in each entry to provide such definition. Of the many chemical names that could be used, the ones selected for this compilation are those that have been used as the American Chemical Society's *Chemical Abstracts* (CA) index names; thus, fundamentally and advantageously, they all stem from the same basic system of chemical nomenclature, and they function, through CA, as keys to the world's chemical literature.

The first of these two names usually is the inverted form of the systematic chemical name developed by Chemical Abstracts Service (CAS), in general accordance with the recommendations of the International Union of Pure and Applied Chemistry (IUPAC) and the International Union of Biochemistry and Molecular Biology (IUBMB), and employed in the current issues of CA. The second name, generated in accordance with the recommendations of these scientific unions, is included in view of the general recognition that it is neither practical nor desirable to rely solely on the CA index names for all purposes of identification and reference. The

[6] Pub.L. 97-414.

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inverted form of the first name is provided because it guides the user *directly* to the CA literature—since that is the style in which chemical substances are indexed in that literature. Conversion to the uninverted form of the name is readily accomplished. Thus:

Hydrazinecarboximidamide, 2-[-(2,6-dichlorophenoxy)ethyl]-, sulfate, (2:1)

becomes

2-[2-(2,6-Dichlorophenoxy)ethyl]hydrazinecarboximidamide sulfate (2:1).

Benzeneacetic acid, α-(hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester, 8-oxide, hydrochloride, *endo*-(±)-

becomes

(±)-*endo*-α-(Hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl benzeneacetate 8-oxide hydrochloride.

This second name is given in uninverted form and is of a systematic type formerly used in CA; it is identical with, or closely resembles, the chemical name sanctioned and employed by the IUPAC and by the WHO.

These two types of chemical names differ primarily in that while the IUPAC names make generous use of nonsystematic and semisystematic (often referred to as *trivial*) names and qualifying terms, all of which impede electro-mechanical manipulation, the CAS names are more systematic for most substances. It is primarily by virtue of this stricter adherence to systematic nomenclature that the CAS chemical names are more readily amenable to the ever-increasing demand for electronic processing by various means, thus greatly facilitating literature searches and the processing of other queries based on chemical composition described in terms of nomenclature.

A third chemical name is occasionally supplied in an entry herein, especially in instances where that name is of a type that has become firmly established through long-continued use, e.g., see bolasterone; calcium glubionate; panthenol; and taleranol. Also, a CAS chemical synonym is occasionally supplied as an additional name in the relatively rare instances where the CA index name for a chemical substance is not a chemical name, e.g., see cosyntropin; pepstatin.

[NOTE—The foregoing does not apply to chemical names shown for entries other than USAN and current compendial names established before the USAN Program began. In those other entries, any chemical name shown, whether conforming to CAS nomenclature or otherwise, is given only for descriptive purposes to help identify the substance. The chemical name shown in an independent INN entry is usually that provided by the WHO.]

Identification of Names by Number

To meet the need for rapid handling of data on drugs for many purposes, compounds and preparations are being identified by number. This trend in no way minimizes the importance of adopting the best possible nonproprietary names for drugs; indeed, its success is related to the soundness of the names program, to the end that taken together the nonproprietary name and the number(s) assigned to it provide increasingly effective control of data and information on drugs.

In the system developed and being used by the CAS, registry numbers are assigned to compounds at random, and although unique, the numbers convey no compositional or other kinds of information. The FDA maintains the National Drug Code Directory, in which a three-part number is assigned to identify the manufacturer or distributor or repackager, the drug product, and the package. Other numerical classifications exist for literature searching.

In this book USAN entries and other entries, such as from current or former revisions of the *USP* and the *NF*, carry CAS registry numbers. A given entry usually carries only one such number, but because of (a) variations in the way in which information is reported in the literature, and therefore stored in automated files, and (b) the variety of searches expected to be conducted on such files, sometimes two, or occasionally more, CAS numbers are pertinent to a single entry. For example, information on the pharmacology of ampicillin may be stored in a file under either ampicillin anhydrous or ampicillin trihydrate, depending on how it was reported in the literature, and each of these substances carries its own CAS registry number. Similarly, information on the synthesis of doxorubicin hydrochloride may be stored under that entry or under the parent substance, doxorubicin.

With entries carrying multiple CAS registry numbers, the one carrying no annotation enclosed within brackets (usually the first one) is the registry number assigned to that entry. Each additional number is followed by a bracketed term which, as is apparent from the following examples, discloses its relationship to the assigned number. Prominent categories of entries carrying more than one CAS registry number are exemplified in the following:

Hydrated substances carry one registry number for the hydrate and another one for the anhydrous substance. Examples:

Theophylline 5967-84-0; 58-55-9 [anhydrous]
Ampicillin 69-53-4; 7177-48-2 [trihydrate]

Addition salts of organic bases carry one registry number for the salt and another one for the organic base. Examples:

Promethazine Hydrochloride 58-33-3; 60-87-7 [promethazine]
Acetophenazine Maleate 5714-00-1; 2751-68-0 [acetophenazine]

Quaternary salts carry one registry number for the salt and another one for the quaternary radical, if that radical has had a number assigned to it by CAS. Examples:

Bretylium Tosylate 61-75-6; 59-41-6 [bretylium]
Choline Chloride 67-48-1; 62-49-7 [choline]

Metal salts of uncommon organic acids and all salt-like substances carry one registry number for the salt and another one for the acid or acidic substance. Examples:

Edetate Sodium 64-02-8; 60-00-4 [edetic acid]
Hexobarbital Sodium 50-09-9; 56-29-1 [hexobarbital]

Entries for which CAS has replaced a registry number with another one carry both numbers, as recommended by CAS since the replaced number was in use prior to its replacement. Examples:

Aspartocin 4117-65-1; 1402-89-7 [replaced]
Phendimetrazine Tartrate 50-58-8; 21102-82-9 [replaced]; 634-03-7 [phendimetrazine]

In general, when using CAS registry numbers as search terms, all numbers *deemed pertinent* to the search at hand should be used. To omit one or more of such numbers is to risk failing to retrieve all of the stored information pertinent to the search. This does not mean that all of the registry numbers associated with a substance in this book must always be used in searches involving that substance. According to the nature of the query that has prompted the search, one can decide whether one or more of the registry numbers are not pertinent and can therefore be omitted.

Appendix V provides a tabulation of entries in the order of increasing CAS registry number.This is followed by a similar tabulation in the order of increasing NSC (National Service Center of the National Cancer Institute, National Institutes of Health) number; the corresponding NSC numbers are also in the respective individual entries.

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Graphic Formulas

Consonant with the employment of Chemical Abstracts nomenclature, and also in the interest of uniformity of style, the orientation of ring systems and the depiction of stereoisomeric features in graphic formulas are generally consistent with CAS practices. Either alternating double bonds or a circle within a hexagon is used in graphic formulas to represent the bonding in benzene rings and all others that contain six atoms of any kind that are connected in conjugate (Kekulé) style in one or more of the individual resonant structures that contribute to the hybrid structure actually present in the molecule.

Many structures depicted in the Dictionary were drawn by hand. All the USP and NF graphic formulas contained herein were drawn electronically to achieve a consistent style and uniform format. The existing hand-drawn structures were converted to bit-mapped images in the Tagged Image File Format (TIFF) that were then converted with commercial structure-recognition software to display the structure.

Molecular Weights

The standard atomic weights of the elements that are used in the tabulation of molecular weights are those recommended in 2001 by the IUPAC Commission on Atomic Weights and Isotopic Abundances. The exact atomic weights are used in the computations. The molecular weights derived from these atomic weights are systematically rounded off to two decimal places using the method adopted by the Executive Committee of the USP Division of General Policies, Requirements, Nomenclature. That is, retain only the number to include the digits in the first three decimal places of the sum of the atomic weights: discard the last digit if it is smaller than 5 to obtain the molecular weight or discard the last digit if it is 5 or larger and increase the digit in the second decimal place by one to obtain the molecular weight.

Radioactive Pharmaceuticals

Since the radioactive pharmaceuticals are specially packaged in distinctive containers, labeled with the internationally recognized symbols for radioactivity, and available only to specially trained personnel, the USAN Council has agreed on the general principle that for these drugs the nonproprietary name should include the name of the basic compound serving as the carrier for the radioactivity, the symbol for the radioactive isotope, and the atomic weight (inasmuch as several radioactive isotopes of a given element may be in use).

Brand Names

The *2007 USP Dictionary* shows the beginnings of a change in philosophy on the inclusion of brand names. Emphasizing that this is a dictionary of drug substance names, not a list of drug products, references to combination drug products and their brand names have been dropped. References to drug products marketed only under their nonproprietary names have been dropped. Brand names no longer used in the USA, as determined primarily by reference to FDA s Orange Book, and occasionally to the National Drug Code Directory and various other sources, have been dropped.

Brand names still being used are sometimes difficult to attribute ownership thereof. The sale of a drug name from one company to another, the many company mergers on the one hand and spinoffs on the other and the consequent name changes of companies, plus the trend for two companies to co-market the same drug under one brand name are challenging to keep up with. In general, only one player in a co-marketing arrangement is listed.

Current labelers (marketers) of a drug may have had nothing to do with its original research. However, that connection is not necessarily lost, as the researcher's code for the drug, where available, is included in the main entry and cross-referenced to Appendix IV.

The formulator and labeler of a drug product are not necessarily the same firm. Moreover, sometimes a single formulator produces a drug product for several labelers and sometimes a single labeler purchases a drug product from more than one formulator. There is no general effort to make in this book a distinction between the formulator and the labeler of a product.

It should be noted that the pharmacologic and/or therapeutic category stated in an entry may not necessarily apply to every brand name listed in that entry; e.g., the category may pertain to one or more dosage forms whereas a particular brand name may represent such dosage form(s) or perhaps some other dosage form not contemplated by the stated category.

Code Designations

Alphanumeric combinations frequently are used during the investigational phase required to demonstrate the utility of new, potentially therapeutic substances. The alphabetic portion of a code designation usually is identifiable with the institution or firm that assigns the code designation to the agent under test. For example, among the code designations commonly encountered are some that include the initials "NSC." Code designations find their way into the scientific literature because it is customary to use them in identifying the compounds in early publications prior to adoption of a USAN.

Summary of Types of Information Provided

The individual entries in this volume comprise, in general, the following: (1) USAN (in **boldface** type), with year of its adoption in brackets; (2) official names (usually of the drug substances as distinct from the dosage forms) from the current revisions of the *United States Pharmacopeia* and the *National Formulary* (in **boldface** type), with some exceptions, e.g., combinations; (3) names that were official in previous revisions of the *USP* and the *NF*; (4) international and other nonproprietary names; (5) miscellaneous older names that had been in general use at various times in the past; (6) brand names; and (7) code designations.

The statement of a category or categories of pharmacologic and/or therapeutic activity is italicized in USAN entries and in entries for current *USP* and *NF* names. In the case of many new entries, the sponsors of the USAN may not have complete information insofar as all of the categories of activity are concerned. Comments aimed toward the attainment of greater uniformity and usefulness in the pharmacologic classification system used herein will be welcomed, particularly if they are supported by authoritative information.

Literature references (e.g., "MI" for Merck Index) are given in some entries solely as sources of possible further information about the compound and do not imply any connection with the program for selection of nonproprietary names.

The names of the manufacturers currently or formerly concerned with the respective compounds are mentioned. Mergers and name changes of manufacturers and sales of brand names from one manufacturer to another are common. Where known, the name of the current owner of the brand name is given, but no special attempt is made to be up to date in all entries. Information that a manufacturer is no longer concerned with a compound will be gratefully received.

Further analysis of the content of this edition is given on page 7 under *How to Use This Book*.

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Each of these individuals contributed significantly to this book. They all generously provided their expert knowledge, expeditious cooperation, and patience. Their contributions are sincerely appreciated.

Much of the work on the USAN Program is hidden from view. The results, however, are shared by many, all of whom thus benefit from the labors of the few who give freely of time and effort and of others whose cooperation makes success possible. The continued willing cooperation from all segments of the pharmaceutical industry, which contributes immeasurably to the success of the USAN Program as well as provides helpful information on the various entries throughout this book, is gratefully recorded.

W. Larry Paul, Ph.D., *USP Liaison,*
USP Nomenclature Expert Committee

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PRONUNCIATION GUIDE FOR DRUG NAMES

Adopted by the USAN Council, 10 June 2002
(Revised 14 July 2006)

This pronunciation guide has been developed and approved by the USAN Council, and was revised at the USAN Countil meeting, July 14, 2006, to facilitate pronunciation of USAN and will be used on all future Statements of Adoption.

SYLLABLES: Syllable designations are based upon phonetic considerations. They are meant to show pronunciation without ambiguity, even though word breaks may not follow those that are normally considered correct American English language word breaks.

A prime mark (′) follows the primary accent syllable; a double prime mark (″) follows any secondary accent syllable. All syllables are separated by a blank space. No diacritical marks are used.

SOUNDS AND SPELLING: Vowels, long—spelling designations in all syllables **except the last syllable**, unless indicated otherwise:

a	ay	(may)
e	ee	(lee) (same in last syllable also)
i	eye	(when by itself as a syllable)
	ye	(when in conjunction with a consonant: lye)
o	oh	(when by itself as a syllable)
	oe	(when in conjunction with a consonant: toe)
u	ue	(cue; cure) (same in last syllable also)
y	ee	(oxytocin, ox ee toe′ sin)
	i	(thrombolytic, throm boe lit′ ik)
	eye	(kanamycin, kan a mye′ sin)

Spelling designation **in the last syllable**: The vowels a, i and o assume long vowel sounds by the addition of an e at the end of the syllable.

rate
bite
toe

Short vowel sounds receive no special designations in any syllable.

Digraphs:

ah	father	oo	food
aw	paw	ou	ought
ch	child	ow	out
ng	sing	oy	oil
oi	oil	wh	when

Consonant sounds and examples:

b	bed	q	queen **(kween)**
c	citrate **(si′ trate)**	r	rot
	carbon **(kar′ bon)**	s	sing
d	door		osmotic **(oz mot′ ik)**
f	floor		aspirin **(as′ pir in)**
g	gore		vision **(vi′ zhun)**
	digital **(di′ ji tal)**	t	taught
h	hat	v	vote
j	jar	w	wing
k	king	x	ox
l	low		xanthines **(zan′ theens)**
m	my	y	yes
n	no	z	zinc **(zink)**
p	pot		

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Samsung Bioepis Exhibit No. 1002
Page 12405

PRONUNCIATION OF OTHER WORDS (SECONDARY WORDS)

Acedoben	a″ se doe′ ben
Acefurate	a″ se fue′ rate
Acetate	as′ e tate
Acetonide	a seet′ oh nide
Acetophenide	a seet″ oh fen′ ide
Aceturate	a set′ ue rate
Acid	as′ id
Acistrate	a sis′ trate
Activated	ak″ ti vay′ ted
Aggregated	ag″ re gay′ ted
Alfa	al′ fa
Alfacon	al′ fa kon
Alginate	al′ ji nate
Altumomab	al toom′ oh mab
Aluminate	a loo′ mi nate
Aluminometasilicate	a loo″ mi noe met″ a sil′ i kate
Aluminosilicate	a loo″ mi noe sil′ i kate
Amide	a′ mide
Aminoacetate	a mee″ noe as′ e tate
Aminolevulinate	a mee″ noe lev″ ue lin′ ate
Ammoniated	a moe″ nee ay′ ted
Amylosulfate	am″ i loe sul′ fate
Anhydrous	an hye′ drus
Anisatil	a ni′ sa til
Antitoxin	an″ ti tox′ in
Apcitide	ap′ si tide
Arbamel	ar′ ba mel
Arsenate	ar′ se nate
Ascorbate	a skor′ bate
Aspart	as′ part
Aspartate	a spar′ tate
Axetil	ax′ e til
Balsam	bawl′ sam
Behenate	be hen′ ate
Beloxil	bel ox′ il
Benetonide	ben et′ oh nide
Benzathine	ben′ za theen
Benzoate	ben′ zoe ate
Bepiplasmid	bep″ i plas′ mid
Besylate	bes′ i late
Bicarbonate	bye kar′ bo nate
Bicisate	bye sis′ ate
Bisulfate	bye sul′ fate
Bisulfite	bye sul′ fite
Borate	bor′ ate
Bovine	boe′ vine
Bromide	broe′ mide
Butyrate	bue′ ti rate
Camphorated	kam″ for ay′ ted
Camsylate	kam′ si late
Caproate	kap′ roe ate
Caprylate	kap′ ri late
Carbonate	kar′ bo nate
Carnauba	kar noe′ ba
Chloride	klor′ ide
Chlorohydrate	klor″ oh hye′ drate
Chlorohydrex	klor″ oh hye′ drex
Chorionic	kor″ ee on′ ok
Chromate	kroe′ mate
Chromated	kroe′ may ted
Cinnamate	sin′ a mate
Citrate	sit′ rate
Cituxetan	sye tux′ e tan
Clathrate	klath′ rate
Closylate	kloe′ si late
Conjugated	kon″ joo gay′ ted
Copolymer	koe pol′ i mer
Crosfumaril	kros fue′ ma ril
Cyclotate	sye′ kloe tate
Cypionate	sip′ ee oh nate
Dalanated	dal′ a nay ted
Daloxate	dal ox′ ate
Decanoate	dek″ a noe′ ate
Dehydroacetate	dee hye″ droe as′ e tate
Delta	del′ ta
Detemir	de′ te mir
Diacetate	dye as′ e tate
Dibunate	dye′ bue nate
Dibutyrate	dye bue′ ti rate
Dichloroacetate	dye klor″ oh as′ e tate
Dichlorohydrate	dye klor″ oh hye′ drate
Dichlorohydrex	dye klor″ oh hye′ drex
Dicholine	dye koe′ leen
Dicloacetate	dye kloe as′ e tate
Diftitox	dif′ ti tox
Difumarate	dye fue′ ma rate
Dihydrochloride	dye hye″ droe klor′ ide
Dimaleate	dye mal′ ee ate
Dimeglumine	dye meg′ loo meen
Dimesylate	dye mes′ i late
Dinitrate	dye nye′ trate
Diolamine	dye ole′ a meen
Dioxide	dye ox′ ide
Dipivoxol	dye piv ox′ ol
Dipotassium	dye″ poe tas′ ee um
Dipropionate	dye proe′ pee oh nate
Disalicylate	dye sa lis′ i late
Disodium	dye soe′ dee um
Disoproxil	dye″ soe prox′ il
Distearate	dye steer′ ate
Ditosylate	dye toe′ si late
Ditriflutate	dye trye floo′ tate
Edamine	ed′ a meen
Edisylate	e dis′ i late
Elixir	ee lix′ ir
Enanthate	e nan′ thate
Erbumine	er′ bue meen
Esterified	es ter′ i fide
Estolate	es′ toe late
Etabonate	et″ a boe′ nate
Ethasulfate	eth″ a sul′ fate
Ethylsuccinate	eth″ il sux′ i nate
Ethylsulfate	eth″ il sul′ fate
Excipient	ex sip′ ee ent
Fanolesomab	fan″ oh les′ oh mab
Ferpentetate	fer pen′ te tate
Fluoride	floor′ ide
Fosfatex	fos′ fa tex

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Fumarate	fue′ ma rate
Furifosmin	fure″ i fos′ min
Gadolinium	gad″ oh lin′ ee um
Galactarate	gal ak′ tar ate
Gallate	gal′ ate
Glargine	glar′ jeen
Glubionate	gloo bye′ oh nate
Glucaldrate	gloo kal′ drate
Gluconate	gloo′ koe nate
Glucuronate	gloo kure′ oh nate
Glucuronide	gloo″ kure on′ ide
Glulisine	gloo′ lis een
Glutamate	gloo′ ta mate
Glutamer	gloo′ ta mer
Glycinate	glye′ sin ate
Glycolate	glye′ koe late
Guaiacolsulfonate	gwye″ a kol sul′ foe nate
Hemicellulose	hem″ ee sel′ ue lose
Hemifumarate	hem″ ee fue′ ma rate
Hemisuccinate	hem″ ee sux′ i nate
Hexacetonide	hex″ a seet′ oh nide
Hexasodium	hex″ a soe′ dee um
Hippurate	hip′ ue rate
Hormone	hor′ mone
Hyclate	hye′ klate
Hydrabamine	hye″ dra bam′ een
Hydrate	hye′ drate
Hydrobromide	hye″ droe broe′ mide
Hydrochloride	hye″ droe klor′ ide
Hydrogenated	hye droj′ en ay″ ted
Hydrolysate	hye drol′ i sate
Hydrophilic	hye droe fil′ ik
Hydroxide	hye drox′ ide
Hydroxytoluene	hye drox″ ee tol′ ue een
Hypochlorite	hye″ poe klor′ ite
Iodide	eye′ oh dide
Iodinated	eye″ oh di nay′ ted
Isobutyl Ketone	eye soe bue′ til kee′ tone
Isophane	eye′ soe fane
Ketolaurate	kee″ toe lawr′ ate
Ketone	kee′ tone
Labetuzumab	la″ be tooz′ oo mab
Lactate	lak′ tate
Lactobionate	lak″ toe bye′ oh nate
Levulinate	lev″ ue lin′ ate
Lexidronam	lex id′ roe nam
Lispro	lis′ pro
Magsulfex	mag sul′ fex
Maleate	mal′ ee ate
Mandelate	man′ de late
Medocaril	me dok′ a ril
Medoxil	me dox′ il
Medoxomil	me dox′ oh mil
Merpentan	mer pen′ tan
Mertansine	mer tan′ seen
Mertiatide	mer tye′ a tide
Mesylate	mes′ i late
Mesylates	mes′ i lates
Metabisulfite	met″ a bye sul′ fite
Metaphosphate	met″ a fos′ fate
Methacrylate	meth ak′ ri late
Methylbromide	meth″ il broe′ mide
Microcrystalline	mye″ kroe kris′ ta lin
Mofetil	moe′ fe til
Molybdate	moe lib′ date
Monoacetate	mon″ oh as′ e tate
Monofluorophosphate	mon″ oh flur″ oh fos′ fate
Monoglycerides	mon″ oh glis′ er idze
Monohydrate	mon oh″ hye′ drate
Monolaurate	mon″ oh lawr′ ate
Monolinoleate	mon″ oh lin oh′ lee ate
Mononitrate	mon″ oh nye′ trate
Monooleate	mon″ oh oh′ lee ate
Monopalmitate	mon″ oh pal′ mi tate
Monopotassium	mon″ oh poe tas′ ee um
Monostearate	mon″ oh steer′ ate
Mucate	mue′ kate
Mustard	mus′ tard
Myristate	mir′ is tate
Nafate	naf′ ate
Napsylate	nap′ si late
Niacinate	nye′ a sin ate
Nitrate	nye′ trate
Nitridocade	nye trid′ oh kade
Nitrite	nye′ trite
Nitroprusside	nye″ troe prus′ ide
Nofetumomab	noe″ fe toom′ oh mab
Octachlorohydrate	ok″ ta klor″ oh hye′ drate
Octachlorohydrex Gly	ok″ ta klor″ oh hye′ drex glye
Olamine	ole′ a meen
Oleoresin	oh″ lee oh rez′ in
Ovine	oh′ vine
Oxalate	ox′ a late
Oxide	ox′ ide
Oxidized	ox′ i dized
Oxidronate	ox″ i droe′ nate
Oxybate	ox′ i bate
Ozogamicin	oh″ zoe ga mye′ sin
Palmitate	pal′ mi tate
Pamoate	pam′ oh ate
Pantothenate	pan toe′ then ate
Pegol	peg′ ol
Pendetide	pen′ de tide
Pentachlorohydrate	pen″ ta klor″ oh hye′ drate
Pentachlorohydrex Gly	pen″ ta klor″ oh hye′ drex glye
Pentahydrochloride	pen″ ta hye″ droe klor′ ide
Pentetreotide	pen″ te tree′ oh tide
Perborate Monohydrate	per bore′ ate mon oh″ hye′ drate
Perchlorate	per klor′ ate
Permanganate	per man′ ga nate
Peroxide	per ox′ ide
Persodium	per soe′ di um
Pertechnetate	per tek′ ne tate
Phenpropionate	fen proe′ pee oh nate
Phenylacetate	fen″ il as′ e tate
Phenylbutyrate	fen″ il bue′ ti rate
Phosphanilate	fos fan′ i late
Phosphate	fos′ fate
Phthalate	thal′ ate
Piconol	pik′ a nol
Picrate	pik′ rate
Pivalate	piv′ a late
Pivoxetil	piv ox′ e til
Polacrilex	pol″ a kril′ ex
Poliglumex	pol″ ee gloo′ mex
Polistirex	pol″ ee stye′ rex
Polylysine	pol″ ee lye′ seen
Polyoxylglycerides	pol″ ee ox″ il glis′ er ides
Polyphosphate	pol″ ee fos′ fate
Polystyrene	pol″ ee stye′ reen
Polysulfate	pol″ ee sul′ fate
Polyvalent	pol″ ee vay′ lent
Porcine	por′ sine
Precipitated	pree sip′ a tay″ ted

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Pregelatinized	pree jel at′ i nized
Probenate	proe′ be nate
Probutate	proe bue′ tate
Propionate	proe′ pee oh nate
Protamine	proe′ ta meen
Proxetil	prox′ e til
Pyro- and trimeta- Phosphates	pye″ roe and trye met″ a fos′ fates
Pyrophosphate	pye″ roe fos′ fate
Raffimer	raf′ fi mer
Resin	rez′ in
Rinfabate	rin′ fa bate
Saccharate	sak′ a rate
Satumomab	sa toom′ oh mab
Sebacate	seb′ a kate
Sesquichlorohydrate	ses″ kwi klor″ oh hye′ drate
Sesquichlorohydrex	ses″ kwi klor″ oh hye′ drex
Sesquioleate	ses″ kwi oh′ lee ate
Sestamibi	ses″ ta mib′ ee
Siboroxime	sye″ boe rox′ eem
Silicate	sil′ i kate
Sorbate	sor′ bate
Sorbitex	sor′ bi tex
Stearate	steer′ ate
Stearyl	steer′ il
Subacetate	sub as′ e tate
Subcarbonate	sub kar′ bo nate
Subgallate	sub gal′ ate
Subnitrate	syb nye′ trate
Subsalicylate	sub sa lis′ i late
Subsulfate	sub sul′ fate
Succinate	sux′ i nate
Sudotox	soo′ doe tox
Suleptanate	sul ep′ ta nate
Sulfate	sul′ fate
Sulfide	sul′ fide
Sulfite	sul′ fite
Sulfonate	sul′ foe nate
Sulfosalicylate	sul″ foe sa lis′ i late
Sulfoxide	sul fox′ ide
Sulfoxylate	sul fox′ il ate
Sulfurated	sul″ fur ay′ ted
Tacatuzumab	tak″ a tooz′ oo mab
Tannate	tan′ ate
Tannex	tan′ ex
Tartrate	tar′ trate
Teboroxime	te″ boe rox′ eem
Tebutate	teb′ ue tate
Terephthalate	ter″ e thal′ ate
Tetrachlorohydrate	tet″ ra klor″ oh hye′ drate
Tetrachlorohydrex Gly	tet″ ra klor″ oh hye′ drex glye
Tetranitrate	tet″ ra nye′ trate
Tetrasodium	tet″ ra soe′ dee um
Thiosulfate	thye″ oh sul′ fate
Tidoxil	tye dox′ il
Tiuxetan	tye ux′ e tan
Tosylate	toe′ si late
Trichlorohydrate	trye″ klor oh hye′ drate
Trichlorohydrex Gly	trye″ klor oh hye′ drex glye
Triethiodide	trye′ eth eye′ oh dide
Triflutate	trye′ floo tate
Trihydrochloride	trye hye″ droe klor′ ide
Trimetaphosphate	trye met″ a fos′ fate
Trioleate	trye oh′ lee ate
Trioxide	trye ox′ ide
Trisilicate	trye sil′ i kate
Trisodium	trye soe′ di um
Tristearate	trye steer′ ate
Trisulfide	trye sul′ fide
Undecanoate	un dek″ a noe′ ate
Undecylate	un de′ sil ate
Undecylenate	un de′ sil en ate
Valerate	val′ er ate
Vanillin	va nil′ in
Xinafoate	zye naf′ oh ate
Zirconium	zir koe′ nee um

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ABBREVIATIONS

AMA-DE	*AMA Drug Evaluations,* former publication of the American Medical Association	ND	*New Drugs,* former publication of the American Medical Association
BAN	British Approved Name	NF	National Formulary
BVC	British Veterinary Codex	NND	*New and Nonofficial Drugs,* former publication of the American Medical Association
CA	*Chemical Abstracts,* published by the American Chemical Society	NNR	*New and Nonofficial Remedies*, former publication of the American Medical Association
CAS	Chemical Abstracts Service		
CID	*CTFA Cosmetic Ingredient Dictionary,* published by The Cosmetic, Toiletry and Fragrance Association, Inc.	NSC	National Service Center, National Cancer Institute, National Institutes of Health
DCF	Dénomination Commune Française (French approved nonproprietary name)	PEN	Pharmacy Equivalent Name
		PHS	Public Health Service [United States]
INN	International Nonproprietary Name	USAN	United States Adopted Names
		USP	United States Pharmacopeia
JAN	Japanese Accepted Name	USP DI	Vol. I—*Drug Information for the HealthCare Professional*
MI	*Merck Index,* published by Merck & Company, Inc.		

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Samsung Bioepis Exhibit No. 1002
Page 12409

New Nonproprietary Names Appearing in this 2007 Edition

During the past year, the *2006 USP Dictionary* has been extensively updated, with over 50% of its entries being revised in some way. Thousands of these changes have been a result of the USP's continuing effort to improve the pronunciations and graphic formulas presented in the dictionary. The brand name and manufacturers' information in the dictionary has been updated using current information sources, and historical information that is no longer relevant has been deleted.

The following is a list of new nonproprietary names appearing in the *2007 USP Dictionary*. Names shown in **boldface type** are USAN and/or *USP* or *NF* monograph titles.

Abagovomab
Aclidinium Bromide
Acofilcon A
Acofilcon B
Afimoxifene
Aflibercept
Alcaftadine
Aleglitazar
Alferminogene Tadenovec
Aliskiren Fumarate
Alogliptin Benzoate
Alvespimycin Hydrochloride
Amibegron
Amolimogene Bepiplasmid
Apilimod Mesylate
Aplaviroc Hydrochloride
Apricitabine
Atacicept
Azilsartan
Aztreonam Lysine
Balamapimod
Batabulin
Bavituximab
Bedoradrine Sulfate
Belagenpumatucel-L
Beperminogene Perplasmid
Beroctocog Alfa
Bevirimat Dimeglumine
Bifeprunox Mesylate
Bisdisulizole Disodium
Bremelanotide
Bucelipase Alfa
Camobucol
Capadenoson
Capeserod
Carbomer Homopolymer
Carbosilfocon A
Carisbamate
Casopitant Mesylate
Catramilast
Cediranib
Celivarone
Cevipabulin Fumarate
Cevoglitazar
Contusugene ladenovec
Denagliptin Tosylate
Denibulin Hydrochloride
Dexamethasone Cipecilate
Dexelvucitabine
Dilopetine
Disomotide
Dutacatib
Efungumab
Elacytarabine
Elocalcitol
Elsibucol
Enflufocon A
Enflufocon B
Epoetin Theta
Fentanyl
Ferroquine
Fimasartan
Firategrast
Flusilfocon A
Flusilfocon B
Flusilfocon C
Flusilfocon D
Flusilfocon E
Fluticasone Furoate
Forodesine
Fosalvudine Tidoxil
Fosaprepitant Dimeglumine
Gabapentin Enacarbil
Gamithromycin
Genfilcon A
Giripladib
Hemoglobin Glutamer-256 (Human)
Hexafocon A
Hioxifilcon D
Honey, Purified
Hyaluronidase (Human Recombinant)
Hybufocon A
Ibuprofen Lysine
Ilepatril
Imisopasem Manganese
Inakalant
Indantadol
Iodofiltic Acid I 123
Isomalt
Lapaquistat Acetate
Lapuleucel-T
Larotaxel
Lauroyl Polyoxylglycerides
Levonadifloxacin
Lexatumumab
Lificiguat
Linaclotide Acetate
Lobeglitazone
Lodenafil Carbonate
Lorcaserin Hydrochloride
Lotifocon B
Lotifocon C

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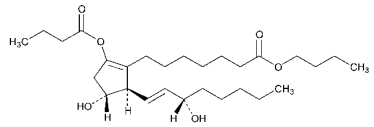
Samsung Bioepis Exhibit No. 1002
Page 12410

Lotrafilcon A
Lotrafilcon B
Masilukast
Methylnaltrexone Bromide
Mifamurtide
Mirodenafil
Motavizumab
Naproxcinod
Nebivolol Hydrochloride
Neotame
Nilotinib
Nimotuzumab
Obatoclax
Oglemilast
Olanzapine Pamoate
Olaparib
Omafilcon A
Omtriptolide Sodium
Onamelatucel-L
Orvepitant
Ovemotide
Ozarelix
Paflufocon D-HEM-Iberfilcon A
Pafuramidine Maleate
Paquinimod
Parogrelil
Piraxostat
Potassium Alginate
Potassium Bromide
Pramiconazole
Prinaberel
Propylene Glycol Dilaurate
Propylene Glycol Monolaurate
Pruvanserin Hydrochloride
Relacatib
Rilonacept
Rinfabate
Rolipoltide
Romidepsin
Rosabulin
Rusalatide Acetate
Sagopilone
Sapacitabine
Senicapoc
Sergliflozin
Sevelamer Carbonate
Siflufocon A
Sipuleucel-T
Sitagliptin Phosphate
Sodelglitazar
Sodium Bromide
Sofigatran
Sontuzumab
Sorafenib Tosylate
Succinobucol
Sunflower Oil
Tadocizumab
Tanespimycin
Taribavirin Hydrochloride
Tedisamil
Tedisamil Sesquifumarate
Tefilcon A
Telaprevir
Tesamorelin
Tezampanel
Ticagrelor
Ticilimumab
Tigapotide Triflutate
Tipelukast
Tomopenem
Transferrin Aldifitox
Tucotuzumab Celmoleukin
Tylosin Tartrate
Tylvalosin
Vabicaserin Hydrochloride
Vapitadine Dihydrochloride
Vasurfilcon A
Veliflapon
Vernakalant Hydrochloride
Verpasep Caltespen
Vitespen
Volinanserin
Yttrium Y 90 Tacatuzumab Tetraxetan
Zibotentan
Zotarolimus

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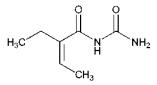
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droxy-5-[(1*E*,3*S*)-3-hydroxy-1-octenyl]-1-cyclopentene-1-heptanoate, 2-butyrate. *CAS-136892-64-3*. INN. *Treatment of peripheral arterial occlusive disease.* ✧*AS-013*



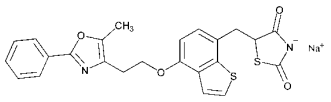
Ecromeximab [*2002*] (e″ kroe mex′ i mab). Immunoglobulin G1, anti-(GD3 ganglioside) (human-mouse monoclonal KM871 γ1-chain), disulfide with human-mouse monoclonal KM871 κ-chain, dimer. Molecular weight is approximately 145,255 daltons, according to the predicted amino acid sequence. *CAS-292819-64-8*. INN. *Treatment of malignant melanoma (monoclonal antibody).* ✧*KW-2871; KM871*

Ectylurea. $C_7H_{12}N_2O_2$. 156.18. *cis*-(2-Ethylcrotonyl)urea. *CAS-95-04-5*. BAN; MI.



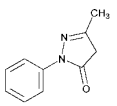
Eculizumab [*2002*] (e″ kue liz′ oo mab). Immunoglobulin, anti-(human complement C5 α-chain) (human-mouse monoclonal 5G1.1 heavy chain), disulfide with human-mouse monoclonal 5G.1.1 light chain, dimer. Molecular weight is approximately 150,000 daltons. *CAS-219685-50-4*. INN. *Treatment of autoimmune disease such as rheumatoid arthritis, membranous nephritis, lupus nephritis, dermatomyositis, and autoimmune hemolytic anemias.* ✧*h5G1.1; h5G1.1VHC+h5G1.1VLC*

Edaglitazone Sodium [*2005*] (e″ da gli′ ta zone soe′ dee um). $C_{24}H_{19}N_2NaO_4S_2$. 486.54. [Edaglitazone is INN.] (1) 2,4-Thiazolidinedione, 5-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzo[b]thien-7-yl]methyl]-, sodium salt; (2) Sodium(5*RS*)-5-[[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-1-benzothiophen-7-yl]methyl]-2,4-dioxothiazolidin-3-ide. *CAS-369631-81-2; CAS-213411-83-7* [edaglitazone]. *Treatment of Type 2 diabetes.* ✧*RO2052349-602*



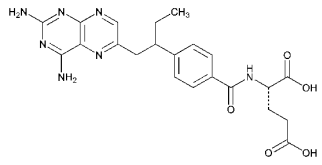
Edamine — *See* Ethylenediamine.

Edaravone. $C_{10}H_{10}N_2O$. 174.20. 3-Methyl-1-phenyl-2-pyrazolin-5-one. *CAS-89-25-8*. INN.

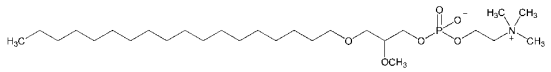


Edathamil (previously used name for active moiety) — *See* Edetate Calcium Disodium.

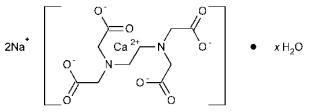
Edatrexate [*1990*] (e″ da trex′ ate). $C_{22}H_{25}N_7O_5$. 467.48. (1) L-Glutamic acid, *N*-[4-[1-[(2,4-diamino-6-pteridinyl)methyl]propyl]benzoyl]-; (2) *N*-[*p*-[1-[(2,4-Diamino-6-pteridinyl)methyl]propyl]benzoyl]-L-glutamic acid. *CAS-80576-83-6*. INN. *Antineoplastic*. ✧*CGP 30694*



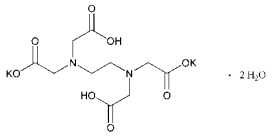
Edelfosine. $C_{27}H_{58}NO_6P$. 523.73. Choline hydroxide, (±)-2-methoxy-3-(octadecyloxy)propyl hydrogen phosphate, inner salt. *CAS-70641-51-9*. INN.



Edetate Calcium Disodium [*1962*] (e′ de tate kal′ see um dye soe′ dee um). **USP**. $C_{10}H_{12}CaN_2Na_2O_8.xH_2O$. 374.27 (anhydrous). [Sodium Calcium Edetate is INN, BAN and JAN; Calcium Disodium Edetate is JAN.] (1) Calciate (2-), [[*N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycinato]](4-)-*N*,*N*′,*O*,*O*′,O^N,$O^{N'}$]-, disodium, hydrate, (*OC*-6-21)-; (2) Disodium[(ethylenedinitrilo)tetraacetato] calciate(2-) hydrate. *CAS-23411-34-9; CAS-62-33-9* [anhydrous]; *CAS-60-00-4* [edetic acid]. *Chelating agent (metal)*. Calcium Disodium Versenate (3M Pharmaceuticals) *[Names previously used: Diazinon; Edathamil for active moiety.]*



Edetate Dipotassium [*1982*] (e′ de tate dye″ po tas′ ee um). $C_{10}H_{14}K_2N_2O_8.2H_2O$. 404.45. (1) Glycine, *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)-, dipotassium salt, dihydrate; (2) Dipotassium dihydrogen (ethylenedinitrilo)tetraacetate, dihydrate. *CAS-25102-12-9; CAS-2001-94-7* [anhydrous]; *CAS-58167-76-3* [monohydrate]. *Pharmaceutic aid (chelating agent).* ✧*32-046*



Edetate Disodium (e′ de tate dye soe′ dee um). **USP**. $C_{10}H_{14}N_2Na_2O_8.2H_2O$. 372.24. [Disodium Edetate is BAN and JAN.] (1) Glycine, *N*,*N*′-1,2-ethanediylbis[*N*-(carboxymethyl)-, disodium salt, dihydrate; (2) Disodium (ethylenedinitrilo)tetraacetate dihydrate. *CAS-6381-92-6; CAS-139-33-3* [anhydrous]; *CAS-60-00-4* [edetic acid]. *Chelating agent (metal); pharmaceutic aid (chelating agent)*. Endrate (Hospira); Sodium Versenate (3M Pharmaceuticals)

Edetate Sodium [*1966*] (e′ de tate soe′ dee um). $C_{10}H_{12}N_2Na_4O_8$. 380.17. (1) Glycine, *N*,*N*′-1,2-ethanediylbis[*N*-carboxymethyl-, tetrasodium salt; (2)

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Samsung Bioepis Exhibit No. 1002
Page 12412

Appendix IV

Code Designations for USAN and Other Nonproprietary Names

A 5MP. Code designation for Adenosine Phosphate.
A0026. Code designation for Faropenem Medoxomil.
A-41-304. Code designation for Desoximetasone.
A 46 745. Code designation for Gestrinone.
A-82. Code designation for Nitroxoline.
A110. Code designation for Pagibaximab.
A-118. Code designation for Sultroponium.
A-272. Code designation for Rutamycin.
A-1981-12. Code designation for Prodilidine Hydrochloride.
A-2205. Code designation for Profadol Hydrochloride.
A-2371. Code designation for Plicamycin.
A-2655. Code designation for Dioxamate.
A-3217. Code designation for Ocfentanil Hydrochloride.
A-3331. Code designation for Brifentanil Hydrochloride.
A-3508.HCl. Code designation for Mirfentanil Hydrochloride.
A-3665.HCl. Code designation for Trefentanil Hydrochloride.
A-4020 Linz. Code designation for Midodrine Hydrochloride.
A-4166. Code designation for Nateglinide.
A-4180. Code designation for Isometamidium Chloride.
A-4492. Code designation for Pentamorphone.
A-4696. Code designation for Actaplanin.
A-4828. Code designation for Trofosfamide.
A-5610. Code designation for Azelastine Hydrochloride.
A-7283. Code designation for Guanoctine Hydrochloride.
A-8103. Code designation for Pipobroman.
A 8999. Code designation for Aspartocin.
A-12253A. Code designation for Nebramycin.
A-16612. Code designation for Teroxalene Hydrochloride.
A-17624. Code designation for Ditolamide.
A-19120. Code designation for Pargyline Hydrochloride.
A-19757. Code designation for Encyprate.
A-20968. Code designation for Piposulfan.
A-27053. Code designation for Chromonar Hydrochloride.
A-32686. Code designation for Proscillaridin.
A 33547. Code designation for Remoxipride.
A 33547.HCl.H_2O. Code designation for Remoxipride Hydrochloride.
A-35957. Code designation for Altrenogest.
A-53986. Code designation for Fostedil.
A-60386X. Code designation for Beractant.
A-61589. Code designation for Docebenone.
A-65006. Code designation for Lansoprazole.
A-71100. Code designation for Voglibose.
A-73001. Code designation for Seratrodast.
A-75200 mesylate. Code designation for Napitane Mesylate.
A-77000. Code designation for Pazinaclone.
A-81229. Code designation for Alemcinal.
A-85761.0. Code designation for Atreleuton.
A-93431.1. Code designation for Adrogolide Hydrochloride.
A-147627.1. Code designation for Atrasentan Hydrochloride.
A-154475.0. Code designation for Lestaurtinib.
A-157378.0. Code designation for Lopinavir.
A-165594. Code designation for Tebanicline Tosylate.
A-166594.47. Code designation for Tebanicline Tosylate.
A-174606.0. Code designation for Valomaciclovir Stearate.
A-182091.0. Code designation for Omaciclovir.
A-185980.1. Code designation for Fiduxosin Hydrochloride.
A-195773. Code designation for Cethromycin.
A IX. Code designation for Demecycline.
A-A-1. Code designation for Dalbavancin.
AA-673. Code designation for Amlexanox.
AA-861. Code designation for Docebenone.
AA-2414. Code designation for Seratrodast.
AAB-001, humanized 3D-6 monoclonal antibody. Code designation for Bapineuzumab.
AAD 216. Code designation for Ardacin.
AAFC. Code designation for Flurocitabine.
AB08. Code designation for Doxycycline Fosfatex.
AB-100. Code designation for Uredepa.
AB-103. Code designation for Benzodepa.
AB-132. Code designation for Meturedepa.
AB-A 663. Code designation for Cimaterol.
Abbot-147627. Code designation for Atrasentan Hydrochloride.
Abbott-16900. Code designation for Teflurane.
Abbott-19957. Code designation for Lorbamate.
Abbott-22370. Code designation for Trimetozine.
Abbott-24091. Code designation for Berythromycin.
Abbott-34842. Code designation for Butamben Picrate.
Abbott-35616. Code designation for Clorazepate Dipotassium.
Abbott-36581. Code designation for Butamirate Citrate.
Abbott-38579. Code designation for Protirelin.
Abbott-38642. Code designation for Fosfonet Sodium.
Abbott-39083. Code designation for Clorazepate Monopotassium.
Abbott-40728. Code designation for Cetocycline Hydrochloride.
Abbott-41070. Code designation for Gonadorelin Acetate.
Abbott-43326. Code designation for Carteolol Hydrochloride.
Abbott-43818. Code designation for Leuprolide Acetate.
Abbott 44090. Code designation for Valproate Sodium.
Abbott-44747. Code designation for Astromicin Sulfate.
Abbott-45975. Code designation for Terazosin Hydrochloride.
Abbott-46811. Code designation for Cefsulodin Sodium.
Abbott-47631. Code designation for Estazolam.
Abbott-48999. Code designation for Cefotiam Hydrochloride.
Abbott-50192 (HCl). Code designation for Cefmenoxime Hydrochloride.
Abbott-50711. Code designation for Divalproex Sodium.
Abbott-56268. Code designation for Clarithromycin.
Abbott-56619. Code designation for Difloxacin Hydrochloride.
Abbott-56620. Code designation for Sarafloxacin Hydrochloride.
Abbott-57135 [sarafloxacin]. Code designation for Sarafloxacin Hydrochloride.
Abbott-61827. Code designation for Tosufloxacin.
Abbott-62254. Code designation for Temafloxacin Hydrochloride.
Abbott-64077. Code designation for Zileuton.
Abbott-64662. Code designation for Enalkiren.
Abbott-70569.1. Code designation for Tiagabine Hydrochloride.
Abbott-70569.HCl. Code designation for Tiagabine Hydrochloride.
Abbott-72517. Code designation for Zankiren Hydrochloride.
Abbott-73001. Code designation for Seratrodast.
Abbott-74187. Code designation for Nasaruplase Beta.
Abbott-76120. Code designation for Urokinase Alfa.
Abbott-76745. Code designation for Fenleuton.
Abbott-81229.0. Code designation for Alemcinal.
Abbott-84538. Code designation for Ritonavir.
Abbott-85761. Code designation for Atreleuton.

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Samsung Bioepis Exhibit No. 1002
Page 12413

Abbott-195773. Code designation for Cethromycin.
ABC 12/3. Code designation for Doxofylline.
ABOB. Code designation for Moroxydine.
ABT-001. Code designation for Seratrodast.
ABT-091. Code designation for Omaciclovir.
ABT-120. Code designation for Urokinase Alfa.
ABT-187. Code designation for Nasaruplase Beta.
ABT-229. Code designation for Alemcinal.
ABT-378. Code designation for Lopinavir.
ABT-431. Code designation for Adrogolide Hydrochloride.
ABT-569. Code designation for Tiagabine Hydrochloride.
ABT-578. Code designation for Zotarolimus.
ABT-594. Code designation for Tebanicline Tosylate.
ABT-606. Code designation for Valomaciclovir Stearate.
ABT-627. Code designation for Atrasentan Hydrochloride.
ABT-761. Code designation for Atreleuton.
ABT-773. Code designation for Cethromycin.
ABT-980. Code designation for Fiduxosin Hydrochloride.
ABX-EGF. Code designation for Panitumumab.
AC001. Code designation for Amlintide.
AC0137. Code designation for Pramlintide.
AC0137. Code designation for Pramlintide Acetate.
AC-528. Code designation for Dioxation.
AC-601. Code designation for Buramate.
AC 1198. Code designation for Dimethadione.
AC 1370. Code designation for Cefpimizole.
AC002993. Code designation for Exenatide.
AC2993. Code designation for Exenatide.
AC 2993. Code designation for Exenatide.
AC-2993. Code designation for Exenatide.
AC2993A. Code designation for Exenatide.
AC 3810. Code designation for Bamifylline Hydrochloride.
AC4464. Code designation for Torsemide.
AC 263,780. Code designation for Cimaterol.
ACC-9089. Code designation for Flestolol Sulfate.
ACC-9653-010 (sodium salt). Code designation for Fosphenytoin Sodium.
ACEA 1021. Code designation for Licostinel.
ACH-126,443. Code designation for Elvucitabine.
Ad5CMV-p53. Code designation for Contusugene ladenovec.
AD 32. Code designation for Valrubicin.
AD 106. Code designation for Cicrotoic Acid.
AD-810. Code designation for Zonisamide.
ADD-3878. Code designation for Ciglitazone.
ADD 243037. Code designation for Lacosamide.
ADL 8-2698. Code designation for Alvimopan.
ADR-033. Code designation for Tripamide.
ADR-529. Code designation for Dexrazoxane.
AE-9. Code designation for Feclobuzone.
AE-705W. Code designation for Neutramycin.
AF102B. Code designation for Cevimeline Hydrochloride.
AF0144. Code designation for Perflubrodec.
AF0150. Code designation for Perflexane.
AF-438 [as citrate]. Code designation for Oxolamine.
AF-634. Code designation for Proxazole Citrate.
AF-864. Code designation for Benzydamine Hydrochloride.
AF-1161. Code designation for Trazodone Hydrochloride.
AF 1934 [lysine]. Code designation for Bendazac.
AF 2139. Code designation for Dapiprazole Hydrochloride.
AF 2838. Code designation for Bindarit.
AG-3. Code designation for Chromonar Hydrochloride.
AG331. Code designation for Metesind Glucuronate.
AG1343. Code designation for Nelfinavir Mesylate.
AG-1749. Code designation for Lansoprazole.
AG2037. Code designation for Pelitrexol.
AG3340. Code designation for Prinomastat.
AG7088. Code designation for Rupintrivir.
AG-013736. Code designation for Axitinib.
AG 58107. Code designation for Ioxitalamic Acid.
AG-EE 623 ZW. Code designation for Repaglinide.
Agent M-01. Code designation for Sucrosofate Potassium.
AGI-1067. Code designation for Succinobucol.
AGI-1096. Code designation for Elsibucol.
AGIX-4207. Code designation for Camobucol.
AGN 20. Code designation for Metamfazone.
AGN 511 [as hydrochloride]. Code designation for Prazitone.
AGN 616. Code designation for Fantridone Hydrochloride.
AGN 190168. Code designation for Tazarotene.
AGN 190342-LF. Code designation for Brimonidine Tartrate.
AGN 192013. Code designation for Alitretinoin.
AGN 192024. Code designation for Bimatoprost.
AGR-1240. Code designation for Minaprine.
AH 3923. Code designation for Salmefamol.
AH 5158A. Code designation for Labetalol Hydrochloride.
AH 8165D. Code designation for Fazadinium Bromide.
AH 19065. Code designation for Ranitidine Hydrochloride.
AH 22216. Code designation for Lamtidine.
AH 23844 [lavoltidine]. Code designation for Lavoltidine Succinate.
AH 23844A. Code designation for Lavoltidine Succinate.
AH 25352X. Code designation for Sufotidine.
AHR-224. Code designation for Pyroxamine Maleate.
AHR-438. Code designation for Metaxalone.
AHR-504. Code designation for Glycopyrrolate.
AHR-619. Code designation for Doxapram Hydrochloride.
AHR-857. Code designation for Sulfameter.
AHR-1118. Code designation for Pridefine Hydrochloride.
AHR-1680. Code designation for Fenpipalone.
AHR-2277 [as hydrochloride]. Code designation for Lenperone.
AHR-2438B. Code designation for Polignate Sodium.
AHR-3000. Code designation for Butaperazine.
AHR-3002. Code designation for Fenfluramine Hydrochloride.
AHR-3015. Code designation for Cintazone.
AHR-3018. Code designation for Apazone.
AHR-3053. Code designation for Carbocysteine.
AHR-3070-C. Code designation for Metoclopramide Hydrochloride.
AHR-4698. Code designation for Isosorbide Mononitrate.
AHR-5531C. Code designation for Dazopride Fumarate.
AHR-5850D. Code designation for Amfenac Sodium.
AHR-6134. Code designation for Cloroperone Hydrochloride.
AHR 6646. Code designation for Duoperone Fumarate.
AHR-8559. Code designation for Fluzinamide.
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AHR-9434. Code designation for Nepafenac.
AHR-10282B. Code designation for Bromfenac Sodium.
AHR-10718. Code designation for Suricainide Maleate.
AHR-11190-B. Code designation for Zacopride Hydrochloride.
AHR-11325-D. Code designation for Rocastine Hydrochloride.
AHR-11748. Code designation for Dezinamide.
AI-700. Code designation for Perflubutane.
AI-27,303. Code designation for Cetamolol Hydrochloride.
AICA. Code designation for Orazamide.
AIT-082. Code designation for Leteprinim Potassium.
AJ-2615. Code designation for Monatepil Maleate.
AL 20 [as hydrochloride]. Code designation for Clemizole.
Al-0361. Code designation for Hydroxyphenamate.
AL 0559. Code designation for Fenamole.
AL 842. Code designation for Deterenol Hydrochloride.
AL-1021. Code designation for Carperone.
AL1577A. Code designation for Levobetaxolol Hydrochloride.
AL02145. Code designation for Apraclonidine Hydrochloride.
AL02725. Code designation for Pyrithione Sodium.
AL-3432A. Code designation for Emedastine Difumarate.
AL-3789. Code designation for Anecortave Acetate.
AL-4862. Code designation for Brinzolamide.

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AL-6221. Code designation for Travoprost.
AL-6515. Code designation for Nepafenac.
AL-12959. Code designation for Icomucret.
ALCA. Code designation for Alcloxa.
ALDA. Code designation for Aldioxa.
Allergan 211. Code designation for Idoxuridine.
ALO 1401-02. Code designation for Betaxolol Hydrochloride.
ALO 2184. Code designation for Resocortol Butyrate.
ALRT1057. Code designation for Alitretinoin.
AL-T30. Code designation for Vinafocon A.
AL-T150. Code designation for Oxyfilcon A.
ALT-711. Code designation for Alagebrium Chloride.
ALX1-11. Code designation for Parathyroid Hormone.
ALX 0600. Code designation for Teduglutide.
AM-684-Beta. Code designation for Relomycin.
AM-1155. Code designation for Gatifloxacin.
AMA 1080(2Na). Code designation for Carumonam Sodium.
AMD473. Code designation for Picoplatin.
AMD3100. Code designation for Plerixafor.
AMG073. Code designation for Cinacalcet.
AMG073 HCl. Code designation for Cinacalcet Hydrochloride.
AMG 162. Code designation for Denosumab.
AMI-25. Code designation for Ferumoxides.
AMI-121. Code designation for Ferumoxsil.
AMR-69. Code designation for Pirfenidone.
AN021. Code designation for Tizanidine Hydrochloride.
AN-051. Code designation for Dezinamide.
AN 1317. Code designation for Perimetazine.
AN 1324. Code designation for Glybuzole.
Anesthetic Compound No. 347. Code designation for Enflurane.
ANP 246. Code designation for Clofexamide.
ANP 3260. Code designation for Clofezone.
Antibiotic 241a. Code designation for Biniramycin.
Antibiotic A-5283. Code designation for Natamycin.
anti-CD11a. Code designation for Efalizumab.
anti-CD40L. Code designation for Toralizumab.
anti-CD154. Code designation for Toralizumab.
Antifoam A. Code designation for Simethicone.
Antifoam AF. Code designation for Simethicone.
anti-gp39. Code designation for Toralizumab.
anti-SSEA-1. Code designation for Technetium Tc 99m Fanolesomab.
AO-128. Code designation for Voglibose.
AO-407. Code designation for Hydrofilcon A.
AOMA. Code designation for Surfomer.
AO-PLUTO. Code designation for Mesifilcon A.
AP 67. Code designation for Chlorthenoxazine.
APC8015. Code designation for Sipuleucel-T.
APC8024. Code designation for Lapuleucel-T.
APD356. Code designation for Lorcaserin Hydrochloride.
API-GP3. Code designation for Motexafin Gadolinium.
APM. Code designation for Aspartame.
APSAC. Code designation for Anistreplase.
APT 070. Code designation for Mirococept.
AQ-110. Code designation for Tretoquinol.
AR 12008. Code designation for Trapidil.
ara-A. Code designation for Vidarabine.
ara-AC. Code designation for Fazarabine.
AR-C68397AA. Code designation for Sibenadet Hydrochloride.
AR-C69931MX. Code designation for Cangrelor Tetrasodium.
AR-C69931XX. Code designation for Cangrelor.
ARC I-K-1. Code designation for Methopholine.
ARDF 26. Code designation for Gliquidone.
AR-H039242XX. Code designation for Tesaglitazar.
AS-013. Code designation for Ecraprost.
AS 101. Code designation for Arsanilic Acid.
AS-17665. Code designation for Nifurthiazole.
ASA 158/5 [as phosphate]. Code designation for Benproperine.
ASL-279. Code designation for Dopamine Hydrochloride.
ASL-601. Code designation for Acecainide Hydrochloride.
ASL-603. Code designation for Bretylium Tosylate.
ASL-607. Code designation for Pentastarch.
ASL-8052. Code designation for Esmolol Hydrochloride.
Asta 3746. Code designation for Ciclonium Bromide.
Astra 1512. Code designation for Prilocaine Hydrochloride.
Astra 1572. Code designation for Iron Sorbitex.
AT-101. Code designation for Isosorbide.
AT-125. Code designation for Acivicin.
AT 327. Code designation for Tipepidine.
AT-2266. Code designation for Enoxacin.
AT-4140. Code designation for Sparfloxacin.
ATC Code G03 GA Gonadotropins. Code designation for Choriogonadotropin Alfa.
ATC G03 GA Gonadotropins. Code designation for Lutropin Alfa.
ATI 01. Code designation for Sinapultide.
ATI 02. Code designation for Lucinactant.
AW 10. Code designation for Sitogluside.
AW 14′2333. Code designation for Perlapine.
AW-14′2446. Code designation for Clodazon Hydrochloride.
AW 105-843. Code designation for Naftifine Hydrochloride.
AY4166. Code designation for Nateglinide.
AY-5312. Code designation for Chlorhexidine Hydrochloride.
AY-5710. Code designation for Magaldrate.
AY-6108. Code designation for Ampicillin.
AY 6204 [as hydrochloride]. Code designation for Pronetalol.
AY-6608. Code designation for Pentagastrin.
AY-8682. Code designation for Cyheptamide.
AY-11,440. Code designation for Clogestone Acetate.
AY-11,483. Code designation for Estrofurate.
AY-15,613. Code designation for Citenamide.
AY-20,385. Code designation for Nequinate.
AY-20,694. Code designation for Dexpropranolol Hydrochloride.
AY-21,011. Code designation for Practolol.
AY-21,367. Code designation for Furobufen.
AY-21,554. Code designation for Talopram Hydrochloride.
AY-22,124. Code designation for Intriptyline Hydrochloride.
AY-22,214. Code designation for Taclamine Hydrochloride.
AY-22,241. Code designation for Actodigin.
AY-22,284A. Code designation for Alrestatin Sodium.
AY 22,469. Code designation for Deprostil.
AY-22989. Code designation for Sirolimus.
AY-23,028. Code designation for Butaclamol Hydrochloride.
AY-23,289. Code designation for Prodolic Acid.
AY-23,713. Code designation for Pirandamine Hydrochloride.
AY-23,946. Code designation for Tandamine Hydrochloride.
AY-24,031. Code designation for Gonadorelin Hydrochloride.
AY-24,169. Code designation for Dexclamol Hydrochloride.
AY-24,236. Code designation for Etodolac.
AY-24,269. Code designation for Proroxan Hydrochloride.
AY-24,559. Code designation for Doxaprost.
AY-24,856. Code designation for Pareptide Sulfate.
AY-25,329. Code designation for Azaclorzine Hydrochloride.
AY-25,712. Code designation for Acifran.
AY-27,110. Code designation for Ciladopa Hydrochloride.
AY-27,255. Code designation for Vinpocetine.
AY-27,773. Code designation for Tolrestat.
AY-28,228. Code designation for Atiprosin Maleate.
AY-28,768. Code designation for Pelrinone Hydrochloride.
AY-30,715. Code designation for Pemedolac.
AY-61122. Code designation for Methallibure.
AY-61123. Code designation for Clofibrate.
AY-62014. Code designation for Butriptyline Hydrochloride.
AY-62021. Code designation for Clopenthixol.
AY-62022. Code designation for Medrogestone.
AY 64043. Code designation for Propranolol Hydrochloride.
AZD2563. Code designation for Posizolid.

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AZL O 211089. Code designation for Dimethyl Fumarate.
AZQ. Code designation for Diaziquone.
AZT. Code designation for Zidovudine.
B1 61.012. Code designation for Sargramostim.
B1Q 16. Code designation for Hedaquinium Chloride.
B28-Asp-Insulin. Code designation for Insulin Aspart.
B-360. Code designation for Paroxypropione.
B-436. Code designation for Prenylamine.
B992. Code designation for Stannsoporfin.
B1287. Code designation for Eritoran Tetrasodium.
B 1312 [as hydrochloride]. Code designation for Bupranolol.
B 1464. Code designation for Guanacline Sulfate.
B2036-PEG. Code designation for Pegvisomant.
B-2311. Code designation for Morinamide.
B-4130. Code designation for Iodamide.
B9302-107. Code designation for Roflumilast.
B 10610. Code designation for Iodoxamic Acid.
B 11420. Code designation for Iopronic Acid.
B19036/7. Code designation for Gadobenate Dimeglumine.
B-35251. Code designation for Mitocromin.
BA 679. Code designation for Tiotropium Bromide.
BA 4164-8. Code designation for Diflumidone Sodium.
BA 4197. Code designation for Flucrylate.
BA 4223. Code designation for Triflumidate.
BA 7602-06. Code designation for Talniflumate.
BA 7604-02. Code designation for Talosalate.
BA 7605-06. Code designation for Talmetacin.
Ba 13155 [as tartrate]. Code designation for Meladrazine.
Ba-20684. Code designation for Etonitazene.
Ba-29038. Code designation for Boldenone Undecylenate.
Ba-29837. Code designation for Deferoxamine Hydrochloride.
Ba-30803. Code designation for Benzoctamine Hydrochloride.
BA 32644. Code designation for Niridazole.
Ba-32968. Code designation for Delfantrine.
Ba-33112. Code designation for Deferoxamine Mesylate.
Ba-34,276 [as hydrochloride]. Code designation for Maprotiline.
Ba-34,647. Code designation for Baclofen.
BA 36278A. Code designation for Cephacetrile Sodium.
Ba-39,089. Code designation for Oxprenolol Hydrochloride.
Ba-40088. Code designation for Proxibutene.
Ba 41166/E. Code designation for Rifampin.
Ba-41795. Code designation for Codactide.
BAFF. Code designation for Ardenermin.
BAL5788. Code designation for Ceftobiprole Medocaril.
BAL5788-001. Code designation for Ceftobiprole Medocaril.
BAL9141-000. Code designation for Ceftobiprole.
BAQD 10. Code designation for Dequalinium Chloride.
BASF 43915. Code designation for Pelretin.
BASF 47011. Code designation for Doretinel.
BASF 52404. Code designation for Linarotene.
BAX 422Z. Code designation for Albutoin.
BAX 1400Z. Code designation for Dimethadione.
BAX 1515. Code designation for Sutilains.
BAX 1526. Code designation for Chymopapain.
BAX 2739Z. Code designation for Bamifylline Hydrochloride.
BAX-ACC-1638. Code designation for Atilmotin.
BAY 12-8039. Code designation for Moxifloxacin Hydrochloride.
BAY 12-9566. Code designation for Tanomastat.
BAY 43-9006. Code designation for Sorafenib.
BAY 54-9085. Code designation for Sorafenib Tosylate.
BAY 59-7939. Code designation for Rivaroxaban.
BAY 1500. Code designation for Mefruside.
BAY 1521. Code designation for Noxiptiline.
BAY 2353. Code designation for Niclosamide.
BAY 4059 Va. Code designation for Brotianide.
BAY 4503. Code designation for Propiram Fumarate.
BAY 5097. Code designation for Clotrimazole.
BAY 9002. Code designation for Naftalofos.
Bay a 1040. Code designation for Nifedipine.
BAY B 4231. Code designation for Glisoxepide.
Bay d 1107. Code designation for Etofenamate.
BAY d 8815 [hydrochloride]. Code designation for Amidantel.
Bay e 5009. Code designation for Nitrendipine.
BAY e 9736. Code designation for Nimodipine.
BAY g 2821. Code designation for Muzolimine.
Bay g 5421. Code designation for Acarbose.
Bay g 6575. Code designation for Nafazatrom.
BAY h 2049. Code designation for Daniquidone.
Bay h 4502. Code designation for Bifonazole.
Bay h 5757. Code designation for Febantel.
BAY i 3930. Code designation for Isomalt.
BAY i 7433. Code designation for Copovithane.
Bay k 5552. Code designation for Nisoldipine.
Bay m 1099. Code designation for Miglitol.
BAY o 1248. Code designation for Emiglitate.
Bay o 9867 monohydrate. Code designation for Ciprofloxacin Hydrochloride.
Bay q 3939. Code designation for Ciprofloxacin.
Bay q 4218. Code designation for Butaprost.
BAY q 7821. Code designation for Ipsapirone Hydrochloride.
BAY u 3405. Code designation for Ramatroban.
BAY V1 4718. Code designation for Etisomicin.
BAY V1 6045. Code designation for Flumethrin.
BAY Va 1470. Code designation for Xylazine Hydrochloride.
Bay VA 9387. Code designation for Etisazole.
BAY Va 9391. Code designation for Olaquindox.
BAY Vh 5757. Code designation for Febantel.
Bay Vi 9142. Code designation for Toltrazuril.
BAY Vk 4999. Code designation for Fuzlocillin.
Bay Vl 1704. Code designation for Cyfluthrin.
Bay Vn 6528. Code designation for Fenfluthrin.
Bay Vp 2674. Code designation for Enrofloxacin.
BAY w 6228. Code designation for Cerivastatin Sodium.
BAY w 6240. Code designation for Factor VIII (rDNA).
Bay w 6341. Code designation for Abafungin.
Bay x 1005. Code designation for Veliflapon.
BAY X 1351. Code designation for Nerelimomab.
BAY y 7432. Code designation for Ecadotril.
Bayer 1362. Code designation for Butaperazine.
Bayer 1420. Code designation for Propanidid.
Bayer 2502. Code designation for Nifurtimox.
Bayer 3231. Code designation for Triaziquone.
Bayer 5360. Code designation for Metronidazole.
Bayer 9015. Code designation for Niclofolan.
Bayer 9037. Code designation for Quintiofos.
Bayer 9053. Code designation for Phoxim.
Bayer 21199. Code designation for Coumaphos.
Bayer A 128. Code designation for Aprotinin.
Bayer L 1359. Code designation for Trichlorfon.
BAYNAC. Code designation for Fenfluthrin.
BB-94. Code designation for Batimastat.
BB-882. Code designation for Lexipafant.
BB-2516. Code designation for Marimastat.
BB-3644. Code designation for Solimastat.
BB-10010. Code designation for Nagrestipen.
BB-K8. Code designation for Amikacin Sulfate.
BBM-2478A. Code designation for Elsamitrucin.
BBR 2778. Code designation for Pixantrone.
BBR 3438. Code designation for Nortopixantrone.
BBR 3464. Code designation for Triplatin Tetranitrate.
BBR 3576 (dihydrochloride). Code designation for Topixantrone.
BC-105. Code designation for Pizotyline.
BCG65-E7. Code designation for Verpasep Caltespen.
BCH-4556. Code designation for Troxacitabine.
BCM. Code designation for Mannomustine.
BCNU. Code designation for Carmustine.

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BCX-34. Code designation for Peldesine.
BCX-1777. Code designation for Forodesine Hydrochloride.
BCX-1777. Code designation for Forodesine.
BCX 2600. Code designation for Stiripentol.
BD 40A. Code designation for Formoterol Fumarate.
BDF5896. Code designation for Moxonidine.
BDH 1298. Code designation for Megestrol Acetate.
BDH 1921. Code designation for Melengestrol Acetate.
Be-100. Code designation for Ibuprofen Piconol.
BE 419. Code designation for Ioglycamic Acid.
Be-1293. Code designation for Xipamide.
BE5895. Code designation for Moxonidine.
BEC2. Code designation for Mitumomab.
BEMT. Code designation for Bemotrizinol.
BG 8301. Code designation for Teceleukin.
BG8967. Code designation for Bivalirudin.
BG9273. Code designation for Alefacept.
BG9588. Code designation for Ruplizumab.
BG9712. Code designation for Alefacept.
BG9719. Code designation for Naxifylline.
BI397. Code designation for Dalbavancin.
BIBR 277 SE. Code designation for Telmisartan.
BIBV 308 SE. Code designation for Terbogrel.
BIIP 20 XX. Code designation for Apaxifylline.
BI-L-239. Code designation for Enofelast.
BILA 2011 BS. Code designation for Palinavir.
BILN 2061 ZW. Code designation for Ciluprevir.
BIM-23014C. Code designation for Lanreotide Acetate.
BIMT 17. Code designation for Flibanserin.
BIMT 17 BS. Code designation for Flibanserin.
BIRG 0587. Code designation for Nevirapine.
BIRM-270. Code designation for Ontazolast.
BI-RR-0001. Code designation for Enlimomab.
BIRR004. Code designation for Tremacamra.
BL 191. Code designation for Pentoxifylline.
BL-3912A. Code designation for Dimoxamine Hydrochloride.
BL-4162a. Code designation for Anagrelide Hydrochloride.
BL-5111. Code designation for Tiodazosin.
BL-5572M. Code designation for Proxorphan Tartrate.
BL-5641A. Code designation for Etintidine Hydrochloride.
BL-P 804. Code designation for Hetacillin.
BL-P 1322. Code designation for Cephapirin Sodium.
BL-P 1462. Code designation for Suncillin Sodium.
BL-P1761. Code designation for Sarpicillin.
BL-P1780. Code designation for Sarmoxicillin.
BL-R 743. Code designation for Intrazole.
BL-S578. Code designation for Cefadroxil.
BL-S640. Code designation for Cefatrizine.
BL-S786. Code designation for Ceforanide.
BLyS. Code designation for Ardenermin.
BM01.004. Code designation for Metipranolol.
BM02.015. Code designation for Torsemide.
BM 06.019. Code designation for Epoetin Beta.
BM 06.022. Code designation for Reteplase.
BM 13.177. Code designation for Sulotroban.
BM 13.505. Code designation for Daltroban.
BM 14.190. Code designation for Carvedilol.
BM 15.075. Code designation for Bezafibrate.
BM 21.0955 · Na · H_2O. Code designation for Ibandronate Sodium.
BM 22.145. Code designation for Isosorbide Mononitrate.
BM 41.332. Code designation for Ciamexon.
BM 41.440. Code designation for Ilmofosine.
BM 51052. Code designation for Carazolol.
BMIPP. Code designation for Iodofiltic Acid I 123.
BMS068645. Code designation for Apadenoson.
BMS-180048. Code designation for Avitriptan Fumarate.
BMS-180048-02. Code designation for Avitriptan Fumarate.
BMS-180194. Code designation for Lobucavir.
BMS-180291. Code designation for Ifetroban.
BMS-180291-02. Code designation for Ifetroban Sodium.
BMS 180549. Code designation for Ferumoxtran-10.
BMS-181158. Code designation for Mequinol.
BMS-181173. Code designation for Gusperimus Trihydrochloride.
BMS-181176. Code designation for Becatecarin.
BMS-181339-01. Code designation for Paclitaxel.
BMS-182751. Code designation for Satraplatin.
BMS-186091. Code designation for Ammonium Lactate.
BMS-186295. Code designation for Irbesartan.
BMS-186716. Code designation for Omapatrilat.
BMS-186716-01. Code designation for Omapatrilat.
BMS-188667. Code designation for Abatacept.
BMS-189921. Code designation for Gemopatrilat.
BMS-200475-01. Code designation for Entecavir.
BMS-200980. Code designation for Lanoteplase.
BMS-204352. Code designation for Flindokalner.
BMS-204756-07. Code designation for Brasofensine Maleate.
BMS-205603-01. Code designation for Uracil.
BMS-206584-01. Code designation for Gatifloxacin.
BMS-207940-02. Code designation for Edonentan.
BMS-217380-01. Code designation for Tesmilifene Hydrochloride.
BMS-224818. Code designation for Belatacept.
BMS-224819. Code designation for Teneliximab.
BMS-232632-05. Code designation for Atazanavir Sulfate.
BMS-234303-01. Code designation for Naminidil.
BMS 247550-01. Code designation for Ixabepilone.
BMS 275291-01. Code designation for Rebimastat.
BMS-284756-01. Code designation for Garenoxacin Mesylate.
BMS-298585. Code designation for Muraglitazar.
BMS-354825-03. Code designation for Dasatinib.
BMS-426707-1. Code designation for Peliglitazar.
BMS-477118. Code designation for Saxagliptin.
BMS-561389. Code designation for Razaxaban Hydrochloride.
BMS-562247-01. Code designation for Apixaban.
BMY-05763-1-D. Code designation for Dexsotalol Hydrochloride.
BMY 13754. Code designation for Nefazodone Hydrochloride.
BMY 13805-1. Code designation for Gepirone Hydrochloride.
BMY 13859-1. Code designation for Tiospirone Hydrochloride.
BMY-21891. Code designation for Belfosdil.
BMY-25182. Code designation for Cefbuperazone.
BMY-25801-01. Code designation for Batanopride Hydrochloride.
BMY-26517. Code designation for Pemirolast Potassium.
BMY-27557. Code designation for Becatecarin.
BMY-27857. Code designation for Stavudine.
BMY-28090. Code designation for Elsamitrucin.
BMY-28100-03-800. Code designation for Cefprozil.
BMY-28142. Code designation for Cefepime.
BMY-28142 2HCl.H_2O. Code designation for Cefepime Hydrochloride.
BMY-30056. Code designation for Halobetasol Propionate.
BMY-30120. Code designation for Chlorhexidine Phosphanilate.
BMY-33419. Code designation for Tesmilifene Hydrochloride.
BMY-40327. Code designation for Modecainide.
BMY 40481. Code designation for Etoposide Phosphate.
BMY-40900. Code designation for Didanosine.
BMY-41606. Code designation for Vapreotide.
BMY-42215-1. Code designation for Gusperimus Trihydrochloride.
BMY-45594. Code designation for Satraplatin.
BN110 base. Code designation for Axomadol.
BN 200 (base). Code designation for Tapentadol.
(±)-BN-1270. Code designation for Cicletanine.
BNAG. Code designation for Donepezil Hydrochloride.
BNP-166. Code designation for Etiprednol Dicloacetate.
BOF-A2. Code designation for Emitefur.

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BP 1.02. Code designation for Ecadotril.
BP-13. Code designation for Iosimenol.
BP 400. Code designation for Pimethixene.
BP-1184. Code designation for Guanoctine Hydrochloride.
BRI. Code designation for Sulfur Hexafluoride.
BRL-284. Code designation for Levopropylcillin Potassium.
BRL-804. Code designation for Hetacillin.
BRL-1241. Code designation for Methicillin Sodium.
BRL-1288. Code designation for Benapryzine Hydrochloride.
BRL-1341. Code designation for Ampicillin.
BRL-1621. Code designation for Cloxacillin Sodium.
BRL-1702. Code designation for Dicloxacillin.
BRL 2039. Code designation for Floxacillin.
BRL-2064. Code designation for Carbenicillin Disodium.
BRL 2288. Code designation for Ticarcillin Disodium.
BRL 2333. Code designation for Amoxicillin.
BRL-2333AB-B. Code designation for Amoxicillin Sodium.
BRL 2534. Code designation for Azidocillin.
BRL-3475. Code designation for Carbenicillin Phenyl Sodium.
BRL 4664. Code designation for Nonabine.
BRL 4910A. Code designation for Mupirocin.
BRL 4910F. Code designation for Mupirocin Calcium.
BRL 8988 Hydrochloride. Code designation for Talampicillin Hydrochloride.
BRL 12594. Code designation for Ticarcillin Cresyl Sodium.
BRL 13856. Code designation for Clopirac.
BRL 14151. Code designation for Clavulanic Acid.
BRL 14151K. Code designation for Clavulanate Potassium.
BRL 14777. Code designation for Nabumetone.
BRL 17421 [as sodium]. Code designation for Temocillin.
BRL 26921. Code designation for Anistreplase.
BRL 29060. Code designation for Paroxetine.
BRL 30892. Code designation for Denbufylline.
BRL 34915. Code designation for Cromakalim.
BRL-38227. Code designation for Levcromakalim.
BRL 38705. Code designation for Epsiprantel.
BRL-39123. Code designation for Penciclovir.
BRL-39123-D. Code designation for Penciclovir Sodium.
BRL 40015. Code designation for Diproteverine.
BRL-42810. Code designation for Famciclovir.
BRL 43694. Code designation for Granisetron.
BRL 43694A. Code designation for Granisetron Hydrochloride.
BRL-49653-C. Code designation for Rosiglitazone Maleate.
BRL 61063. Code designation for Cipamfylline.
BS 100-141. Code designation for Guanfacine Hydrochloride.
BS 749. Code designation for Metacetamol.
B.S. 6534. Code designation for Bufenadrine.
BS 6748. Code designation for Xyloxemine.
BS 6987. Code designation for Deptropine Citrate.
BS 7161 D [as hydrochloride]. Code designation for Pytamine.
B.S. 7173-D. Code designation for Xylocoumarol.
B.S. 7561 [as hydrochloride]. Code designation for Tixadil.
B.S. 7573-a. Code designation for Acridorex.
BS 7723 [as maleate]. Code designation for Tropirine.
BS 7977 D [as dihydrochloride]. Code designation for Xipranolol.
BSH. Code designation for Borocaptate Sodium B 10.
BSSG. Code designation for Sitogluside.
BT 621 [as hydrochloride]. Code designation for Todralazine.
BTPABA, PFT. Code designation for Bentiromide.
BTS 49 465. Code designation for Flosequinan.
BTS 7706. Code designation for Debropol.
BTS 13622. Code designation for Hexaprofen.
BTS 17345. Code designation for Fluprofen.
BTS 18,322. Code designation for Flurbiprofen.
BTS 24332. Code designation for Esflurbiprofen.
BTS 54524. Code designation for Sibutramine Hydrochloride.
BU-2231A. Code designation for Talisomycin.
BW 33A. Code designation for Atracurium Besylate.
BW 33-T-57. Code designation for Methisazone.
BW 49-210. Code designation for Diaveridine.
BW 56-72. Code designation for Trimethoprim.
BW 56-158. Code designation for Allopurinol.
BW-57-322. Code designation for Azathioprine.
BW 57-323. Code designation for Thiamiprine.
BW 58-271. Code designation for Rolodine.
BW-61-32. Code designation for Stilbazium Iodide.
BW 63-90. Code designation for Butacetin.
BW 64-9. Code designation for Butoxamine Hydrochloride.
BW 72U. Code designation for Trimethoprim Sulfate.
BW 207U. Code designation for Xenalipin.
BW 234U dihydrochloride. Code designation for Rimcazole Hydrochloride.
BW 248U sodium. Code designation for Acyclovir Sodium.
BW 301U isethionate. Code designation for Piritrexim Isethionate.
BW 323. Code designation for Bupropion Hydrochloride.
BW 325U. Code designation for Trifenagrel.
BW 356-C-61. Code designation for Gloxazone.
BW 430C. Code designation for Lamotrigine.
BW-467-C-60. Code designation for Bethanidine Sulfate.
BW-524W91. Code designation for Emtricitabine.
BW 532U. Code designation for Cinflumide.
BW 647U hydrochloride. Code designation for Bipenamol Hydrochloride.
BW 759U. Code designation for Ganciclovir.
BW 825C. Code designation for Acrivastine.
BW A256C. Code designation for Palatrigine.
BW A509U. Code designation for Zidovudine.
BW A515U. Code designation for Desciclovir.
BW A770U mesylate. Code designation for Crisnatol Mesylate.
BW A938U dichloride. Code designation for Doxacurium Chloride.
BW B109OU dichloride. Code designation for Mivacurium Chloride.
Bx 311. Code designation for Cinoxolone.
BX 341. Code designation for Bifluranol.
BX 363A [as disodium salt]. Code designation for Cicloxolone.
BX 591. Code designation for Acefluranol.
BX 650 A. Code designation for Ipsalazide.
BX661A. Code designation for Balsalazide Disodium.
BY217. Code designation for Roflumilast.
BY 1023. Code designation for Pantoprazole.
BYK20869. Code designation for Roflumilast.
BZ 55. Code designation for Carbutamide.
C-1. Code designation for Edrecolomab.
C-3. Code designation for Capobenate Sodium.
C-3. Code designation for Capobenic Acid.
C-4. Code designation for Imciromab Pentetate.
c7E3. Code designation for Abciximab.
C225. Code designation for Cetuximab.
C-238. Code designation for Pridinol.
C-434. Code designation for Trimedoxime Bromide.
C-1428. Code designation for Cyclarbamate.
C 1656. Code designation for Clometacin.
C-11925. Code designation for Phanquone.
C-12669. Code designation for Demecolcine.
C-49802B-Ba. Code designation for Oxaprotiline Hydrochloride.
CA-7. Code designation for Brinolase.
Ca 1022. Code designation for Carbutamide.
CAB-2001. Code designation for Trafermin.
CAM-807. Code designation for Bialamicol Hydrochloride.
CAS 276. Code designation for Molsidomine.
CAS 936. Code designation for Pirsidomine.
CB 11 [as hydrochloride]. Code designation for Phenadoxone.
CB-154. Code designation for Bromocriptine.
CB-154 mesylate. Code designation for Bromocriptine Mesylate.
CB 302. Code designation for Ferric Fructose.

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CB 304. Code designation for Azaribine.
CB 309. Code designation for Fenabutene.
CB-311. Code designation for Somatropin.
CB 313. Code designation for Mitotane.
CB-337. Code designation for Meglutol.
CB 804. Code designation for Bucloxic Acid.
CB 1048. Code designation for Chlornaphazine.
CB 1664. Code designation for Acepromethazine.
CB 1678. Code designation for Propiomazine.
CB 2201. Code designation for Amfepentorex.
CB 3025. Code designation for Melphalan.
CB 3697. Code designation for Racefemine.
CB 4260. Code designation for Nortetrazepam.
CB 4261. Code designation for Tetrazepam.
CB 4857. Code designation for Menitrazepam.
CB 4985. Code designation for Acequinoline.
CB 7432. Code designation for Idoxifene.
CB 7598. Code designation for Abiraterone.
CB 7630 [as acetate]. Code designation for Abiraterone.
CB 10615. Code designation for Nifurmazole.
CB 11380. Code designation for Nifurizone.
CB 12592. Code designation for Subendazole.
CB-30038. Code designation for Minaprine.
CC-5013. Code designation for Lenalidomide.
CCA. Code designation for Lobenzarit Sodium.
CCD 1042. Code designation for Ganaxolone.
CCI-779. Code designation for Temsirolimus.
CCI 4725. Code designation for Clobetasol Propionate.
CCI 5537. Code designation for Clobetasone Butyrate.
C.C.I. 12923. Code designation for Minaxolone.
CCI 15641. Code designation for Cefuroxime Axetil.
CCI 18773. Code designation for Cloticasone Propionate.
CCI 18781. Code designation for Fluticasone Propionate.
CCI 23628. Code designation for Cefuroxime Pivoxetil.
CCNU. Code designation for Lomustine.
CCRG-81045. Code designation for Temozolomide.
CD 271. Code designation for Adapalene.
CDC-501. Code designation for Lenalidomide.
CDDD 1815. Code designation for Alprenoxime Hydrochloride.
CDDD 2803. Code designation for Adaprolol Maleate.
CDDD 3602. Code designation for Tematropium Methylsulfate.
CDDD 5604. Code designation for Loteprednol Etabonate.
CDP571. Code designation for Senlizumab.
CDP-771. Code designation for Gemtuzumab Ozogamicin.
CDP870. Code designation for Certolizumab Pegol.
CE-10. Code designation for Synthetic Conjugated Estrogens, B.
CEN 000029. Code designation for Priliximab.
CEP-151. Code designation for Mecasermin.
CEP-701. Code designation for Lestaurtinib.
CEP 1538. Code designation for Modafinil.
CEP-10953. Code designation for Armodafinil.
CEPH [as hydrochloride]. Code designation for Todralazine.
CERM 730. Code designation for Amoproxan.
CERM 1978. Code designation for Bepridil Hydrochloride.
CERM 10202. Code designation for Vedaprofen.
CG 201. Code designation for Bevonium Metilsulfate.
CG-315E. Code designation for Tramadol Hydrochloride.
CG5503 (base). Code designation for Tapentadol.
CG53135-05. Code designation for Velafermin.
CGA 18809. Code designation for Azamethiphos.
CGA-23654. Code designation for Nitroscanate.
CGA 72662. Code designation for Cyromazine.
CGP 2175C. Code designation for Metoprolol Fumarate.
CGP-2175E. Code designation for Metoprolol Tartrate.
CGP-7174/E. Code designation for Cefsulodin Sodium.
CGP 7760B. Code designation for Prenalterol Hydrochloride.
CGP 9000. Code designation for Cefroxadine.
CGP-14221/E. Code designation for Cefotiam Hydrochloride.
CGP-14,458. Code designation for Halobetasol Propionate.
CGP 21690E. Code designation for Oxiracetam.
CGP 23339AE. Code designation for Pamidronate Disodium.
CGP 25827A. Code designation for Formoterol Fumarate.
CGP 30694. Code designation for Edatrexate.
CGP 32349. Code designation for Formestane.
CGP 33101. Code designation for Rufinamide.
CGP 39393. Code designation for Desirudin.
CGP 41251. Code designation for Midostaurin.
CGP 42446. Code designation for Zoledronic Acid.
CGP 42446A. Code designation for Zoledronate Disodium.
CGP 42446B. Code designation for Zoledronate Trisodium.
CGP 45840B. Code designation for Diclofenac Potassium.
CGP 48933. Code designation for Valsartan.
CGS 5391B (anhydrous). Code designation for Enolicam Sodium.
CGS 7135A. Code designation for Azaloxan Fumarate.
CGS 7525A. Code designation for Aptazapine Maleate.
CGS 10078B. Code designation for Bendacalol Mesylate.
CGS 10746B. Code designation for Pentiapine Maleate.
CGS 10787D. Code designation for Prinomide Tromethamine.
CGS 13080. Code designation for Pirmagrel.
CGS 13429A. Code designation for Batelapine Maleate.
CGS 13945. Code designation for Pentopril.
CGS 14824A HCl. Code designation for Benazepril Hydrochloride.
CGS 14831. Code designation for Benazeprilat.
CGS 15040A. Code designation for Serazapine Hydrochloride.
CGS 15855A. Code designation for Isomolpan Hydrochloride.
CGS 16617. Code designation for Libenzapril.
CGS 16949A. Code designation for Fadrozole Hydrochloride.
CGS 18416A. Code designation for Zoniclezole Hydrochloride.
CGS 19755. Code designation for Selfotel.
CGS 20267. Code designation for Letrozole.
CGS 25019C. Code designation for Moxilubant Maleate.
CGS 26214. Code designation for Axitirome.
CGT003. Code designation for Edifoligide Sodium.
CH 3565. Code designation for Triclosan.
CH690001. Code designation for Tetronasin Sodium.
CHP. Code designation for Chlorhexidine Phosphanilate.
CHX-100. Code designation for Masoprocol.
CHX 3673. Code designation for Amlexanox.
CI-100. Code designation for Acetosulfone Sodium.
CI-107. Code designation for Argipressin Tannate.
CI-301. Code designation for Bialamicol Hydrochloride.
CI-336. Code designation for Carbocloral.
CI-366. Code designation for Ethosuximide.
CI-379. Code designation for Benzilonium Bromide.
CI-395. Code designation for Phencyclidine Hydrochloride.
CI 403A. Code designation for Pararosaniline Pamoate.
CI-406. Code designation for Oxymetholone.
CI-416. Code designation for Triclofenol Piperazine.
CI-419. Code designation for Fenimide.
CI 427. Code designation for Prodilidine Hydrochloride.
CI-433. Code designation for Clamoxyquin Hydrochloride.
CI 440. Code designation for Flufenamic Acid.
CI-456. Code designation for Diapamide.
CI-473. Code designation for Mefenamic Acid.
CI-501. Code designation for Cycloguanil Pamoate.
CI-515. Code designation for Guanoxyfen Sulfate.
CI-546. Code designation for Alipamide.
CI 556. Code designation for Acedapsone.
CI-572. Code designation for Profadol Hydrochloride.
CI-581. Code designation for Ketamine Hydrochloride.
CI-583. Code designation for Meclofenamic Acid.
CI-633. Code designation for Clioxanide.
CI-634. Code designation for Tiletamine Hydrochloride.
CI-636. Code designation for Sulfacytine.
CI-642. Code designation for Butirosin Sulfate.

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CI 673. Code designation for Vidarabine.
CI-686.HCl. Code designation for Trebenzomine Hydrochloride.
CI-705. Code designation for Methaqualone.
CI-716. Code designation for Zolazepam Hydrochloride.
CI-718. Code designation for Bentazepam.
CI-719. Code designation for Gemfibrozil.
CI-720. Code designation for Gemcadiol.
CI-781. Code designation for Zometapine.
CI 787. Code designation for Tioperidone Hydrochloride.
CI-825. Code designation for Pentostatin.
CI-874. Code designation for Indeloxazine Hydrochloride.
CI-879. Code designation for Pramiracetam Hydrochloride.
CI-879 [sulfate]. Code designation for Pramiracetam Sulfate.
CI-880. Code designation for Amsacrine.
CI-881. Code designation for Ametantrone Acetate.
CI-882. Code designation for Sparfosate Sodium.
CI-888. Code designation for Procaterol Hydrochloride.
CI-897. Code designation for Tebuquine.
CI-898. Code designation for Trimetrexate.
CI-904. Code designation for Diaziquone.
CI-906. Code designation for Quinapril Hydrochloride.
CI-907. Code designation for Indolapril Hydrochloride.
CI-908. Code designation for Dezaguanine.
CI-908 mesylate. Code designation for Dezaguanine Mesylate.
CI-909. Code designation for Tiazofurin.
CI-911. Code designation for Rolziracetam.
CI-912. Code designation for Zonisamide.
CI-914. Code designation for Imazodan Hydrochloride.
CI-919. Code designation for Enoxacin.
CI-920. Code designation for Fostriecin Sodium.
CI-921. Code designation for Asulacrine.
CI 925. Code designation for Moexipril Hydrochloride.
CI-928. Code designation for Quinaprilat.
CI-942. Code designation for Piroxantrone Hydrochloride.
CI-945. Code designation for Gabapentin.
CI-946. Code designation for Ralitoline.
CI-958. Code designation for Ledoxantrone Trihydrochloride.
CI-958. Code designation for Sedoxantrone Trihydrochloride.
CI-960 HCl. Code designation for Clinafloxacin Hydrochloride.
CI-970. Code designation for Tacrine Hydrochloride.
CI-977. Code designation for Enadoline Hydrochloride.
CI-978. Code designation for Sparfloxacin.
CI-979. Code designation for Milameline Hydrochloride.
CI-980. Code designation for Mivobulin Isethionate.
CI-981. Code designation for Atorvastatin Calcium.
CI-982. Code designation for Fosphenytoin Sodium.
CI-983. Code designation for Cefdinir.
CI-991. Code designation for Troglitazone.
CI-994. Code designation for Tacedinaline.
CI-1003. Code designation for Suramin Hexasodium.
CI-1004. Code designation for Darbufelone Mesylate.
CI-1008. Code designation for Pregabalin.
CI-1011. Code designation for Avasimibe.
CI-1014. Code designation for Zenarestat.
CI-1019. Code designation for Igmesine Hydrochloride.
CI-1025. Code designation for Conivaptan Hydrochloride.
CI-1027. Code designation for Gemcabene Calcium.
CI-1033. Code designation for Canertinib Dihydrochloride.
CI-1034. Code designation for Fandosentan Potassium.
CI-1041. Code designation for Besonprodil.
CI-1042. Code designation for Lontucirev (Replicating Adenovirus).
CI-9148. Code designation for Cysteamine Hydrochloride.
CIBA 1906. Code designation for Thiambutosine.
CJ-11, 974. Code designation for Ezlopitant.
CJ 91B. Code designation for Olsalazine Sodium.
CJ-11,972. Code designation for Maropitant Citrate.
CK-0383. Code designation for Verofylline.
CK-0569 [as the base]. Code designation for Ipexidine Mesylate.
CK-1752A. Code designation for Sematilide Hydrochloride.
CK0238273. Code designation for Ispinesib Mesylate.
CKD-602. Code designation for Belotecan Hydrochloride.
CL09. Code designation for Icometasone Enbutate.
Cl 337. Code designation for Azaserine.
CL 369. Code designation for Ketamine Hydrochloride.
CL 399. Code designation for Tiletamine Hydrochloride.
Cl-583.Na salt. Code designation for Meclofenamate Sodium.
CL-639C. Code designation for Dioxadrol Hydrochloride.
Cl-661. Code designation for Oxiramide.
Cl-683. Code designation for Ripazepam.
Cl-775. Code designation for Bevantolol Hydrochloride.
Cl-808. Code designation for Vidarabine Phosphate.
Cl-808 sodium. Code designation for Vidarabine Sodium Phosphate.
Cl-845. Code designation for Pirmenol Hydrochloride.
CL-867. Code designation for Piridicillin Sodium.
Cl-871. Code designation for Piracetam.
CL-911C. Code designation for Dexoxadrol Hydrochloride.
CL-912C. Code designation for Levoxadrol Hydrochloride.
CL-1388R. Code designation for Guanadrel Sulfate.
CL-1848C. Code designation for Etoxadrol Hydrochloride.
CL 2422. Code designation for Guancydine.
CL 5,279. Code designation for Nithiamide.
CL 10304. Code designation for Aminocaproic Acid.
CL 12,625. Code designation for Natamycin.
CL 13,900. Code designation for Puromycin.
CL 14377. Code designation for Methotrexate.
CL 16,536. Code designation for Puromycin Hydrochloride.
CL 22415. Code designation for Demecycline.
CL 25477. Code designation for Azetepa.
CL 26193. Code designation for Simtrazene.
CL 27,071. Code designation for Descinolone Acetonide.
CL 34433. Code designation for Triamcinolone Hexacetonide.
CL 34699. Code designation for Amcinonide.
CL 36467. Code designation for Methotrimeprazine.
CL 39743. Code designation for Methotrimeprazine.
CL 39808. Code designation for Thozalinone.
CL 40881. Code designation for Ethambutol Hydrochloride.
CL 48156. Code designation for Imidoline Hydrochloride.
CL 53415. Code designation for Cyproximide.
CL 54131. Code designation for Piperamide Maleate.
CL 54998. Code designation for Brocresine.
CL 59112. Code designation for Roletamide.
CL 61965. Code designation for Triamcinolone Acetonide Sodium Phosphate.
CL 62,362. Code designation for Loxapine.
Cl-64,976. Code designation for Zilantel.
CL 65205. Code designation for Boxidine.
CL 65336. Code designation for Tranexamic Acid.
CL 65,562. Code designation for Triflocin.
CL 67,772. Code designation for Amoxapine.
CL 71563. Code designation for Loxapine Succinate.
CL 81,587. Code designation for Avoparcin.
CL 82,204. Code designation for Fenbufen.
CL 83,544. Code designation for Felbinac.
CL 84,633. Code designation for Nimidane.
CL 88,893. Code designation for Clazolimine.
CL 90,748. Code designation for Azolimine.
CL 98984. Code designation for Cinodine Hydrochloride.
CL 106359. Code designation for Triamcinolone Acetonide Sodium Phosphate.
CL 108,756. Code designation for Brocresine.
CL 112,302. Code designation for Buprenorphine Hydrochloride.
CL 115,347. Code designation for Viprostol.
CL 118,532. Code designation for Triptorelin.
CL 184,116. Code designation for Porfimer Sodium.

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CL 184,824. Code designation for Alovudine.
CL 186,815. Code designation for Biapenem.
CL 203,821. Code designation for Cetaben Sodium.
CL 205925. Code designation for Iprocinodine Hydrochloride.
CL 206,214. Code designation for Butamisole Hydrochloride.
CL 206,576. Code designation for Sulbenox.
CL 206,797. Code designation for Cypothrin.
CL 216,942. Code designation for Bisantrene Hydrochloride.
CL 217,658. Code designation for Imcarbofos.
CL 220,075. Code designation for Bicifadine Hydrochloride.
CL 227,193. Code designation for Piperacillin Sodium.
CL 232,315. Code designation for Mitoxantrone Hydrochloride.
CL 273,547. Code designation for Ocinaplon.
CL 273,703. Code designation for Maduramicin.
CL 274,471. Code designation for Colestolone.
CL 284,635. Code designation for Cefixime.
CL 284,846. Code designation for Zaleplon.
CL 286,558. Code designation for Zeniplatin.
CL 287,088. Code designation for Nemadectin.
CL 287,110. Code designation for Enloplatin.
CL 287,389. Code designation for Nilvadipine.
CL 291,894. Code designation for Somagrebove.
CL 297,939. Code designation for Bisoprolol.
CL 297,939. Code designation for Bisoprolol Fumarate.
CL 298,741. Code designation for Tazobactam.
CL 301,423. Code designation for Moxidectin.
CL 307,579. Code designation for Tazobactam Sodium.
CL 307,782. Code designation for Levoleucovorin Calcium.
CL 318,952. Code designation for Verteporfin.
CLY-503. Code designation for Simfibrate.
CM 31-916. Code designation for Ceftiofur Sodium.
CMA-676. Code designation for Gemtuzumab Ozogamicin.
CMC-544. Code designation for Inotuzumab Ozogamicin.
CN-1883. Code designation for Acedapsone.
CN-5834-5931B. Code designation for Triclofenol Piperazine.
CN-10,395. Code designation for Ethosuximide.
CN-14,329-23A. Code designation for Cycloguanil Pamoate.
CN-15,573-23A. Code designation for Pararosaniline Pamoate.
CN-15,757. Code designation for Azaserine.
CN-16146. Code designation for Carbocloral.
CN-17,900-2B. Code designation for Clamoxyquin Hydrochloride.
CN-20,172-3. Code designation for Benzilonium Bromide.
CN-25,253-2. Code designation for Phencyclidine Hydrochloride.
CN-27,554. Code designation for Flufenamic Acid.
CN-34,799-5A. Code designation for Guanoxyfen Sulfate.
CN-35355. Code designation for Mefenamic Acid.
CN-36,337. Code designation for Diapamide.
CN-38,474. Code designation for Alipamide.
CN 38703. Code designation for Methaqualone.
CN-52,372-2. Code designation for Ketamine Hydrochloride.
CN-54521-2. Code designation for Tiletamine Hydrochloride.
CN 59,567. Code designation for Clioxanide.
CNS 1102. Code designation for Aptiganel Hydrochloride.
CNTO 148. Code designation for Golimumab.
CO 405. Code designation for Butidrine.
Co 200461. Code designation for Besonprodil.
Code 7227. Code designation for Ferumoxtran-10.
Code 7228. Code designation for Ferumoxytol.
CO-I. Code designation for Nadide.
COL-3. Code designation for Incyclinide.
Compound 68-198. Code designation for Diamfenetide.
Compound 469. Code designation for Isoflurane.
Compound 497. Code designation for Dieldrin.
Compound 904. Code designation for Alexidine.
Compound 24266. Code designation for Pentetate Calcium Trisodium Yb 169.
Compound 42339. Code designation for Acronine.
Compound 49510. Code designation for Paricalcitol.
Compound 53616. Code designation for Frentizole.
Compound 56063. Code designation for Melizame.
Compound 57926. Code designation for Sinefungin.
Compound 79891. Code designation for Narasin.
Compound 81929. Code designation for Dobutamine.
Compound 83405. Code designation for Cefamandole.
Compound 83846. Code designation for Aprindine Hydrochloride.
Compound 85287. Code designation for Nibroxane.
Compound 89218. Code designation for Nisoxetine.
Compound 90459. Code designation for Benoxaprofen.
Compound 90606. Code designation for Isamoxole.
Compound 93819. Code designation for Fluretofen.
Compound 99170. Code designation for Aprindine.
Compound 99638. Code designation for Cefaclor.
Compound 109168. Code designation for Nifluridide.
Compound 112531. Code designation for Vindesine.
Compound 113878. Code designation for Ciprefadol Succinate.
Compound 113935. Code designation for Pentomone.
Compound 122587. Code designation for Drobuline.
Compound 133314. Code designation for Trioxifene Mesylate.
Compound LY 131126. Code designation for Butopamine.
Compound S. Code designation for Zidovudine.
Continuous Curve-CAB Contact Lens. Code designation for Porofocon B.
COP-1. Code designation for Glatiramer Acetate.
Copolymer-1. Code designation for Glatiramer Acetate.
Corus1020. Code designation for Aztreonam Lysine.
COX-189. Code designation for Lumiracoxib.
CP-15-639-2. Code designation for Carbenicillin Disodium.
CP-88, 059-27. Code designation for Ziprasidone Mesylate.
CP-0127. Code designation for Deltibant.
CP 172 AP. Code designation for Clopirac.
CP-556S. Code designation for Suloctidil.
CP 1044 J3. Code designation for Bufexamac.
CP 1552 S. Code designation for Milacemide Hydrochloride.
CP-10,188. Code designation for Fenclonine.
CP-10,303-8. Code designation for Quinterenol Sulfate.
CP-10,423-16. Code designation for Pyrantel Pamoate.
CP-10,423-18. Code designation for Pyrantel Tartrate.
CP-11,332-1. Code designation for Quinazosin Hydrochloride.
CP-12,009-18. Code designation for Morantel Tartrate.
CP-12,252-1. Code designation for Thiothixene Hydrochloride.
CP-12,299-1. Code designation for Prazosin Hydrochloride.
CP-12,521-1. Code designation for Piquizil Hydrochloride.
CP-12,574. Code designation for Tinidazole.
CP-13,608. Code designation for Tesicam.
CP-14,185-1. Code designation for Hoquizil Hydrochloride.
CP-14,368-1. Code designation for Lometraline Hydrochloride.
CP-14,445-16. Code designation for Oxantel Pamoate.
CP-15,464-2. Code designation for Carbenicillin Indanyl Sodium.
CP-15,467-61. Code designation for Lithium Carbonate.
CP-15,973. Code designation for Sudoxicam.
CP-16,171. Code designation for Piroxicam.
CP-16,171-85. Code designation for Piroxicam Olamine.
CP-16,533-1. Code designation for Verapamil.
CP-18,524. Code designation for Tibric Acid.
CP-19,106-1. Code designation for Trimazosin Hydrochloride.
CP-20,961. Code designation for Avridine.
CP-22,341. Code designation for Temodox.
CP-22,665. Code designation for Flumizole.
CP-24,314-1. Code designation for Pirbuterol Hydrochloride.
CP-24,314-14. Code designation for Pirbuterol Acetate.
CP-24,441-1. Code designation for Tametraline Hydrochloride.
CP-24,877. Code designation for Drinidene.
CP-25,673. Code designation for Tiazuril.
CP-26,154. Code designation for Tolimidone.
CP-27,634. Code designation for Gliamilide.

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CP-28,720. Code designation for Glipizide.
CP-31,081. Code designation for Polydextrose.
CP-32,387. Code designation for Pirolate.
CP-33,994-2. Code designation for Pirbenicillin Sodium.
CP-34,089. Code designation for Sulprostone.
CP-36,584. Code designation for Flutroline.
CP-38,754. Code designation for Plauracin.
CP-44,001-1. Code designation for Nantradol Hydrochloride.
CP-45,634. Code designation for Sorbinil.
CP-45,899-2. Code designation for Sulbactam Sodium.
CP-45,899-99. Code designation for Sulbactam Benzathine.
CP-47,904. Code designation for Sulbactam Pivoxil.
CP-48,810-27. Code designation for Fanetizole Mesylate.
CP-48,867-9. Code designation for Ristianol Phosphate.
CP-49,952. Code designation for Sultamicillin.
CP-50,556-1. Code designation for Levonantradol Hydrochloride.
Cp-51,974-1. Code designation for Sertraline Hydrochloride.
CP-52,640-2. Code designation for Cefoperazone Sodium.
CP-54,802. Code designation for Alitame.
CP-57,361-01. Code designation for Zaltidine Hydrochloride.
CP-62,993. Code designation for Azithromycin.
CP-65703. Code designation for Ampiroxicam.
CP-66,248. Code designation for Tenidap.
CP-66,248-2. Code designation for Tenidap Sodium.
CP-70,429. Code designation for Sulopenem.
CP-70,490-09. Code designation for Enazadrem Phosphate.
CP-72,133. Code designation for Ilonidap.
CP-72,467-2. Code designation for Englitazone Sodium.
CP-73,049. Code designation for Binfloxacin.
CP-73,850. Code designation for Zopolrestat.
CP-76,136-27. Code designation for Danofloxacin Mesylate.
CP-80,794. Code designation for Terlakiren.
CP-86,325-2. Code designation for Darglitazone Sodium.
CP-88,059-1. Code designation for Ziprasidone Hydrochloride.
CP-88,818. Code designation for Tiqueside.
CP-93,393-1. Code designation for Sunepitron Hydrochloride.
CP-99,219-27. Code designation for Trovafloxacin Mesylate.
CP-101,606-27. Code designation for Traxoprodil Mesylate.
CP-116,517-27. Code designation for Alatrofloxacin Mesylate.
CP-118,954-11. Code designation for Icopezil Maleate.
CP-148,623. Code designation for Pamaqueside.
CP-325,366. Code designation for Tofimilast.
CP-336,156-CB. Code designation for Lasofoxifene Tartrate.
CP-358,774-01. Code designation for Erlotinib Hydrochloride.
CP-368,296. Code designation for Ingliforib.
CP-424,391-18. Code designation for Capromorelin Tartrate.
CP-448,187-01. Code designation for Elzasonan Hydrochloride.
CP-448,187-10. Code designation for Elzasonan Citrate.
CP-472,295. Code designation for Tulathromycin.
CP-526,555-18. Code designation for Varenicline Tartrate.
CP-529,414. Code designation for Torcetrapib.
CP-547,272. Code designation for Tulathromycin.
CP-675,206. Code designation for Ticilimumab.
CP-742,033. Code designation for Dirlotapide.
CPC-111. Code designation for Fosfructose Trisodium.
CPC-211. Code designation for Sodium Dichloroacetate.
Cpd. 5411. Code designation for Iopentol.
Cpd 109514. Code designation for Nabilone.
CR/662. Code designation for Tipepidine.
CRL 40476. Code designation for Modafinil.
CS-045. Code designation for Troglitazone.
CS-151. Code designation for Crofilcon A.
CS-514. Code designation for Pravastatin Sodium.
CS-622. Code designation for Temocapril Hydrochloride.
CS-807. Code designation for Cefpodoxime Proxetil.
CS-866. Code designation for Olmesartan Medoxomil.
CSAG-144. Code designation for Mebeverine Hydrochloride.
CT 1501R. Code designation for Lisofylline.
CT-2103. Code designation for Paclitaxel Poliglumex.
CT 53518. Code designation for Tandutinib.
CTR 6110. Code designation for Nitrodan.
CTX. Code designation for Lornoxicam.
CV-11974. Code designation for Candesartan.
CV 57533. Code designation for Xenyhexenic Acid.
CV 58903. Code designation for Xenazoic Acid.
CVT-124. Code designation for Naxifylline.
CVT-303. Code designation for Ranolazine.
CVT-510. Code designation for Tecadenoson.
CVT-3146. Code designation for Regadenoson.
CX691. Code designation for Farampator.
CY 39. Code designation for Psilocybine.
CY-116. Code designation for Aminocaproic Acid.
CY 153. Code designation for Acexamic Acid.
CY 216. Code designation for Nadroparin Calcium.
CYT-103^{111}In. Code designation for Indium In 111 Satumomab Pendetide.
CYT-356. Code designation for Capromab Pendetide.
CYT-424. Code designation for Samarium Sm 153 Lexidronam Pentasodium.
D2E7. Code designation for Adalimumab.
d4T. Code designation for Stavudine.
D 47. Code designation for Sulbentine.
D 00079. Code designation for Anoxomer.
D 237. Code designation for Cloforex.
D-254. Code designation for Pipazethate.
D-365. Code designation for Verapamil.
D-775. Code designation for Homofenazine.
D-1262. Code designation for Cloxypendyl.
D-1593. Code designation for Diapamide.
D-1721. Code designation for Alipamide.
D-1959.HCl. Code designation for Reproterol Hydrochloride.
D2083. Code designation for Desonide.
D2163. Code designation for Rebimastat.
D 4028. Code designation for Enprofylline.
D 7093. Code designation for Mesna.
D-9998. Code designation for Flupirtine Maleate.
D-18506. Code designation for Miltefosine.
D-20761. Code designation for Cetrorelix Acetate.
D-23129. Code designation for Retigabine.
DA-398. Code designation for Epirizole.
DA 688. Code designation for Gefarnate.
DA-708. Code designation for Teflurane.
DA-808. Code designation for Nafcaproic Acid.
DA-893. Code designation for Roflurane.
DA-914. Code designation for Nafiverine.
DA-992. Code designation for Naftypramide.
DA 1773. Code designation for Sodium Picosulfate.
DA 2370. Code designation for Feprazone.
DAB$_{389}$IL2. Code designation for Denileukin Diftitox.
DAB-452. Code designation for Aplindore Fumarate.
DAC. Code designation for Decitabine.
DADDS. Code designation for Acedapsone.
(–)-DAPD. Code designation for Amdoxovir.
DAPD. Code designation for Amdoxovir.
D.A.T. Code designation for Acetiamine.
DATC. Code designation for Tiocarlide.
DAU6215CL. Code designation for Itasetron.
DB289. Code designation for Pafuramidine Maleate.
DBM. Code designation for Mitobronitol.
DBV. Code designation for Buformin.
DCA. Code designation for Sodium Dichloroacetate.
DCH 21 [as sodium salt]. Code designation for Exiproben.
DCLHb. Code designation for Hemoglobin Crosfumaril.
Cis-DDP. Code designation for Cisplatin.
DDVP. Code designation for Dichlorvos.
DETF. Code designation for Trichlorfon.

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DF 118. Code designation for Dihydrocodeine Bitartrate.
DF 1681Y. Code designation for Reparixin.
DG-031. Code designation for Veliflapon.
DH-524. Code designation for Fenmetozole Hydrochloride.
DH-581. Code designation for Probucol.
DIC. Code designation for Dacarbazine.
DIM-SA. Code designation for Succimer.
DJN 608. Code designation for Nateglinide.
DK-7419. Code designation for Argatroban.
DL 152. Code designation for Bietaserpine.
DL-164. Code designation for Tiodonium Chloride.
DL-588. Code designation for Napactadine Hydrochloride.
DL-8280. Code designation for Ofloxacin.
dl HM-PAO. Code designation for Exametazime.
DMI. Code designation for Desipramine Hydrochloride.
DMO. Code designation for Dimethadione.
DMP 115. Code designation for Perflutren.
DMP 754. Code designation for Roxifiban Acetate.
DMP 840. Code designation for Bisnafide Dimesylate.
DMSA. Code designation for Succimer.
DMSC. Code designation for Doxycycline Fosfatex.
DMSO. Code designation for Dimethyl Sulfoxide.
DN-2327. Code designation for Pazinaclone.
DO6. Code designation for Lexipafant.
DOTA. Code designation for Tetraxetan.
DP178. Code designation for Enfuvirtide.
DPC-817. Code designation for Dexelvucitabine.
DPDP. Code designation for Fodipir.
DPE. Code designation for Dipivefrin.
DPN. Code designation for Nadide.
DPPE. Code designation for Tesmilifene Hydrochloride.
DR-3355. Code designation for Levofloxacin.
DS 103-282. Code designation for Tizanidine Hydrochloride.
DS-4152. Code designation for Tecogalan Sodium.
DSB*2NMG. Code designation for Bevirimat Dimeglumine.
DT-3. Code designation for Detrothyronine.
DT-327. Code designation for Clopamide.
DTI-0009. Code designation for Selodenoson.
DTIC. Code designation for Dacarbazine.
DTPA. Code designation for Pentetic Acid.
DTPA-SMS. Code designation for Pentetreotide.
D-Trp LHRH-PEA. Code designation for Deslorelin.
DU-6859a. Code designation for Sitafloxacin.
DU-21220. Code designation for Ritodrine.
DU-21445. Code designation for Tiprenolol Hydrochloride.
DU 22550 [as sulfate]. Code designation for Caproxamine.
DU23000. Code designation for Fluvoxamine Maleate.
DU-23187. Code designation for Quincarbate.
DU123265. Code designation for Cilansetron Hydrochloride.
DU127090. Code designation for Bifeprunox Mesylate.
DuP 128. Code designation for Lecimibide.
DuP 753. Code designation for Losartan Potassium.
Dup 785. Code designation for Brequinar Sodium.
DuP 921. Code designation for Sibopirdine.
DUP 937. Code designation for Teloxantrone Hydrochloride.
DUP 941. Code designation for Losoxantrone Hydrochloride.
DuP 996. Code designation for Linopirdine.
DV-1006. Code designation for Cetraxate Hydrochloride.
DW-61. Code designation for Flavoxate Hydrochloride.
DW-62. Code designation for Dimefline Hydrochloride.
DW 75. Code designation for Norleusactide.
DX-88. Code designation for Ecallantide.
DX-890. Code designation for Depelestat.
DX-8951f. Code designation for Exatecan Mesylate.
DyDTPA-BMA. Code designation for Sprodiamide.
E3A. Code designation for Estradiol Acetate.
E 39. Code designation for Inproquone.
E-52. Code designation for Pentafilcon A.
E-106-E [as cyclamate]. Code designation for Furfenorex.
E 141. Code designation for Ethamsylate.
E414. Code designation for Salcaprozate Sodium.
E-614. Code designation for Tripamide.
E-0659. Code designation for Azelastine Hydrochloride.
E-1000. Code designation for Amiloxate.
E2020. Code designation for Donepezil Hydrochloride.
E2080. Code designation for Rufinamide.
E-2663. Code designation for Bentiromide.
E-3810. Code designation for Rabeprazole Sodium.
E5564. Code designation for Eritoran Tetrasodium.
E7070. Code designation for Indisulam.
E 9002. Code designation for Naftalofos.
EA-166. Code designation for Guanoxyfen Sulfate.
EAA-090. Code designation for Perzinfotel.
EACA. Code designation for Aminocaproic Acid.
EC 3.1.6.13. Code designation for Idursulfase.
EC 3.2.1.22. Code designation for Agalsidase Alfa.
EDU. Code designation for Edoxudine.
EE_3ME. Code designation for Mestranol.
EF9. Code designation for Temoporfin.
EGTA. Code designation for Egtazic Acid.
EGYT 201. Code designation for Bencyclane Fumarate.
EHB 776. Code designation for Foscarnet Sodium.
EKB-569. Code designation for Pelitinib.
EL349. Code designation for Somidobove.
EL737. Code designation for Ractopamine Hydrochloride.
EL-857. Code designation for Apramycin.
EL870. Code designation for Tilmicosin.
EL-970. Code designation for Fampridine.
EL-974. Code designation for Ticarbodine.
ELD 950. Code designation for Eledoisin.
EM574. Code designation for Idremcinal.
EMBAY 8440. Code designation for Praziquantel.
EMD 15 700. Code designation for Nitrefazole.
EMD 33 512. Code designation for Bisoprolol.
EMD 9806. Code designation for Pramiverine.
EMD 19698 [as hydrogen maleate]. Code designation for Perazole.
EMD 128130. Code designation for Sarizotan Hydrochloride.
EMD 273066. Code designation for Tucotuzumab Celmoleukin.
EMD 390920. Code designation for Pruvanserin.
EN-141. Code designation for Josamycin.
EN-313. Code designation for Moricizine.
EN-970. Code designation for Fluquazone.
EN-1010. Code designation for Pyrrocaine.
EN-1620A. Code designation for Nalmexone Hydrochloride.
EN-1639A. Code designation for Naltrexone Hydrochloride.
EN-1639A [as hydrochloride]. Code designation for Naltrexone.
EN-1661L. Code designation for Bisobrin Lactate.
EN-1733A. Code designation for Molindone Hydrochloride.
EN-2234A. Code designation for Nalbuphine Hydrochloride.
EN-15304. Code designation for Naloxone Hydrochloride.
EN 137774. Code designation for Ramatroban.
ENA-713. Code designation for Rivastigmine.
ENT-20852. Code designation for Butonate.
ENT-23969. Code designation for Carbaril.
ENT-25567. Code designation for Naftalofos.
ENT 29,106. Code designation for Nimidane.
EO9. Code designation for Apaziquone.
EPO. Code designation for Epoetin Alfa.
EPOCH. Code designation for Epoetin Beta.
ERB-041. Code designation for Prinaberel.
ERL 080. Code designation for Mycophenolate Sodium.
ES 304. Code designation for Nicofuranose.
estradiol-3-acetate. Code designation for Estradiol Acetate.
ET-394. Code designation for Tribromsalan.
ET-495. Code designation for Piribedil.

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ET-743. Code designation for Trabectedin.
ETTN. Code designation for Propatyl Nitrate.
EU-1063. Code designation for Proquinolate.
EU-1085. Code designation for Leniquinsin.
EU-1093. Code designation for Buquinolate.
EU-1806. Code designation for Nafronyl Oxalate.
EU-2826. Code designation for Benurestat.
EU-2972. Code designation for Nolinium Bromide.
EU-3120. Code designation for Acodazole Hydrochloride.
EU-3325. Code designation for Triafungin.
EU-3421. Code designation for Oxifungin Hydrochloride.
EU-4093. Code designation for Azumolene Sodium.
EU-4200. Code designation for Piribedil.
EU-4534. Code designation for Flurofamide.
EU-4584. Code designation for Tolfamide.
EU-4891. Code designation for Diacetolol Hydrochloride.
EU-4906. Code designation for Sitogluside.
EU-5306. Code designation for Pefloxacin.
EUDR. Code designation for Edoxudine.
EV2-7. Code designation for Sevirumab.
EX 10-029-C. Code designation for Elantrine.
EX 10-781. Code designation for Metizoline Hydrochloride.
EX 12-095. Code designation for Eterobarb.
EX 4355. Code designation for Desipramine Hydrochloride.
EX 4810. Code designation for Ambuside.
Ex 4883. Code designation for Rolicyprine.
EXP-105-1. Code designation for Amantadine Hydrochloride.
EXP 126. Code designation for Rimantadine Hydrochloride.
EXP 338. Code designation for Midaflur.
EXP 999. Code designation for Metopimazine.
EYE001. Code designation for Pegaptanib Sodium.
EZ-246. Code designation for Pegamotecan.
F-368. Code designation for Dantrolene.
F-413. Code designation for Clodanolene.
F-440. Code designation for Dantrolene Sodium.
F-605 (as the sodium). Code designation for Clodanolene.
F-691. Code designation for Furodazole.
F-776. Code designation for Orpanoxin.
F-853. Code designation for Nitrafudam Hydrochloride.
F 1500. Code designation for Succisulfone.
F 1983. Code designation for Pyrovalerone Hydrochloride.
F 6066. Code designation for Cyclofenil.
F28249α. Code designation for Nemadectin.
Fa 402. Code designation for Fentonium Bromide.
FAT 70'884. Code designation for Bemotrizinol.
FAT 75'634. Code designation for Bisoctrizole.
FBA 1420. Code designation for Propanidid.
FBA 4059. Code designation for Brotianide.
FBB 4231. Code designation for Glisoxepide.
FBB 6896. Code designation for Clenpirin.
FC41-12 (Perflenapent/Perflisopent mixture). Code designation for Perflenapent.
FC41-12 (Perflenapent/Perflisopent mixture). Code designation for Perflisopent.
FC-1157a. Code designation for Toremifene Citrate.
Fc-1271. Code designation for Ospemifene.
FC-1271a. Code designation for Ospemifene.
FCE 20124. Code designation for Reboxetine Mesylate.
FCE 21336. Code designation for Cabergoline.
FCE24304. Code designation for Exemestane.
FCF 89. Code designation for Roquinimex.
F-ddA. Code designation for Lodenosine.
^{18}FDG. Code designation for Fludeoxyglucose F 18.
FER-1443. Code designation for Ticlatone.
FG 5111. Code designation for Melperone.
FG-10571. Code designation for Panadiplon.
FI 5852. Code designation for Oxabolone Cipionate.
F.I. 6146. Code designation for Buzepide Metiodide.
FI 6337. Code designation for Metergoline.
FI 6339 [as the base]. Code designation for Daunorubicin Hydrochloride.
F.I. 6426. Code designation for Stallimycin Hydrochloride.
F.I. 6654. Code designation for Caroxazone.
F.I. 6820. Code designation for Brofoxine.
FK 027. Code designation for Cefixime.
FK228. Code designation for Romidepsin.
FK 235. Code designation for Nilvadipine.
FK-366. Code designation for Zenarestat.
FK463. Code designation for Micafungin Sodium.
FK 482. Code designation for Cefdinir.
FK 506. Code designation for Tacrolimus.
FK 749. Code designation for Ceftizoxime Sodium.
FKS-508. Code designation for Cevimeline Hydrochloride.
FLA 731. Code designation for Remoxipride.
FLA 731(–). Code designation for Remoxipride Hydrochloride.
FMdC. Code designation for Tezacitabine.
FP-GP1. Code designation for Motexafin Gadolinium.
FPL.670. Code designation for Cromolyn Sodium.
FPL 12924AA. Code designation for Remacemide Hydrochloride.
FPL 58668KC. Code designation for Probicromil Calcium.
FPL 59002. Code designation for Nedocromil.
FPL 59002KC. Code designation for Nedocromil Calcium.
FPL 59002KP. Code designation for Nedocromil Sodium.
FPL 59360. Code designation for Minocromil.
FPL 60278. Code designation for Dopexamine.
FPL 60278AR. Code designation for Dopexamine Hydrochloride.
FP-LP1. Code designation for Motexafin Lutetium.
FR 13749. Code designation for Ceftizoxime Sodium.
FR 17027. Code designation for Cefixime.
FR-74366. Code designation for Zenarestat.
FR900506. Code designation for Tacrolimus.
FR901228. Code designation for Romidepsin.
FS069. Code designation for Perflutren.
FSH. Code designation for Menotropins.
(–)-FTC. Code designation for Emtricitabine.
FTC-(–). Code designation for Emtricitabine.
FTY720. Code designation for Fingolimod Hydrochloride.
FU-02. Code designation for Fumoxicillin.
FUDR. Code designation for Floxuridine.
FUT-175. Code designation for Nafamostat Mesylate.
FWH 399. Code designation for Troxonium Tosilate.
G-4. Code designation for Dichlorophen.
G-101, SCY-Er. Code designation for Erythromycin Salnacedin.
G-201,SCY. Code designation for Salnacedin.
G3139. Code designation for Oblimersen Sodium.
G-24480. Code designation for Dimpylate.
G-25178. Code designation for Prodeconium Bromide.
G-25766. Code designation for Clorindione.
G 26,872. Code designation for Phenbutazone Sodium Glycerate.
G 30320. Code designation for Clofazimine.
G-32883. Code designation for Carbamazepine.
G-33040. Code designation for Opipramol Hydrochloride.
G-33182. Code designation for Chlorthalidone.
G 34586. Code designation for Clomipramine Hydrochloride.
G-35020. Code designation for Desipramine Hydrochloride.
G 35259. Code designation for Ketipramine Fumarate.
G-704,650. Code designation for Alendronate Sodium.
gadolinium texaphyrin. Code designation for Motexafin Gadolinium.
GA-EPO. Code designation for Epoetin Delta.
GAP (Wyeth). Code designation for Rotigaptide.
GD0039. Code designation for Tridolgosir Hydrochloride.
Gd texaphyrin. Code designation for Motexafin Gadolinium.
GdDTPA-BMA. Code designation for Gadodiamide.
Gd-Tex. Code designation for Motexafin Gadolinium.
GEA 654. Code designation for Alaproclate.

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GER-11. Code designation for Pimagedine Hydrochloride.
GF 120918A. Code designation for Elacridar Hydrochloride.
GG-745. Code designation for Dutasteride.
GI 87084B. Code designation for Remifentanil Hydrochloride.
GI147211C. Code designation for Lurtotecan Dihydrochloride.
GI 198745. Code designation for Dutasteride.
GI262570X. Code designation for Farglitazar.
GM-611. Code designation for Mitemcinal Fumarate.
GMC 89-107. Code designation for Regramostim.
GM-CSF. Code designation for Regramostim.
GN1600. Code designation for Argatroban.
Go-560. Code designation for Febarbamate.
Go 919. Code designation for Piprozolin.
Go 1213. Code designation for Atolide.
Go 1733. Code designation for Suloxifen Oxalate.
Go 2782. Code designation for Iproxamine Hydrochloride.
Go 3026A. Code designation for Ciclafrine Hydrochloride.
GOE 3450. Code designation for Gabapentin.
GOE 5549. Code designation for Tacedinaline.
Goedecke 3282. Code designation for Ozolinone.
GP-1-110. Code designation for Acadesine.
GP-2-121-3. Code designation for Arbutamine Hydrochloride.
GP-121. Code designation for Phencyclidine Hydrochloride.
GP 31406. Code designation for Depramine.
GP 45840. Code designation for Diclofenac Sodium.
GP-47680. Code designation for Oxcarbazepine.
GP 51084. Code designation for Glibutimine.
GPA-878. Code designation for Metazamide.
GPI-200. Code designation for Iometopane I 123.
GR 2/234. Code designation for Alfaxalone.
GR 2/443 [as propionate]. Code designation for Doxibetasol.
GR 2/925. Code designation for Clobetasol Propionate.
GR 2/1214. Code designation for Clobetasone Butyrate.
GR 2/1574. Code designation for Alfadolone.
GR 412. Code designation for Dodeclonium Bromide.
GR 20263. Code designation for Ceftazidime.
GR 30921. Code designation for Mitoquidone.
GR 32191 [vapiprost]. Code designation for Vapiprost Hydrochloride.
GR 32191B. Code designation for Vapiprost Hydrochloride.
GR 33207. Code designation for Ovandrotone Albumin.
GR 33343 G. Code designation for Salmeterol Xinafoate.
GR 33343 X. Code designation for Salmeterol.
GR 38032F. Code designation for Ondansetron Hydrochloride.
GR 43175C. Code designation for Sumatriptan Succinate.
GR 43659X. Code designation for Lacidipine.
GR50360A. Code designation for Fluparoxan Hydrochloride.
GR 50692. Code designation for Cefempidone.
GR 53992B (GX 1296B). Code designation for Teludipine Hydrochloride.
GR 63178K. Code designation for Fosquidone.
GR 68755C. Code designation for Alosetron Hydrochloride.
GR 69153X. Code designation for Cefetecol.
GR 81225C. Code designation for Galdansetron Hydrochloride.
GR 81225X [as the base]. Code designation for Galdansetron Hydrochloride.
GR 85548A. Code designation for Naratriptan Hydrochloride.
GR 87442 N. Code designation for Lurosetron Mesylate.
GR92132X. Code designation for Troglitazone.
GR 109714X. Code designation for Lamivudine.
GR 114297A. Code designation for Picumeterol Fumarate.
GR 114297X [picumeterol]. Code designation for Picumeterol Fumarate.
GR 116526X. Code designation for Isotretinoin Anisatil.
GR 117289C. Code designation for Zolasartan.
GR 121167X. Code designation for Zanamivir.
GR 122311X. Code designation for Ranitidine Bismuth Citrate.
GR 138950C. Code designation for Saprisartan Potassium.
GR205171A. Code designation for Vofopitant Dihydrochloride.
GR215864. Code designation for Zoticasone.
GRT151 base. Code designation for Axomadol.
GS-95. Code designation for Thiethylperazine Maleate.
GS-0393. Code designation for Adefovir.
GS-0504. Code designation for Cidofovir.
GS-0840. Code designation for Adefovir Dipivoxil.
GS-1278. Code designation for Tenofovir.
GS-1339. Code designation for Dymanthine Hydrochloride.
GS 2147. Code designation for Sancycline.
GS-2876. Code designation for Methacycline.
GS-2989. Code designation for Meclocycline.
GS-3065. Code designation for Doxycycline.
GS-3159. Code designation for Carbenicillin Potassium.
GS-4331-05. Code designation for Tenofovir Disoproxil Fumarate.
GS-6244. Code designation for Carbadox.
GS-6742. Code designation for Sulfomyxin.
GS-7443. Code designation for Mequidox.
GT16-026A. Code designation for Sevelamer Hydrochloride.
GT31-104HB. Code designation for Colesevelam Hydrochloride.
GT56-252. Code designation for Deferitrin.
GT160-246. Code designation for Tolevamer Sodium.
GT267-004. Code designation for Tolevamer Potassium Sodium.
GT335-012. Code designation for Sevelamer Carbonate.
GT-2331. Code designation for Cipralisant Maleate.
GV 104326B. Code designation for Sanfetrinem Sodium.
GV 118819X. Code designation for Sanfetrinem Cilexetil.
GV 150526X. Code designation for Gavestinel.
GW64085X. Code designation for Brecanavir.
GW-80126. Code designation for Seprilose.
GW-280430A. Code designation for Gantacurium Chloride.
GW353162A. Code designation for Radafaxine Hydrochloride.
GW427353B. Code designation for Solabegron Hydrochloride.
GW 433908A. Code designation for Fosamprenavir Sodium.
GW 433908G. Code designation for Fosamprenavir Calcium.
GW572016F. Code designation for Lapatinib Ditosylate.
GW597588B. Code designation for Vestipitant Mesylate.
GW677954. Code designation for Sodelglitazar.
GW679769B. Code designation for Casopitant Mesylate.
GW685698X. Code designation for Fluticasone Furoate.
GW786034B. Code designation for Pazopanib Hydrochloride.
GW823093C. Code designation for Denagliptin Tosylate.
GW869682X. Code designation for Sergliflozin.
GW873140A. Code designation for Aplaviroc Hydrochloride.
^{2}H. Code designation for Deuterium Oxide.
H2G. Code designation for Omaciclovir.
h5G1.1. Code designation for Eculizumab.
h5G1.1 scFv. Code designation for Pexelizumab.
h5G1.1 scFv (CDR). Code designation for Pexelizumab.
h5G1.1VHC+h5G1.1VLC. Code designation for Eculizumab.
H 56/28. Code designation for Alprenolol Hydrochloride.
H65-RTA. Code designation for Zolimomab Aritox.
H 93/26 succinate. Code designation for Metoprolol Succinate.
H 102/09 Hydrochloride. Code designation for Zimeldine Hydrochloride.
H 104/08. Code designation for Pamatolol Sulfate.
H 133/22. Code designation for Prenalterol Hydrochloride.
H 154/82. Code designation for Felodipine.
H 168/68. Code designation for Omeprazole.
H 168/68 magnesium. Code designation for Omeprazole Magnesium.
H 168/68 sodium. Code designation for Omeprazole Sodium.
H199/18 magnesium trihydrate. Code designation for Esomeprazole Magnesium.
H199/18 sodium. Code designation for Esomeprazole Sodium.
H324/38. Code designation for Clevidipine Butyrate.
H 365. Code designation for Paroxypropione.
H 376/95. Code designation for Ximelagatran.

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H 3774. Code designation for Alibendol.
H 4132. Code designation for Dotefonium Bromide.
H 4170. Code designation for Tolpiprazole.
H 4723. Code designation for Clobazam.
HA-1A. Code designation for Nebacumab.
hAFP-31. Code designation for Yttrium Y 90 Tacatuzumab.
hAFP-31. Code designation for Yttrium Y 90 Tacatuzumab Tetraxetan.
HB 115. Code designation for Nifurprazine.
HB 419. Code designation for Glyburide.
H.B.F. 386. Code designation for Cactinomycin.
HBOC-201. Code designation for Hemoglobin Glutamer-250 (Bovine).
HBOC-301. Code designation for Hemoglobin Glutamer-200 (Bovine).
HC 1528. Code designation for Decoquinate.
HC 20,511 fumarate. Code designation for Ketotifen Fumarate.
HDPC. Code designation for Miltefosine.
HEOD. Code designation for Dieldrin.
Heparin Fragment Kabi 2165. Code designation for Dalteparin Sodium.
HEPP. Code designation for Pentigetide.
HF 241. Code designation for Bufeniode.
HF 1854. Code designation for Clozapine.
HF 1927. Code designation for Dibenzepin Hydrochloride.
HF-2159. Code designation for Clothiapine.
HFA-134-a. Code designation for Norflurane.
HFZ. Code designation for Homofenazine.
HGP-1. Code designation for Loteprednol Etabonate.
HGP-2. Code designation for Adaprolol Maleate.
HGP-5. Code designation for Alprenoxime Hydrochloride.
HGP-6. Code designation for Tematropium Methylsulfate.
HGS1018. Code designation for Lexatumumab.
HGS-ETR1. Code designation for Mapatumumab.
HGS-ETR2. Code designation for Lexatumumab.
HH105. Code designation for Butetamate.
HH 197. Code designation for Butamirate Citrate.
HIDA. Code designation for Lidofenin.
HL91. Code designation for Upenazime.
HL 267. Code designation for Dipenine Bromide.
HL 275. Code designation for Alvocidib.
HL 362. Code designation for Colforsin.
HL 523 [as hydrochloride]. Code designation for Tiformin.
HM-101. Code designation for Fispemifene.
HM-101a. Code designation for Fispemifene.
HMD. Code designation for Oxymetholone.
HMDP. Code designation for Oxidronic Acid.
HMG. Code designation for Menotropins.
hMN-14. Code designation for Labetuzumab.
HMR 1275. Code designation for Alvocidib.
HMR 1964. Code designation for Insulin Glulisine.
HMR3480. Code designation for Pralnacasan.
HMR3480/VX-740. Code designation for Pralnacasan.
HMR 3647. Code designation for Telithromycin.
HMR4396. Code designation for Epoetin Delta.
HOE 18 680. Code designation for Embutramide.
HOE 39-893d. Code designation for Penbutolol Sulfate.
HOE 42-440. Code designation for Tiamenidine Hydrochloride.
HOE 045. Code designation for Articaine Hydrochloride.
Hoe 045. Code designation for Articaine.
HOE 062 [Roxatidine]. Code designation for Roxatidine Acetate Hydrochloride.
HOE 71GT. Code designation for Insulin Glargine.
HOE 077. Code designation for Lufironil.
Hoe 105. Code designation for Citenazone.
HOE 118. Code designation for Piretanide.
HOE 140. Code designation for Icatibant Acetate.
HOE 216V. Code designation for Luxabendazole.
HOE 280. Code designation for Ofloxacin.
HOE 296. Code designation for Ciclopirox Olamine.
Hoe 296 V. Code designation for Resorantel.
HOE 296b. Code designation for Ciclopirox.
HOE 304. Code designation for Desoximetasone.
HOE 440. Code designation for Tiamenidine.
Hoe 473. Code designation for Aclantate.
HOE 490. Code designation for Glimepiride.
HOE 498. Code designation for Ramipril.
HOE 642. Code designation for Cariporide Mesylate.
HOE 760. Code designation for Roxatidine Acetate Hydrochloride.
HOE 766. Code designation for Buserelin Acetate.
HOE 777. Code designation for Prednicarbate.
Hoe 881V. Code designation for Fenbendazole.
HOE 893d. Code designation for Penbutolol Sulfate.
HOE 901. Code designation for Insulin Glargine.
HOE 984. Code designation for Nomifensine Maleate.
HOE 36801. Code designation for Etifoxine.
Hoechst 10495. Code designation for Norpipanone.
Hoechst 10582. Code designation for Normethadone.
HP 029. Code designation for Velnacrine Maleate.
HP 128. Code designation for Suronacrine Maleate.
HP 290. Code designation for Quilostigmine.
HP 494. Code designation for Fluradoline Hydrochloride.
HP 522. Code designation for Brocrinat.
HP 549. Code designation for Isoxepac.
HP 749. Code designation for Besipirdine Hydrochloride.
HP 873. Code designation for Iloperidone.
HP 1598. Code designation for Guanoxyfen Sulfate.
HP 3522. Code designation for Brocrinat.
HPEK-1. Code designation for Tetroquinone.
hPTH 1-34 (acetate salt). Code designation for Teriparatide Acetate.
HR111V-sulfate. Code designation for Cefquinome Sulfate.
HR 221 [as sodium]. Code designation for Cefodizime.
HR 376. Code designation for Clobazam.
HR 756. Code designation for Cefotaxime Sodium.
HR 810 sulfate. Code designation for Cefpirome Sulfate.
HR 930. Code designation for Fosazepam.
HRP 543. Code designation for Dazepinil Hydrochloride.
HRP 913. Code designation for Neflumozide Hydrochloride.
HS-592. Code designation for Clemastine.
HSP 2986. Code designation for Pramiverine.
HspE7. Code designation for Verpasep Caltespen.
HSPPC-96. Code designation for Vitespen.
HT-11. Code designation for Cloperastine.
HTF 919. Code designation for Tegaserod.
HTF 919. Code designation for Tegaserod Maleate.
HTI-286. Code designation for Taltobulin.
HU1D10. Code designation for Apolizumab.
hu5c8. Code designation for Ruplizumab.
Hu23F2G. Code designation for Rovelizumab.
hu1124. Code designation for Efalizumab.
huC242-DM1. Code designation for Cantuzumab Mertansine.
HUF-2446. Code designation for Clodazon Hydrochloride.
HuM291. Code designation for Visilizumab.
HuMax-CD4. Code designation for Zanolimumab.
HuZAF. Code designation for Fontolizumab.
HWA 285. Code designation for Propentofylline.
HWA-486. Code designation for Leflunomide.
HY-185. Code designation for Carbocloral.
HYO6A. Code designation for Hyaluronidase (Ovine).
I-653. Code designation for Desflurane.
I-2105. Code designation for Afovirsen Sodium.
^{123}I labeled IMP. Code designation for Iofetamine Hydrochloride I 123.
IA-307. Code designation for Acetosulfone Sodium.

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IB-367-03. Code designation for Iseganan Hydrochloride.
IBC. Code designation for Bucrylate.
IC351. Code designation for Tadalafil.
ICA-17043. Code designation for Senicapoc.
ICI 8173. Code designation for Quindoxin.
ICI 28257. Code designation for Clofibrate.
ICI 29661. Code designation for Pyrimitate.
ICI 32865. Code designation for Etoglucid.
ICI-33,828. Code designation for Methallibure.
ICI 35,868. Code designation for Propofol.
ICI 38174 [as hydrochloride]. Code designation for Pronetalol.
ICI 45520. Code designation for Propranolol Hydrochloride.
ICI 45763 [as hydrochloride]. Code designation for Toliprolol.
ICI 46,474. Code designation for Tamoxifen Citrate.
ICI 46683. Code designation for Oxyclozanide.
I.C.I. 47,319. Code designation for Dexpropranolol Hydrochloride.
ICI 48213. Code designation for Cyclofenil.
ICI 50,123. Code designation for Pentagastrin.
I.C.I. 50,172. Code designation for Practolol.
I.C.I. 54,450. Code designation for Fenclozic Acid.
ICI 54,594 [as sodium salt]. Code designation for Brofezil.
ICI 55,052. Code designation for Nequinate.
ICI 55,897. Code designation for Clobuzarit.
ICI 58,834. Code designation for Viloxazine Hydrochloride.
ICI 59118. Code designation for Razoxane.
ICI 66,082. Code designation for Atenolol.
ICI 80,008 [as sodium salt]. Code designation for Fluprostenol Sodium.
ICI 80,996. Code designation for Cloprostenol Sodium.
ICI 81,008. Code designation for Fluprostenol Sodium.
ICI 118,587. Code designation for Xamoterol Fumarate.
ICI 118,630. Code designation for Goserelin.
ICI 125,211. Code designation for Tiotidine.
ICI 128,436. Code designation for Ponalrestat.
ICI 136,753. Code designation for Tracazolate.
ICI 139603. Code designation for Tetronasin Sodium.
ICI 141,292. Code designation for Epanolol.
ICI 156,834. Code designation for Cefotetan.
ICI 176,334. Code designation for Bicalutamide.
ICI 182,780. Code designation for Fulvestrant.
ICI 194,660. Code designation for Meropenem.
ICI 204,219. Code designation for Zafirlukast.
ICI 204,636. Code designation for Quetiapine Fumarate.
ICI D1033. Code designation for Anastrozole.
ICID2079. Code designation for Talibegron Hydrochloride.
ICI-U.S. 457. Code designation for Octazamide.
ICJ 3393. Code designation for Iosimenol.
ICL670A. Code designation for Deferasirox.
ICN-542. Code designation for Ribaminol.
ICN-1256. Code designation for Tocladesine.
ICN-10146. Code designation for Isatoribine.
ICRF 159. Code designation for Razoxane.
ICRF-187. Code designation for Dexrazoxane.
IDD-676. Code designation for Lidorestat.
IDD-000676-01. Code designation for Lidorestat.
IDEC-102. Code designation for Rituximab.
IDEC-114. Code designation for Galiximab.
IDEC-129. Code designation for Ibritumomab Tiuxetan.
IDEC-152. Code designation for Gomiliximab.
IDEC-152. Code designation for Lumiliximab.
IDEC-C2B8. Code designation for Rituximab.
IDEC-Y2B8. Code designation for Ibritumomab Tiuxetan.
IDU. Code designation for Idoxuridine.
IgE Pentapeptide. Code designation for Pentigetide.
IL-1 Trap. Code designation for Rilonacept.
IL13-PE38. Code designation for Cintredekin Besudotox.
IL 5902. Code designation for Spiramycin.
IL 6001. Code designation for Trimipramine.
IL-6302 mesylate. Code designation for Fonazine Mesylate.
IL-17803A. Code designation for Acebutolol Hydrochloride.
IL-19552. Code designation for Pipotiazine Palmitate.
IL 22811 HCl. Code designation for Meptazinol Hydrochloride.
ILX651. Code designation for Tasidotin Hydrochloride.
^{123}I-M123. Code designation for Iofetamine Hydrochloride I 123.
IM862. Code designation for Oglufanide Disodium.
IMI-28. Code designation for Epirubicin Hydrochloride.
IMI 30. Code designation for Idarubicin Hydrochloride.
IMI 58. Code designation for Esorubicin Hydrochloride.
IMMU-4. Code designation for Arcitumomab.
IMMU-hLL2. Code designation for Epratuzumab.
IMMU-LL2. Code designation for Bectumomab.
IMMU-MN3. Code designation for Sulesomab.
IN 29-5931B. Code designation for Triclofenol Piperazine.
IN 379. Code designation for Pimetine Hydrochloride.
IN 461. Code designation for Benzindopyrine Hydrochloride.
IN 511. Code designation for Phenyramidol Hydrochloride.
IN 836. Code designation for Fenyripol Hydrochloride.
IN 1060. Code designation for Cyprolidol Hydrochloride.
INA-X14. Code designation for Insulin Aspart.
INCB-8721. Code designation for Dexelvucitabine.
INF-1837. Code designation for Flufenamic Acid.
INF-3355. Code designation for Mefenamic Acid.
INF 4668. Code designation for Meclofenamic Acid.
INGN 201. Code designation for Contusugene ladenovec.
INH-H2002. Code designation for Tefibazumab.
INN 00835. Code designation for Nemifitide Ditriflutate.
INS365. Code designation for Diquafosol Tetrasodium.
INS37217. Code designation for Denufosol Tetrasodium.
Insulin X14. Code designation for Insulin Aspart.
Interleukin-1 Trap. Code designation for Rilonacept.
IP 302 sodium. Code designation for Citicoline Sodium.
IP 456. Code designation for Pagoclone.
IP631. Code designation for Trospium Chloride.
IP-2105. Code designation for Afovirsen Sodium.
IPA. Code designation for Riboprine.
IPTD. Code designation for Glyprothiazol.
IS 5-MN. Code designation for Isosorbide Mononitrate.
I.S. 499. Code designation for Poldine Methylsulfate.
IS 2596. Code designation for Domoxin.
ISIS-2105. Code designation for Afovirsen Sodium.
ISIS 2302. Code designation for Alicaforsen Sodium.
ISIS 2922. Code designation for Fomivirsen Sodium.
ISIS 5321. Code designation for Aprinocarsen Sodium.
Isomer A. Code designation for Zuclomiphene.
Isomer B. Code designation for Enclomiphene.
J867. Code designation for Asoprisnil.
Janssen R 4929. Code designation for Benzetimide Hydrochloride.
JAV 852. Code designation for Benfosformin.
JB-8181. Code designation for Desipramine Hydrochloride.
JD-96. Code designation for Vinylbital.
JF-1. Code designation for Nalmefene.
JL 512. Code designation for Fenadiazole.
JL-1078. Code designation for Dihexyverine Hydrochloride.
JM-8. Code designation for Carboplatin.
JM-9. Code designation for Iproplatin.
JM-83. Code designation for Oxaliplatin.
JM-216. Code designation for Satraplatin.
JNJ-10234094. Code designation for Carisbamate.
JO-1784. Code designation for Igmesine Hydrochloride.
JTE-522. Code designation for Tilmacoxib.
JTP-19605. Code designation for Tilmacoxib.
K-17. Code designation for Thalidomide.
K-38. Code designation for Glycyclamide.
K85. Code designation for Omega-3-acid Ethyl Esters.
K-386. Code designation for Glycyclamide.

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K-1900. Code designation for Nimorazole.
K 4024. Code designation for Glipizide.
K 4277. Code designation for Indoprofen.
K 9147. Code designation for Tolciclate.
K 11941. Code designation for Alfaprostol.
K 12148. Code designation for Lifibrol.
KABI 925. Code designation for Emylcamate.
Kabi 2234. Code designation for Tolterodine.
KAT 256 [as hydrochloride]. Code designation for Clobutinol.
KB 95. Code designation for Benzpiperylon.
KB-944. Code designation for Fostedil.
KC8857. Code designation for Tedisamil.
KC8857. Code designation for Tedisamil Sesquifumarate.
KC-9946. Code designation for Cilansetron.
KC-9946. Code designation for Cilansetron Hydrochloride.
KCA-757. Code designation for Tipelukast.
K-F 224. Code designation for Naftoxate.
KGF-2. Code designation for Repifermin.
KIN-493. Code designation for Oxcarbazepine.
Kita-ku Toyko. Code designation for Mitemcinal Fumarate.
KL_4-surfactant. Code designation for Lucinactant.
KL-255 [as hydrochloride]. Code designation for Bupranolol.
KM871. Code designation for Ecromeximab.
Ko 592 [as hydrochloride]. Code designation for Toliprolol.
Ko 1173 Cl. Code designation for Mexiletine Hydrochloride.
KO 1366. Code designation for Bunitrolol.
KOS-953. Code designation for Tanespimycin.
KOS-1022. Code designation for Alvespimycin Hydrochloride.
KP-363. Code designation for Butenafine Hydrochloride.
KRM-1648. Code designation for Rifalazil.
KRN-568. Code designation for Tecalcet Hydrochloride.
KS 33. Code designation for Oxyridazine.
KT5555. Code designation for Lestaurtinib.
KUR-1246. Code designation for Bedoradrine Sulfate.
KVX-478. Code designation for Amprenavir.
KW-110. Code designation for Aceglutamide Aluminum.
KW-2189. Code designation for Pibrozelesin Hydrobromide.
KW-2871. Code designation for Ecromeximab.
KW4679; ALO4943A. Code designation for Olopatadine Hydrochloride.
KW-6002. Code designation for Istradefylline.
KWD 2019. Code designation for Terbutaline Sulfate.
L1. Code designation for Deferiprone.
L-8. Code designation for Lypressin.
L-67. Code designation for Prilocaine Hydrochloride.
L 75 1362B. Code designation for Colforsin.
L 86 8275. Code designation for Alvocidib.
L 542. Code designation for Mercurobutol.
L-554. Code designation for Tritoqualine.
L 566. Code designation for Dibemethine.
L-627. Code designation for Biapenem.
L-749. Code designation for Salacetamide.
L846. Code designation for Zaleplon.
L-1573. Code designation for Cysteamine.
L-1633. Code designation for Sodium Dibunate.
L-1718. Code designation for Osalmid.
L-1777. Code designation for Medazomide.
L 2197. Code designation for Benzarone.
L-2214. Code designation for Benzbromarone.
L 2329. Code designation for Benziodarone.
L 2642. Code designation for Etabenzarone.
L-3428. Code designation for Amiodarone.
L-4269. Code designation for Pyridarone.
L-5103 Lepetit. Code designation for Rifampin.
L-5418. Code designation for Diftalone.
L 5818 [as hydrochloride]. Code designation for Coumazoline.
L-6257. Code designation for Oxetorone Fumarate.
L-6400. Code designation for Fluazacort.
L 8027. Code designation for Nictindole.
L-9394. Code designation for Butoprozine Hydrochloride.
L-364,718. Code designation for Devazepide.
L-588357-0. Code designation for Metyrosine.
L-637,510. Code designation for Nelezaprine Maleate.
L-647,339. Code designation for Naxagolide Hydrochloride.
L-668,019. Code designation for Verlukast.
L-669,455. Code designation for Dexibuprofen Lysine.
L-700,462. Code designation for Tirofiban Hydrochloride.
L-735,524. Code designation for Indinavir Sulfate.
LA-012 [as hydrochloride]. Code designation for Quatacaine.
LA 391. Code designation for Sodium Picosulfate.
LA 1221 [as hydrochloride]. Code designation for Butalamine.
LA-6023. Code designation for Metformin.
LA-6023. Code designation for Metformin Hydrochloride.
LA III. Code designation for Diazepam.
LAAM. Code designation for Levomethadyl Acetate.
LAAM. Code designation for Levomethadyl Acetate Hydrochloride.
LAC-43. Code designation for Bupivacaine Hydrochloride.
LACI. Code designation for Tifacogin.
LAF237. Code designation for Vildagliptin.
LAS 3876. Code designation for Almagate.
LAS 9273. Code designation for Clebopride.
LAS 30451. Code designation for Pancopride.
LAS 31025. Code designation for Arofylline.
LAS 31416. Code designation for Almotriptan.
LAS 31416 D,L-malate acid. Code designation for Almotriptan Malate.
LAS W-090. Code designation for Ebastine.
LB-46. Code designation for Pindolol.
LB 125. Code designation for Cyprodenate.
LB-502. Code designation for Furosemide.
LB 20304a. Code designation for Gemifloxacin Mesylate.
LC 44. Code designation for Flupentixol.
LD 335. Code designation for Propyromazine Bromide.
LD 935. Code designation for Dipiproverine Hydrochloride.
LD 2351 [as hydrobromide]. Code designation for Butopiprine.
LD 2480. Code designation for Piprocurarium Iodide.
LD 2630. Code designation for Difencloxazine Hydrochloride.
LD 2988. Code designation for Folescutol.
LD 3055. Code designation for Oxypyrronium Bromide.
LD 3394. Code designation for Fenozolone.
LD 3612. Code designation for Paraflutizide.
LD 4644. Code designation for Pipebuzone.
LDP-03. Code designation for Alemtuzumab.
LDP-341. Code designation for Bortezomib.
Leo 114. Code designation for Polyestradiol Phosphate.
levo-BC-2605. Code designation for Oxilorphan.
levo-BC-2627. Code designation for Butorphanol.
levo-BC-2627 tartrate. Code designation for Butorphanol Tartrate.
levo-BL-4566. Code designation for Moxazocine.
LF00. Code designation for Talactoferrin Alfa.
LF 08-0299. Code designation for Tresperimus.
LFA3TIP. Code designation for Alefacept.
L-FMAU. Code designation for Clevudine.
LG100057. Code designation for Alitretinoin.
LG100069. Code designation for Bexarotene.
LGD1057. Code designation for Alitretinoin.
LGD1069. Code designation for Bexarotene.
LJ 206. Code designation for Carbocysteine.
LJ C10,627. Code designation for Biapenem.
LJC 10,141. Code designation for Felbinac.
LJC 10846. Code designation for Zaleplon.
LJP 394. Code designation for Abetimus Sodium.
LL-705W. Code designation for Neutramycin.
LL 1530. Code designation for Nadoxolol.
LM-94. Code designation for Hymecromone.

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LM 176. Code designation for Cobamamide.
LM 192. Code designation for Viquidil.
LM-427. Code designation for Rifabutin.
LM-1404. Code designation for Lortalamine.
LM 2717. Code designation for Clobazam.
LMD. Code designation for Dextran 40.
L-MTP-PE. Code designation for Mifamurtide.
LMWD. Code designation for Dextran 40.
L.N. 107. Code designation for Broparestrol.
LRX-15. Code designation for Treprostinil.
LS-11. Code designation for Talaporfin Sodium.
LS-121. Code designation for Nafronyl Oxalate.
LS 519 Cl2. Code designation for Pirenzepine Hydrochloride.
LS 2616. Code designation for Roquinimex.
LSD. Code designation for Lysergide.
LSN2420586. Code designation for Pruvanserin Hydrochloride.
LSN2422347. Code designation for Pruvanserin.
Lu 02-030. Code designation for Gaboxadol.
LU3-010. Code designation for Talopram Hydrochloride.
Lu 10-171-B. Code designation for Citalopram Hydrobromide.
Lu 23-174. Code designation for Sertindole.
Lu 25-109-M. Code designation for Alvameline Maleate.
Lu 26-054-0. Code designation for Escitalopram Oxalate.
LU200134. Code designation for Adalimumab.
Lu texaphyrin. Code designation for Motexafin Lutetium.
lutetium texaphyrin. Code designation for Motexafin Lutetium.
Lu-Tex. Code designation for Motexafin Lutetium.
LVD. Code designation for Dextran 40.
LY 048 740. Code designation for Avilamycin.
LY9818. Code designation for Naveglitazar.
LY 12271-72. Code designation for Viroxime.
LY061188. Code designation for Cephalexin Hydrochloride.
LY097964. Code designation for Cefetamet.
LY099094. Code designation for Vindesine Sulfate.
LY104208. Code designation for Vinzolidine Sulfate.
LY 108380. Code designation for Doxpicomine Hydrochloride.
LY110140. Code designation for Fluoxetine Hydrochloride.
LY 119863. Code designation for Vinepidine Sulfate.
LY120363. Code designation for Flumezapine.
LY121019. Code designation for Cilofungin.
LY 122512. Code designation for Anitrazafen.
LY 122772. Code designation for Enviroxime.
LY 123508. Code designation for Lorzafone.
LY 127123. Code designation for Enviradene.
LY 127623. Code designation for Metkephamid Acetate.
LY 127809. Code designation for Pergolide Mesylate.
LY 127935. Code designation for Moxalactam Disodium.
LY 135837. Code designation for Indecainide Hydrochloride.
LY137998. Code designation for Somatropin.
LY 139037. Code designation for Nizatidine.
LY 139381. Code designation for Ceftazidime.
LY-139603. Code designation for Atomoxetine Hydrochloride.
LY 141894. Code designation for Amflutizole.
LY 146032. Code designation for Daptomycin.
LY 150378. Code designation for Clofilium Phosphate.
LY 150720. Code designation for Picenadol Hydrochloride.
LY156758. Code designation for Raloxifene Hydrochloride.
LY163502. Code designation for Quinelorane Hydrochloride.
LY163892 monohydrate. Code designation for Loracarbef.
LY167005. Code designation for Proinsulin Human.
LY170053. Code designation for Olanzapine.
LY170680. Code designation for Sulukast.
LY171555. Code designation for Quinpirole Hydrochloride.
LY171883. Code designation for Tomelukast.
LY 174008. Code designation for Dobutamine Tartrate.
LY 175326. Code designation for Isomazole Hydrochloride.
LY177370. Code designation for Tilmicosin.
LY177370 phosphate. Code designation for Tilmicosin Phosphate.
LY177837. Code designation for Somidobove.
LY186641. Code designation for Sulofenur.
LY 186655. Code designation for Tibenelast Sodium.
LY188011. Code designation for Gemcitabine.
LY188011 hydrochloride. Code designation for Gemcitabine Hydrochloride.
LY 195115. Code designation for Indolidan.
LY 201116. Code designation for Ameltolide.
LY203638. Code designation for Drotrecogin Alfa (activated).
LY206243 lactobionate. Code designation for Levdobutamine Lactobionate.
LY207506. Code designation for Dobutamine Lactobionate.
LY210448 HCl. Code designation for Dapoxetine Hydrochloride.
LY213829. Code designation for Tazofelone.
LY215229 hydrochloride. Code designation for Seproxetine Hydrochloride.
LY231514. Code designation for Pemetrexed Disodium.
LY 237216. Code designation for Dirithromycin.
LY237733. Code designation for Amesergide.
LY246708. Code designation for Xanomeline.
LY246708 tartrate. Code designation for Xanomeline Tartrate.
LY246736. Code designation for Alvimopan.
LY248686 HCl. Code designation for Duloxetine Hydrochloride.
LY253351. Code designation for Tamsulosin Hydrochloride.
LY264618 disodium. Code designation for Lometrexol Sodium.
LY275585. Code designation for Insulin Lispro.
LY277359 maleate. Code designation for Zatosetron Maleate.
LY281067. Code designation for Sergolexole Maleate.
LY287041. Code designation for Tazomeline Citrate.
LY293111. Code designation for Etalocib.
LY293404. Code designation for Rismorelin Porcine.
LY293558. Code designation for Tezampanel.
LY294468 sulfate. Code designation for Efegatran Sulfate.
LY295337. Code designation for Basifungin.
LY300502. Code designation for Bexlosteride.
LY303366. Code designation for Anidulafungin.
LY307640 sodium. Code designation for Rabeprazole Sodium.
LY315920-Na^+. Code designation for Varespladib Sodium.
LY317615. Code designation for Enzastaurin Hydrochloride.
LY320236. Code designation for Izonsteride.
LY326869. Code designation for Moxonidine.
LY333328 diphosphate. Code designation for Oritavancin Diphosphate.
LY 333334. Code designation for Teriparatide.
LY335348. Code designation for Denileukin Diftitox.
LY335979. Code designation for Zosuquidar Trihydrochloride.
LY353381.HCl. Code designation for Arzoxifene Hydrochloride.
LY354740. Code designation for Eglumetad.
LY519818. Code designation for Naveglitazar.
LY544349. Code designation for Sivelestat.
LY544349 Sodium Hydrate. Code designation for Sivelestat Sodium.
LY640315. Code designation for Prasugrel Hydrochloride.
LY2148568. Code designation for Exenatide.
LY2420586. Code designation for Pruvanserin.
LY2422347 HCl. Code designation for Pruvanserin Hydrochloride.
LYO31537. Code designation for Ractopamine Hydrochloride.
M-14. Code designation for Rifamycin.
M. 99 [as hydrochloride]. Code designation for Etorphine.
M-141. Code designation for Spectinomycin Hydrochloride.
M200. Code designation for Volociximab.
M 285. Code designation for Cyprenorphine Hydrochloride.
M-811. Code designation for Salverine.
M-1028 (Meiji). Code designation for Haloprogin.
M. 5050. Code designation for Diprenorphine.
M 18575. Code designation for Dienogest.
M40403. Code designation for Imisopasem Manganese.

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MA-540. Code designation for Quinuclium Bromide.
MA-593. Code designation for Salethamide Maleate.
MA 1277. Code designation for Zolertine Hydrochloride.
MA 1291. Code designation for Quipazine Maleate.
MA 1337. Code designation for Cloperidone Hydrochloride.
MA-1443. Code designation for Letimide Hydrochloride.
MAB35. Code designation for Indium In 111 Altumomab Pentetate.
MAb-B43.13. Code designation for Oregovomab.
m-AMSA. Code designation for Amsacrine.
MAS-1. Code designation for Polyglyconate.
Material A. Code designation for Pentetate Calcium Trisodium Yb 169.
MAY. Code designation for Nelarabine.
MAY. Code designation for Nelzarabine.
M&B 782 [as isethionate]. Code designation for Propamidine.
MB 800 [as isethionate]. Code designation for Pentamidine.
M&B 5062 A. Code designation for Amicarbalide.
M&B 9302. Code designation for Clorgiline.
M&B 15497. Code designation for Decoquinate.
M&B 16942A. Code designation for Diacetolol Hydrochloride.
M&B 17803A. Code designation for Acebutolol Hydrochloride.
M&B 22948. Code designation for Zaprinast.
M&B 33153. Code designation for Oxoprostol.
M&B 39831. Code designation for Temozolomide.
MB 46030. Code designation for Fipronil.
MBBT. Code designation for Bisoctrizole.
MBR-4164-8. Code designation for Diflumidone Sodium.
MBR-4197. Code designation for Flucrylate.
MBR 4223. Code designation for Triflumidate.
MC 903. Code designation for Calcipotriene.
MCC 555. Code designation for Netoglitazone.
MCE. Code designation for Metergoline.
MCI-9038. Code designation for Argatroban.
McN-742. Code designation for Aminorex.
McN-1075. Code designation for Fenmetramide.
McN-1107. Code designation for Clominorex.
McN-1210. Code designation for Pyrinoline.
McN-1231. Code designation for Fluminorex.
McN-1546. Code designation for Flumetramide.
McN-1589. Code designation for Mixidine.
McN-2378. Code designation for Mefenidil.
McN-2378-46. Code designation for Mefenidil Fumarate.
McN-2453. Code designation for Azepindole.
McN-2559. Code designation for Tolmetin.
McN-2559-21-98. Code designation for Tolmetin Sodium.
McN-2783-21-98. Code designation for Zomepirac Sodium.
McN-3113. Code designation for Xilobam.
McN-3377-98. Code designation for Fenobam.
McN-3495. Code designation for Pirogliride Tartrate.
McN-3716. Code designation for Methyl Palmoxirate.
McN-3802 [anhydrous free acid]. Code designation for Palmoxirate Sodium.
McN-3802-21-98. Code designation for Palmoxirate Sodium.
McN 3935. Code designation for Linogliride.
McN-3935. Code designation for Linogliride Fumarate.
McN-4097-12-98. Code designation for Fenoctimine Sulfate.
McN-4853. Code designation for Topiramate.
McN-A-2673-11. Code designation for Etoperidone Hydrochloride.
McN-A-2833. Code designation for Perindopril.
McN-A-2833-109. Code designation for Perindopril Erbumine.
McN-JR-1625. Code designation for Haloperidol.
McN-JR-2498. Code designation for Trifluperidol.
McN-JR-4263-49. Code designation for Fentanyl Citrate.
McN-JR-4584. Code designation for Benperidol.
McN-JR-4749. Code designation for Droperidol.
McN-JR-4929-11. Code designation for Benzetimide Hydrochloride.
McN-JR-6218. Code designation for Fluspirilene.
McN-JR-6238. Code designation for Pimozide.
McN-JR-7242-11. Code designation for Difluanine Hydrochloride.
McN-JR-7904. Code designation for Lidoflazine.
McN-JR-8299-11. Code designation for Tetramisole Hydrochloride.
McN-JR-13,558-11. Code designation for Fetoxylate Hydrochloride.
McN-JR-15,403-11. Code designation for Difenoxin.
McN-JR-16,341. Code designation for Penfluridol.
McN-R-73-Z. Code designation for Rotoxamine.
McN-R-726-47. Code designation for Poldine Methylsulfate.
McN-R-1162-22. Code designation for Potassium Glucaldrate.
McN-R-1967. Code designation for Fenretinide.
McN-X-94. Code designation for Capuride.
McN-X-181. Code designation for Valnoctamide.
MD 141. Code designation for Ethamsylate.
MD-805. Code designation for Argatroban.
MD 2028. Code designation for Fluanisone.
MD 67350 [as maleate]. Code designation for Cinepazide.
MDL 257. Code designation for Zindotrine.
MDL 458. Code designation for Deflazacort.
MDL 473. Code designation for Rifapentine.
MDL 507. Code designation for Teicoplanin.
MDL 11,939. Code designation for Glemanserin.
MDL 14,042. Code designation for Lofexidine Hydrochloride.
MDL 16,455A. Code designation for Fexofenadine Hydrochloride.
MDL 17,043. Code designation for Enoximone.
MDL 18,962. Code designation for Plomestane.
MDL 19,205. Code designation for Piroximone.
MDL 19,744. Code designation for Tipentosin Hydrochloride.
MDL 26,024G0. Code designation for Tetrazolast Meglumine.
MDL 26,479. Code designation for Suritozole.
MDL 28,574A. Code designation for Celgosivir Hydrochloride.
MDL 62,198. Code designation for Ramoplanin.
MDL 62,769. Code designation for Rifamexil.
MDL 64,397. Code designation for Dalbavancin.
MDL 71,754. Code designation for Vigabatrin.
MDL 71,782 A. Code designation for Eflornithine Hydrochloride.
MDL 72,222. Code designation for Bemesetron.
MDL 72,422. Code designation for Tropanserin Hydrochloride.
MDL 72,974A. Code designation for Mofegiline Hydrochloride.
MDL 73,005EF. Code designation for Binospirone Mesylate.
MDL 73,147EF. Code designation for Dolasetron Mesylate.
MDL 73,745. Code designation for Zifrosilone.
MDL 73,945. Code designation for Camiglibose.
MDL 101,731. Code designation for Tezacitabine.
MDL 107,826A. Code designation for Alvocidib.
MDL-201129. Code designation for Beraprost Sodium.
MDL-201229. Code designation for Beraprost.
MDX-010. Code designation for Ipilimumab.
MDX-016. Code designation for Zanolimumab.
MDX-060. Code designation for Iratumumab.
MDX-CTLA-4. Code designation for Ipilimumab.
MEA. Code designation for Cysteamine.
MEDI-507. Code designation for Siplizumab.
MEDI-524. Code designation for Motavizumab.
MER-41. Code designation for Clomiphene Citrate.
meso-NDGA. Code designation for Masoprocol.
Methyl-CCNU. Code designation for Semustine.
MF 934. Code designation for Rufloxacin.
M.G. 143. Code designation for Sulmarin.
MG 559. Code designation for Metamfepramone.
M.G. 624. Code designation for Stilonium Iodide.
M.G. 652. Code designation for Oxamarin Hydrochloride.

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M.G. 1559. Code designation for Xenbucin.
Mg 4833. Code designation for Fencibutirol.
M.G. 5454. Code designation for Guaiapate.
M.G. 5771. Code designation for Butixirate.
M.G. 8823. Code designation for Exaprolol Hydrochloride.
M.G. 8926 [as hydrochloride]. Code designation for Droprenilamine.
M.G. 13054. Code designation for Fenquizone.
M.G. 13608. Code designation for Domiodol.
MGI 114. Code designation for Irofulven.
MH-532. Code designation for Phenprobamate.
Mi-85. Code designation for Apazone.
MI-216. Code designation for Iothalamic Acid.
MIV 606. Code designation for Valomaciclovir Stearate.
MJ 505. Code designation for Phenyramidol Hydrochloride.
MJ 1986. Code designation for Indriline Hydrochloride.
MJ 1987. Code designation for Mesuprine Hydrochloride.
MJ 1988. Code designation for Quazodine.
MJ 1992. Code designation for Soterenol Hydrochloride.
MJ 1998. Code designation for Metalol Hydrochloride.
MJ 1999. Code designation for Sotalol Hydrochloride.
MJ 4309-1. Code designation for Oxybutynin Chloride.
MJ 9022-1. Code designation for Buspirone Hydrochloride.
MJ 9067-1. Code designation for Encainide Hydrochloride.
MJ 9184-1. Code designation for Zinterol Hydrochloride.
MJ 10061. Code designation for Benzbromarone.
MJ 12,175-170. Code designation for Tiprinast Meglumine.
MJ 12,880-1. Code designation for Tipropidil Hydrochloride.
MJ 13,105-1. Code designation for Bucindolol Hydrochloride.
MJ 13401-1-3. Code designation for Fenprinast Hydrochloride.
MJ 13,754-1. Code designation for Nefazodone Hydrochloride.
MJF 9325. Code designation for Ifosfamide.
MJF 10,938. Code designation for Xipamide.
MJF 11567-3. Code designation for Cefadroxil.
MJF-12264. Code designation for Tegafur.
MJF 12637. Code designation for Suloctidil.
MJR-35. Code designation for Dienogest.
MK 57. Code designation for Methyldesorphine.
MK-130 [as the base]. Code designation for Cyclobenzaprine Hydrochloride.
MK-188. Code designation for Zeranol.
MK-196. Code designation for Indacrinone.
MK-208. Code designation for Famotidine.
MK-217. Code designation for Alendronate Sodium.
MK-233. Code designation for Dexibuprofen Lysine.
MK-240. Code designation for Protriptyline Hydrochloride.
MK-250. Code designation for Emylcamate.
MK-329. Code designation for Devazepide.
MK-341. Code designation for Tranilast.
MK-351. Code designation for Methyldopa.
MK-360. Code designation for Thiabendazole.
MK-366. Code designation for Norfloxacin.
MK-383. Code designation for Tirofiban Hydrochloride.
MK-397. Code designation for Eprinomectin.
MK-401. Code designation for Clorsulon.
MK-417. Code designation for Sezolamide Hydrochloride.
MK-422. Code designation for Enalaprilat.
MK-458. Code designation for Naxagolide Hydrochloride.
MK-0462. Code designation for Rizatriptan Benzoate.
MK-476. Code designation for Montelukast Sodium.
MK-507. Code designation for Dorzolamide Hydrochloride.
MK-0517. Code designation for Fosaprepitant Dimeglumine.
MK-521. Code designation for Lisinopril.
MK-591. Code designation for Quiflapon Sodium.
MK-595. Code designation for Ethacrynic Acid.
MK-621. Code designation for Efrotomycin.
MK-639. Code designation for Indinavir Sulfate.
MK-0663. Code designation for Etoricoxib.
MK-0677. Code designation for Ibutamoren Mesylate.
MK-678. Code designation for Seglitide Acetate.
MK-679. Code designation for Verlukast.
MK-0681. Code designation for Trientine Hydrochloride.
MK-733. Code designation for Simvastatin.
MK-781. Code designation for Metyrosine.
MK-0787. Code designation for Imipenem.
MK790. Code designation for Levomethadyl Acetate Hydrochloride.
MK-791. Code designation for Cilastatin Sodium.
MK-793. Code designation for Diltiazem Malate.
MK-801. Code designation for Dizocilpine Maleate.
MK-803. Code designation for Lovastatin.
MK-0826. Code designation for Ertapenem Sodium.
MK-0869. Code designation for Aprepitant.
MK-906. Code designation for Finasteride.
MK-0928. Code designation for Gaboxadol.
MK-0936. Code designation for Abamectin.
MK-0966. Code designation for Rofecoxib.
MK-0991. Code designation for Caspofungin Acetate.
MK-A462. Code designation for Rizatriptan Sulfate.
MKC-442. Code designation for Emivirine.
MKI-833. Code designation for Balamapimod.
ML-1024. Code designation for Theofibrate.
ML 1034. Code designation for Celucloral.
ML-1129. Code designation for Beraprost Sodium.
ML-1229. Code designation for Beraprost.
ML-1,709,460. Code designation for Gamithromycin.
ML-1,785,713. Code designation for Firocoxib.
MM-416775. Code designation for Linaclotide Acetate.
MN-001. Code designation for Tipelukast.
MN-029. Code designation for Denibulin Hydrochloride.
MN-221. Code designation for Bedoradrine Sulfate.
MO-911. Code designation for Pargyline Hydrochloride.
MO-1255. Code designation for Encyprate.
MOT-288. Code designation for Atilmotin.
MP-271. Code designation for Iosefamic Acid.
MP 302 (mixt. with Ioxaglate Sodium). Code designation for Ioxaglate Meglumine.
MP 328. Code designation for Ioversol.
MP-600. Code designation for Betiatide.
MP-620. Code designation for Iocetamic Acid.
MP-1051. Code designation for Silodrate.
MP-1177. Code designation for Gadoversetamide.
MP-1196. Code designation for Versetamide.
MP-1549. Code designation for Furomine.
MP-1554. Code designation for Technetium Tc 99m Furifosmin.
MP-1727. Code designation for Indium In 111 Pentetreotide.
MP 2032. Code designation for Iocarmic Acid.
MP 2032-Meglumine. Code designation for Iocarmate Meglumine.
MP-3047-04. Code designation for Iosimenol.
MP 4006. Code designation for Albumin, Aggregated.
MP 4018. Code designation for Stannous Pyrophosphate.
MP-6026. Code designation for Ioglucol.
MP 7010. Code designation for Stannous Sulfur Colloid.
MP-8000. Code designation for Ioglucomide.
MP-10013. Code designation for Iogulamide.
MPS-21. Code designation for Ovemotide.
MPS-22. Code designation for Disomotide.
MPV-253 AII. Code designation for Detomidine Hydrochloride.
MPV-785. Code designation for Medetomidine Hydrochloride.
MPV-1248. Code designation for Atipamezole.
MPV-1440. Code designation for Dexmedetomidine.
MPV-2426. Code designation for Fadolmidine Hydrochloride.
MR6S4. Code designation for Sevoflurane.
MRA. Code designation for Tocilizumab.
MRE0470. Code designation for Binodenoson.

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MRL 38. Code designation for Hexadiline.
MRL-41. Code designation for Clomiphene Citrate.
MRP-10. Code designation for Pentetate Calcium Trisodium Yb 169.
MRX-115. Code designation for Perflutren.
MRZ 2663BR. Code designation for Methylnaltrexone Bromide.
MS 32520. Code designation for Gadofosveset Trisodium.
MS 325168A. Code designation for Fosveset.
MSI-78. Code designation for Pexiganan Acetate.
MSI-1256F. Code designation for Squalamine Lactate.
MSI-1436. Code designation for Trodusquemine.
MST-997. Code designation for Simotaxel.
MTS 263. Code designation for Tropenziline Bromide.
MY-25 [as bitartrate]. Code designation for Metergotamine.
MY-33-7 [as hydrochloride]. Code designation for Lotucaine.
MY-5116. Code designation for Repirinast.
MYC 8003. Code designation for Mocimycin.
MYO-029. Code designation for Stamulumab.
MZ-144. Code designation for Rimazolium Metilsulfate.
N-3. Code designation for Methetoin.
N-137. Code designation for Carbetimer.
N-0252. Code designation for Laurocapram.
N-399. Code designation for Xenytropium Bromide.
N-553 [as hydrochloride]. Code designation for Tolperisone.
N-714. Code designation for Chlorprothixene.
N-746. Code designation for Clopenthixol.
N-7009. Code designation for Flupentixol.
N-7020. Code designation for Meprotixol.
N10146. Code designation for Isatoribine.
NA-66. Code designation for Pimeclone.
NA-119. Code designation for Bromamid.
NA 274. Code designation for Bromhexine Hydrochloride.
NAB 365. Code designation for Clenbuterol.
NAD. Code designation for Nadide.
NARI-10146. Code designation for Isatoribine.
NASH. Code designation for Borocaptate Sodium B 10.
NAT-327. Code designation for Trimoxamine Hydrochloride.
NAT-333. Code designation for Fenspiride Hydrochloride.
NB 68. Code designation for Dacuronium Bromide.
NBI-34060. Code designation for Indiplon.
NC-123. Code designation for Mesoridazine.
NC 150. Code designation for Phenazopyridine Hydrochloride.
NC-503. Code designation for Eprodisate Disodium.
NC-758. Code designation for Tramiprosate.
NC 1264. Code designation for Thonzonium Bromide.
NC-1968. Code designation for Fungimycin.
NC-7197. Code designation for Esproquin Hydrochloride.
NCNU. Code designation for Pentamustine.
ND 50. Code designation for Octopamine.
NDC 0082-4155. Code designation for Daunorubicin Hydrochloride.
NDR 263. Code designation for Propenzolate Hydrochloride.
NDR 304. Code designation for Ethyl Dibunate.
NDR-5061A. Code designation for Aletamine Hydrochloride.
NDR-5523A. Code designation for Trimoxamine Hydrochloride.
NDR-5998A. Code designation for Fenspiride Hydrochloride.
NE-10064. Code designation for Azimilide Dihydrochloride.
NE 11740. Code designation for Tebufelone.
NE-19550. Code designation for Olvanil.
NE-58095. Code designation for Risedronate Sodium.
NE 97221. Code designation for Piridronate Sodium.
NESP. Code designation for Darbepoetin Alfa.
NEU 3002. Code designation for Corticorelin Acetate.
NF-71. Code designation for Nifurmerone.
NF-84. Code designation for Nifuraldezone.
NF-161. Code designation for Nifursemizone.
NF-246. Code designation for Nifuradene.
NF-602. Code designation for Levofuraltadone.
NF-902 [as hydrochloride]. Code designation for Levofuraltadone.
NF-963. Code designation for Furazolium Chloride.
NF-1010. Code designation for Nifurdazil.
NF-1088. Code designation for Nifurquinazol.
NF-1120. Code designation for Nifurimide.
NF-1425. Code designation for Furazolium Tartrate.
NFS1776. Code designation for Isovaleramide.
NGX424. Code designation for Tezampanel.
NIB. Code designation for Nabitan Hydrochloride.
NIH 2933. Code designation for Dimepheptanol.
NIH 7574. Code designation for Benzethidine.
NIH 7607. Code designation for Etonitazene.
NIH 7667. Code designation for Noracymethadol Hydrochloride.
NIH 7672. Code designation for Methopholine.
NIH 8805. Code designation for Buprenorphine Hydrochloride.
NK 204. Code designation for Basifungin.
NK-631. Code designation for Peplomycin Sulfate.
NK 1006. Code designation for Bekanamycin.
NKK-105. Code designation for Malotilate.
NKT-01. Code designation for Gusperimus Trihydrochloride.
NM-147. Code designation for Valtorcitabine Dihydrochloride.
NM283. Code designation for Valopicitabine Dihydrochloride.
NN-304. Code designation for Insulin Detemir.
NNC-05-0328. Code designation for Tiagabine Hydrochloride.
NO-05-0328. Code designation for Tiagabine Hydrochloride.
NO-1886. Code designation for Ibrolipim.
NOET. Code designation for Ditiocade Sodium.
NOR-701. Code designation for Apaziquone.
NorMDP. Code designation for Almurtide.
NP. Code designation for Nifurpipone.
NPAP. Code designation for Prajmalium Bitartrate.
NPS 1506 · HCl. Code designation for Delucemine Hydrochloride.
NPS R-568. Code designation for Tecalcet Hydrochloride.
NPT 15392. Code designation for Nosantine.
NRP104. Code designation for Lisdexamfetamine Dimesylate.
NS-75A. Code designation for Cetrorelix Acetate.
NS 2214. Code designation for Brasofensine Maleate.
NSC 343499. Code designation for Asulacrine.
NSD 1055. Code designation for Brocresine.
NSP-989. Code designation for Tanaproget.
NU-445. Code designation for Sulfisoxazole Diolamine.
Nu-1779. Code designation for Betaprodine.
Nu-1932. Code designation for Betameprodine.
NU-2121. Code designation for Nicotinyl Alcohol.
NV-02B. Code designation for Telbivudine.
NV-02C. Code designation for Torcitabine.
NV-06. Code designation for Idronoxil.
NX 473. Code designation for Picoplatin.
NX1838. Code designation for Pegaptanib Sodium.
NXX-066. Code designation for Quilostigmine.
NXY-059. Code designation for Disufenton Sodium.
NY-198. Code designation for Lomefloxacin Hydrochloride.
OCT. Code designation for Maxacalcitol.
ODA 914. Code designation for Demoxytocin.
(–)-OddC. Code designation for Troxacitabine.
OGT 918. Code designation for Miglustat.
OHM-11638. Code designation for Atilmotin.
l-OHP. Code designation for Oxaliplatin.
OM-977. Code designation for Etaminile.
OMDS. Code designation for Dipyrithione.
OMS No 1825. Code designation for Azamethiphos.
ONO-1078. Code designation for Pranlukast.
ONO-5046. Code designation for Sivelestat.
ONO-5046.Na. Code designation for Sivelestat Sodium.
ONYX-015. Code designation for Lontucirev (Replicating Adenovirus).
OP 21-23. Code designation for Parnaparin Sodium.
OP2000. Code designation for Deligoparin Sodium.

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OPB-2045. Code designation for Olanexidine Hydrochloride.
OPC-21. Code designation for Cilostazol.
OPC-31. Code designation for Aripiprazole.
OPC-1085. Code designation for Carteolol Hydrochloride.
OPC-7251. Code designation for Nadifloxacin.
OPC-8212. Code designation for Vesnarinone.
OPC-13013. Code designation for Cilostazol.
OPC-14597. Code designation for Aripiprazole.
OPC-17116. Code designation for Grepafloxacin Hydrochloride.
OPC-18790. Code designation for Toborinone.
OPC-41061. Code designation for Tolvaptan.
OPF 009. Code designation for Ibrolipim.
OR-611. Code designation for Entacapone.
(–)-OR-1259. Code designation for Levosimendan.
ORF-8063. Code designation for Triflubazam.
ORF 9326. Code designation for Nisterime Acetate.
ORF 10131. Code designation for Norgestimate.
ORF 11676. Code designation for Nalmefene.
ORF 15244. Code designation for Thymopentin.
ORF 15817. Code designation for Edoxudine.
ORF 15927. Code designation for Rioprostil.
ORF 16600. Code designation for Bemarinone Hydrochloride.
ORF 17070. Code designation for Histrelin.
ORF 18704. Code designation for Pelretin.
ORF 20257. Code designation for Doretinel.
ORF 20485. Code designation for Tepoxalin.
ORF 22164. Code designation for Atosiban.
ORF 22867. Code designation for Bemoradan.
Orf-32541. Code designation for Iturelix.
Org 538. Code designation for Testosterone Undecanoate.
Org 817. Code designation for Epimestrol.
ORG 2969. Code designation for Desogestrel.
ORG 3236. Code designation for Etonogestrel.
ORG 3770. Code designation for Mirtazapine.
Org 4428. Code designation for Beloxepin.
Org 5222. Code designation for Asenapine Maleate.
Org 6216. Code designation for Rimexolone.
ORG7417. Code designation for Resocortol Butyrate.
ORG 9426. Code designation for Rocuronium Bromide.
Org 9487. Code designation for Rapacuronium Bromide.
ORG 10172. Code designation for Danaparoid Sodium.
Org 24448. Code designation for Farampator.
Org 25969. Code designation for Sugammadex Sodium.
Org 30659. Code designation for Tosagestin.
ORG 31540. Code designation for Fondaparinux Sodium.
Org 39141. Code designation for Ismomultin Alfa.
Org 50081. Code designation for Esmirtazapine Maleate.
Org GB 94. Code designation for Mianserin Hydrochloride.
Org NA 97. Code designation for Pancuronium Bromide.
ORG NC 45. Code designation for Vecuronium Bromide.
Org OD 14. Code designation for Tibolone.
OSI-774. Code designation for Erlotinib Hydrochloride.
P 7. Code designation for Lauroguadine.
P-12. Code designation for Oxacillin Sodium.
P-25. Code designation for Cloxacillin Sodium.
P-30 Protein. Code designation for Ranpirnase.
P-50. Code designation for Ampicillin.
P53. Code designation for Tetrofosmin.
P 071. Code designation for Cetirizine Hydrochloride.
P-71. Code designation for Lycetamine.
P 71-0129. Code designation for Fendosal.
P 76 2494A. Code designation for Fluradoline Hydrochloride.
P 76 2543. Code designation for Dazepinil Hydrochloride.
P 78 3522. Code designation for Brocrinat.
P79 3913. Code designation for Neflumozide Hydrochloride.
P83 6029A. Code designation for Velnacrine Maleate.
P-113. Code designation for Saralasin Acetate.
P-165. Code designation for Azaserine.
[99mTc]-P246. Code designation for Technetium Tc 99m Apcitide.
P-248. Code designation for Levopropylcillin Potassium.
P280. Code designation for Bibapcitide.
P-286. Code designation for Ioxaglic Acid.
P-301. Code designation for Hydroxyphenamate.
P-463. Code designation for Fenamole.
P-638. Code designation for Puromycin.
P829. Code designation for Depreotide.
P-1011. Code designation for Dicloxacillin Sodium.
P-1026. Code designation for Hexaminolevulinate Hydrochloride.
P-1202. Code designation for Methyl Aminolevulinate Hydrochloride.
P-1306. Code designation for Glyparamide.
P-1496. Code designation for Zeranol.
P-1560. Code designation for Taleranol.
P-1742. Code designation for Fluperolone Acetate.
P-1779. Code designation for Althiazide.
P-1888. Code designation for Isosulfan Blue.
P-2105. Code designation for Epithiazide.
P-2525. Code designation for Polythiazide.
P-2530. Code designation for Methalthiazide.
P-2647. Code designation for Benzquinamide.
P-3232. Code designation for Somfasepor.
P-3693A. Code designation for Doxepin Hydrochloride.
P-3895. Code designation for Somfasepor.
P-3896. Code designation for Guanisoquin Sulfate.
P-4125. Code designation for Isosulfan Blue.
P-4385B. Code designation for Clothixamide Maleate.
P-4599. Code designation for Cidoxepin Hydrochloride.
P-4657 B. Code designation for Thiothixene.
P-5227. Code designation for Pinoxepin Hydrochloride.
P-5604. Code designation for Loteprednol Etabonate.
P-7138. Code designation for Nifurpirinol.
P 720549. Code designation for Isoxepac.
PA-144. Code designation for Plicamycin.
PA-457. Code designation for Bevirimat Dimeglumine.
PA-457 di-NMG. Code designation for Bevirimat Dimeglumine.
PA-457N. Code designation for Bevirimat Dimeglumine.
PA103001. Code designation for Bevirimat Dimeglumine.
PA103001-01. Code designation for Bevirimat Dimeglumine.
PA103001-04. Code designation for Bevirimat Dimeglumine.
PAA-701. Code designation for Bialamicol Hydrochloride.
PAA-3854. Code designation for Clamoxyquin Hydrochloride.
PAI-039. Code designation for Tiplasinin.
PAI-749. Code designation for Diaplasinin.
PAM-MR-807-23a. Code designation for Cycloguanil Pamoate.
PAM-MR-1165. Code designation for Acedapsone.
PAMN [as methonitrate]. Code designation for Prampine.
PASIT. Code designation for Glyprothiazol.
PAT. Code designation for Fenamole.
PB 89 [as hydrochloride]. Code designation for Fominoben.
p-BIDA. Code designation for Butilfenin.
PC-603. Code designation for Iproclozide.
PC1020 acetate. Code designation for Prezatide Copper Acetate.
PC-1421. Code designation for Piperacetazine.
PCI-0120. Code designation for Motexafin Gadolinium.
PCI-0123. Code designation for Motexafin Lutetium.
PCK3145. Code designation for Tigapotide Triflutate.
PD-93. Code designation for Piromidic Acid.
PD-0072953. Code designation for Gemcabene Calcium.
PD 81565. Code designation for Pentostatin.
PD 90,695-73. Code designation for Dezaguanine Mesylate.
PD 107779. Code designation for Enoxacin.
PD-110843. Code designation for Zonisamide.
PD 123654. Code designation for Tacedinaline.
PD 180988. Code designation for Fandosentan Potassium.
PD 180988-0016. Code designation for Fandosentan Potassium.
PD-183805. Code designation for Canertinib Dihydrochloride.

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PD-0183805. Code designation for Canertinib Dihydrochloride.
PD 0196860. Code designation for Besonprodil.
PDB. Code designation for Prifinium Bromide.
PDLA. Code designation for Foscolic Acid.
PDX. Code designation for Pralatrexate.
PE1-1. Code designation for Tuvirumab.
PEG-SOD. Code designation for Pegorgotein.
Pentapeptide DSDPR. Code designation for Pentigetide.
PF-26. Code designation for Mepramidil.
PF-804950. Code designation for Edotecarin.
PFA-186. Code designation for Salicylate Meglumine.
PG 430. Code designation for Febuverine.
PG490-88Na. Code designation for Omtriptolide Sodium.
PG-501. Code designation for Mazaticol.
$PGF_2\alpha$ THAM. Code designation for Dinoprost Tromethamine.
PH 218. Code designation for Edogestrone.
PH 5776. Code designation for Nitazoxanide.
PHA-290940AD. Code designation for Sunitinib Malate.
PHA-738144. Code designation for Certolizumab Pegol.
PHA 739,521. Code designation for Mavacoxib.
PHM-101. Code designation for Eufauserase.
PHXA41. Code designation for Latanoprost.
Pierrel-TQ 86. Code designation for Azipramine Hydrochloride.
PIXY321. Code designation for Milodistim.
PK 10169. Code designation for Enoxaparin Sodium.
PKC 412. Code designation for Midostaurin.
PLA-695. Code designation for Giripladib.
PLA-725. Code designation for Ecopladib.
PLA-902. Code designation for Efipladib.
PM 150. Code designation for Vedaprofen.
PM-671. Code designation for Ethosuximide.
PM 1807. Code designation for Fenimide.
PM-1952. Code designation for Fenacetinol.
PM-3944. Code designation for Flucetorex.
PM-185184. Code designation for Secnidazole.
PMD-387. Code designation for Crilvastatin.
PMPA. Code designation for Tenofovir.
PMPA Prodrug. Code designation for Tenofovir Disoproxil Fumarate.
PN 200-110. Code designation for Isradipine.
PNU-98528E. Code designation for Pramipexole Dihydrochloride.
PNU-101387G. Code designation for Sonepiprazole Mesylate.
PNU-140690E. Code designation for Tipranavir Disodium.
PNU-155950E. Code designation for Reboxetine Mesylate.
PNU-155971. Code designation for Exemestane.
PNU-180638E. Code designation for Almotriptan Malate.
PNU-200583E. Code designation for Tolterodine Tartrate.
POLI 67. Code designation for Tetrydamine.
POR 8. Code designation for Ornipressin.
POT.mes. Code designation for Paroxetine Mesylate.
PP 563. Code designation for Cyhalothrin.
PPI-149. Code designation for Abarelix.
PR-741-976A. Code designation for Somantadine Hydrochloride.
PR-0818-156A. Code designation for Verilopam Hydrochloride.
PR-870-714A. Code designation for Veradoline Hydrochloride.
PR-877-530L. Code designation for Flavodilol Maleate.
PR 879-317A. Code designation for Oxamisole Hydrochloride.
PR 934-423A. Code designation for Remacemide Hydrochloride.
PR-3847. Code designation for Teroxalene Hydrochloride.
PR070769. Code designation for Ocrelizumab.
PR-G 138-CL [as hydrochloride]. Code designation for Ciclosidomine.
Protease 1. Code designation for Brinolase.
PS-341. Code designation for Bortezomib.
PS-1286. Code designation for Pararosaniline Pamoate.
PS 2383. Code designation for Trimetozine.
PT-9. Code designation for Betahistine Hydrochloride.
PT-100. Code designation for Talabostat.
PT-100. Code designation for Talabostat Mesylate.
PT-141. Code designation for Bremelanotide.
PT-523. Code designation for Talotrexin Ammonium.
PT523. Code designation for Talotrexin Ammonium.
PTK787. Code designation for Vatalanib.
PTP-112. Code designation for Ertiprotafib.
PU-239. Code designation for Benzilonium Bromide.
PY 108-068. Code designation for Darodipine.
PZ68. Code designation for Pentosan Polysulfate Sodium.
PZ 1511. Code designation for Carpipramine Dihydrochloride.
Q-12. Code designation for Technetium Tc 99m Furifosmin.
QB-1. Code designation for Cloquinozine.
QRX 101. Code designation for Becocalcidiol.
QZ-2. Code designation for Methaqualone.
R 10.100. Code designation for Ethonam Nitrate.
R 48. Code designation for Chlornaphazine.
R 50 970. Code designation for Metrenperone.
R 51 163. Code designation for Tameridone.
R-52. Code designation for Mannosulfan.
R 62 818. Code designation for Lorcinadol.
R 64 766. Code designation for Risperidone.
R106-1. Code designation for Basifungin.
R-148. Code designation for Methaqualone.
R-411. Code designation for Valategrast Hydrochloride.
R 516. Code designation for Cinnarizine.
R-548. Code designation for Tricetamide.
R-568. Code designation for Tecalcet Hydrochloride.
R 610. Code designation for Racemoramide.
R 661. Code designation for Buzepide Metiodide.
R 798. Code designation for Rimiterol Hydrobromide.
R-803. Code designation for Furaprofen.
R 805. Code designation for Nimesulide.
R-830. Code designation for Prifelone.
R-830T. Code designation for Prifelone.
R-835. Code designation for Ibafloxacin.
R-837. Code designation for Imiquimod.
R-850. Code designation for Sotirimod.
R 1303. Code designation for Carbofenotion.
R 1406. Code designation for Phenoperidine.
R 1575. Code designation for Cinnarizine.
R-1625. Code designation for Haloperidol.
R 1658. Code designation for Moperone.
R 1707. Code designation for Glafenine.
R 1881. Code designation for Metribolone.
R 1929. Code designation for Azaperone.
R 2028. Code designation for Fluanisone.
R 2113. Code designation for Desoximetasone.
R 2159. Code designation for Anisopirol.
R 2167. Code designation for Fluanisone.
R 2323. Code designation for Gestrinone.
R 2453. Code designation for Demegestone.
R-2498. Code designation for Trifluperidol.
R 2858. Code designation for Moxestrol.
R 2962. Code designation for Amiperone.
R 3248. Code designation for Aceperone.
R 3345. Code designation for Pipamperone.
R 3365. Code designation for Piritramide.
R3827. Code designation for Abarelix.
R 3959. Code designation for Clometacin.
R 4082. Code designation for Propyperone.
R-4263. Code designation for Fentanyl Citrate.
R 4318. Code designation for Floctafenine.
R 4444. Code designation for Duometacin.
R-4584. Code designation for Benperidol.
R 4714. Code designation for Oxiperomide.
R-4749. Code designation for Droperidol.
R 4845. Code designation for Bezitramide.
R 5046. Code designation for Cinperene.

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R 5147. Code designation for Spiperone.
R 5188. Code designation for Spiroxatrine.
R 5385. Code designation for Acoxatrine.
R 5808. Code designation for Spiramide.
R 6109. Code designation for Spirilene.
R 6218. Code designation for Fluspirilene.
R 6238. Code designation for Pimozide.
R 6438. Code designation for Antazonite.
R 7242. Code designation for Difluanine Hydrochloride.
R 7464. Code designation for Propoxate.
R 7904. Code designation for Lidoflazine.
R 8025. Code designation for Antienite.
R 8141. Code designation for Antienite.
R-8193. Code designation for Antafenite.
R 8284. Code designation for Proclonol.
R 8299. Code designation for Tetramisole Hydrochloride.
R 9298. Code designation for Seperidol Hydrochloride.
R 10,948. Code designation for Diamocaine Cyclamate.
R 11,333. Code designation for Bromperidol.
R 12,563 [as hydrochloride]. Code designation for Dexamisole.
R 12,564. Code designation for Levamisole Hydrochloride.
R-13423. Code designation for Dicloxacillin.
R 13,558. Code designation for Fetoxylate Hydrochloride.
R-13,672. Code designation for Haloperidol Decanoate.
R 14,827. Code designation for Econazole Nitrate.
R 14,889. Code designation for Miconazole Nitrate.
R 14,950. Code designation for Flunarizine Hydrochloride.
R 15,403 [as hydrochloride]. Code designation for Difenoxin.
R-15,454 [as nitrate salt]. Code designation for Isoconazole.
R 15,556. Code designation for Orconazole Nitrate.
R 15,889. Code designation for Lorcainide Hydrochloride.
R 16,341. Code designation for Penfluridol.
R 16,470 [as hydrochloride]. Code designation for Dexetimide.
R 17,147. Code designation for Cyclobendazole.
R 17,635. Code designation for Mebendazole.
R 17,889. Code designation for Flubendazole.
R 17,934. Code designation for Nocodazole.
R 18,553. Code designation for Loperamide Hydrochloride.
R 18,910. Code designation for Fluperamide.
R 19,317. Code designation for Rodocaine.
R 22,700 [as hydrochloride]. Code designation for Rodocaine.
R 23,050. Code designation for Salantel.
R 23,633. Code designation for Fludazonium Chloride.
R 23,979. Code designation for Enilconazole.
R-25,061. Code designation for Suprofen.
R-25,160. Code designation for Cliprofen.
R 25,540. Code designation for Imafen Hydrochloride.
R 25,831 [as the free base]. Code designation for Carnidazole.
R 26,412. Code designation for Sulnidazole.
R 27,500. Code designation for Sepazonium Chloride.
R 28,096 [as hydrochloride]. Code designation for Carnidazole.
R-28,644. Code designation for Azaconazole.
R 28,930. Code designation for Fluspiperone.
R 29,764. Code designation for Clopimozide.
R 29,860. Code designation for Nitramisole Hydrochloride.
R 30,730. Code designation for Sufentanil.
R 31,520. Code designation for Closantel.
R 33,204. Code designation for Declenperone.
R 33,799. Code designation for Carfentanil Citrate.
R 33800. Code designation for Sufentanil Citrate.
R 33,812. Code designation for Domperidone.
R 34,000. Code designation for Doconazole.
R 34,009. Code designation for Milenperone.
R 34,301. Code designation for Halopemide.
R-34,803. Code designation for Etibendazole.
R 34,995. Code designation for Lofentanil Oxalate.
R 35,443. Code designation for Oxatomide.
R 38,198. Code designation for Buterizine.
R 39,209. Code designation for Alfentanil Hydrochloride.
R 39,500. Code designation for Parconazole Hydrochloride.
R 41,400. Code designation for Ketoconazole.
R-41,468. Code designation for Ketanserin.
R-42,470. Code designation for Terconazole.
R 43,512. Code designation for Astemizole.
R-43512. Code designation for Tecastemizole.
R-45,486. Code designation for Flumeridone.
R-46,541. Code designation for Bromperidol Decanoate.
R 46,846. Code designation for Tubulozole Hydrochloride.
R-47,465. Code designation for Pirenperone.
R 50,547. Code designation for Levocabastine Hydrochloride.
R 51,211. Code designation for Itraconazole.
R-51,469. Code designation for Mioflazine Hydrochloride.
R-51,619. Code designation for Cisapride.
R 52,245. Code designation for Setoperone.
R-53,200. Code designation for Altanserin Tartrate.
R 54,718. Code designation for Transcainide.
R 55104. Code designation for Erbulozole.
R 55,667. Code designation for Ritanserin.
R 57959. Code designation for Barmastine.
R58425. Code designation for Loperamide Oxide.
R 58735. Code designation for Sabeluzole.
R 60844. Code designation for Irtemazole.
R62,690. Code designation for Clazuril.
R64,433. Code designation for Diclazuril.
R 64947. Code designation for Noberastine.
R65,824. Code designation for Nebivolol.
R 66905. Code designation for Saperconazole.
R 67408. Code designation for Fenclofenac.
R067555. Code designation for Nebivolol Hydrochloride.
R 68070. Code designation for Ridogrel.
R 72063. Code designation for Loreclezole.
R 75231. Code designation for Draflazine.
R 75251. Code designation for Liarozole Hydrochloride.
R 77975. Code designation for Pirodavir.
R 79598. Code designation for Ocaperidone.
R 83842. Code designation for Vorozole.
R 85246. Code designation for Liarozole Fumarate.
R-87926. Code designation for Lubeluzole.
R-89439. Code designation for Loviride.
R 89674. Code designation for Alcaftadine.
R-91274. Code designation for Alniditan Dihydrochloride.
R103757. Code designation for Mitratapide.
R-106056. Code designation for Rivoglitazone.
R115500. Code designation for Catramilast.
R115777. Code designation for Tipifarnib.
R126638. Code designation for Pramiconazole.
R129160. Code designation for Vapitadine Dihydrochloride.
RA-8. Code designation for Dipyridamole.
RA-C-384. Code designation for Iodocetylic Acid I 123.
RAD001. Code designation for Everolimus.
RB5 IgM. Code designation for Technetium Tc 99m Fanolesomab.
rBPI-$_{21}$. Code designation for Opebacan.
RC 61-91. Code designation for Ifenprodil.
RC-160. Code designation for Vapreotide.
RC-167. Code designation for Niceverine.
RC-172. Code designation for Aldioxa.
RC-173. Code designation for Alcloxa.
RC-27109. Code designation for Nifuroxazide.
RCH 314. Code designation for Benhepazone.
RCM 258. Code designation for Fepentolic Acid.
Rd 292. Code designation for Fenpentadiol.
RD 328. Code designation for Pasiniazid.
RD 406. Code designation for Cyprodenate.
RD 2801. Code designation for Pyritidium Bromide.
RD 9338 [as hydrochloride]. Code designation for Norbudrine.
RD 11654. Code designation for Ibufenac.

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RD 17345. Code designation for Fluprofen.
rDSPA alpha 1. Code designation for Desmoteplase.
Rec 7/0267. Code designation for Dimefline Hydrochloride.
Rec 15 0122. Code designation for Nifurpipone.
Rec 15/1476. Code designation for Fenticonazole Nitrate.
Rec-15/2375. Code designation for Lercanidipine Hydrochloride.
REV 3659-(S). Code designation for Pivopril.
REV 6000A. Code designation for Delapril Hydrochloride.
RFS 2000. Code designation for Rubitecan.
RG 270. Code designation for Iomeglamic Acid.
RG 12561. Code designation for Dalvastatin.
RG 83606. Code designation for Diltiazem Hydrochloride.
rG-CSF. Code designation for Lenograstim.
RGH 1106. Code designation for Pipecuronium Bromide.
RGW-2938. Code designation for Prinoxodan.
RH-565. Code designation for Uredofos.
RH-32,565. Code designation for Uredofos.
RHC 2871. Code designation for Eclazolast.
RHC 2906. Code designation for Flordipine.
RHC 3659-(S). Code designation for Pivopril.
RHC 3988. Code designation for Quazolast.
rhGAA. Code designation for Alglucosidase Alfa.
rhGm-CSF. Code designation for Regramostim.
rhIGFBP-3. Code designation for Rinfabate.
rhIGF-I/rhIGFBP-3. Code designation for Mecasermin Rinfabate.
r-hTBP-1. Code designation for Onercept.
rhu GM-CSF. Code designation for Sargramostim.
rhu TNFR:Fc. Code designation for Etanercept.
rhuMab 2C4. Code designation for Pertuzumab.
rhuMAb CD18. Code designation for Erlizumab.
rhuMab-E25. Code designation for Omalizumab.
rHuPH20. Code designation for Hyaluronidase (Human Recombinant).
rhVEGF. Code designation for Telbermin.
RI-64. Code designation for Pifexole.
Rifamycin M-14. Code designation for Rifamide.
Riker 52G. Code designation for Aprotinin.
Riker 594. Code designation for Sulthiame.
Riker 595. Code designation for Butaperazine.
Riker 601. Code designation for Triaziquone.
RIT 1140. Code designation for Apicycline.
RM 1601. Code designation for Fipronil.
r-metHuG-CSF. Code designation for Filgrastim.
r-metHuLeptin. Code designation for Metreleptin.
RMI 8090DJ. Code designation for Quindecamine Acetate.
RMI 9,384A. Code designation for Desipramine Hydrochloride.
RMI 9918. Code designation for Terfenadine.
RMI 10,482A. Code designation for Metizoline Hydrochloride.
RMI 16,238. Code designation for Eterobarb.
RMI 16,289. Code designation for Enclomiphene.
RMI 16,312. Code designation for Zuclomiphene.
RMI 80,029. Code designation for Elantrine.
RMI 81,182EF. Code designation for Cilobamine Mesylate.
RMI 81,968. Code designation for Medroxalol.
RMI 81,968 A. Code designation for Medroxalol Hydrochloride.
RMI 83,027. Code designation for Rolicyprine.
RMI 83,047. Code designation for Ambuside.
RMP-7. Code designation for Labradimil.
RNH-5139. Code designation for Temocaprilat.
RNH-6270. Code designation for Olmesartan.
RO 1-5155. Code designation for Nicotinyl Alcohol.
Ro 01-6794/706; Ro 1-6794 (dextrorphan). Code designation for Dextrorphan Hydrochloride.
Ro 1-9334/19. Code designation for Dehydroemetine.
Ro 1-9569. Code designation for Tetrabenazine.
Ro 2-2985. Code designation for Lasalocid.
Ro 2-3773. Code designation for Clidinium Bromide.
Ro 2-9757. Code designation for Fluorouracil.
Ro 2-9915. Code designation for Flucytosine.
Ro 03-7355/000. Code designation for Avizafone.
Ro 03-8799. Code designation for Pimonidazole.
Ro 4-0403. Code designation for Chlorprothixene.
Ro 4-1544-6. Code designation for Sodium Stibocaptate.
Ro 4-1778/1. Code designation for Methopholine.
Ro 4-2130. Code designation for Sulfamethoxazole.
Ro 4-3780. Code designation for Isotretinoin.
RO 4-3816. Code designation for Alcuronium Chloride.
Ro 4-4393. Code designation for Sulfadoxine.
Ro 4-4602. Code designation for Benserazide.
Ro 4-5282. Code designation for Mefenorex Hydrochloride.
Ro 4-5360. Code designation for Nitrazepam.
Ro 4-6467/1. Code designation for Procarbazine Hydrochloride.
Ro 5-0690. Code designation for Chlordiazepoxide Hydrochloride.
Ro 5-2092. Code designation for Demoxepam.
Ro 5-2807. Code designation for Diazepam.
Ro 5-3059. Code designation for Nitrazepam.
RO 5-3307/1. Code designation for Debrisoquin Sulfate.
Ro 5-3350. Code designation for Bromazepam.
Ro 5-4023. Code designation for Clonazepam.
Ro 5-4200. Code designation for Flunitrazepam.
Ro 5-4556. Code designation for Medazepam Hydrochloride.
Ro 5-4645/010. Code designation for Coumermycin Sodium.
Ro 5-6901. Code designation for Flurazepam Hydrochloride.
Ro 5-9110/1. Code designation for Dorastine Hydrochloride.
Ro 5-9754. Code designation for Ormetoprim.
Ro 6-4563. Code designation for Glibornuride.
Ro 7-0207. Code designation for Ornidazole.
Ro 7-0582. Code designation for Misonidazole.
Ro 7-1554. Code designation for Ipronidazole.
Ro 7-4488/1. Code designation for Cuprimyxin.
Ro 09-1978/000. Code designation for Capecitabine.
Ro 10-1670/000. Code designation for Acitretin.
Ro 10-6338. Code designation for Bumetanide.
Ro 10-9070. Code designation for Amdinocillin.
Ro 10-9071. Code designation for Amdinocillin Pivoxil.
Ro 10-9359. Code designation for Etretinate.
Ro 11-1163/000. Code designation for Moclobemide.
Ro 11-1430. Code designation for Motretinide.
Ro 11-1781/023. Code designation for Tiapamil Hydrochloride.
Ro 12-0068/000. Code designation for Tenoxicam.
Ro 13-5057. Code designation for Aniracetam.
Ro 13-6438/006. Code designation for Quazinone.
Ro 13-8996. Code designation for Oxiconazole Nitrate.
Ro 13-9297. Code designation for Lornoxicam.
Ro 13-9904. Code designation for Ceftriaxone Sodium.
Ro 14-4767/000. Code designation for Amorolfine.
Ro 14-9706/000. Code designation for Sumarotene.
Ro 15-1570/000. Code designation for Etarotene.
Ro 15-1788/000. Code designation for Flumazenil.
Ro 16-6028/000. Code designation for Bretazenil.
Ro 17-2301/006. Code designation for Carumonam Sodium.
Ro 18-0647/002. Code designation for Orlistat.
Ro 19-6327/000. Code designation for Lazabemide.
Ro 19-6327/001. Code designation for Lazabemide Hydrochloride.
Ro 20-5720/000. Code designation for Carprofen.
Ro 21-0702. Code designation for Flurocitabine.
Ro 21-3981/001. Code designation for Midazolam Maleate.
Ro 21-3981/003. Code designation for Midazolam Hydrochloride.
Ro 21-5535. Code designation for Calcitriol.
Ro 21-5998. Code designation for Mefloquine.
Ro 21-5998/001. Code designation for Mefloquine Hydrochloride.
Ro 21-6937/000. Code designation for Trimoprostil.
Ro 21-8837/001. Code designation for Estramustine Phosphate Sodium.

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Ro 22-1319/003. Code designation for Piquindone Hydrochloride.
Ro 22-2296/000. Code designation for Estramustine.
Ro 22-3747/000. Code designation for Tiacrilast.
Ro 22-3747/007. Code designation for Tiacrilast Sodium.
Ro 22-7796. Code designation for Cifenline.
Ro 22-7796/001. Code designation for Cifenline Succinate.
Ro 22-8181. Code designation for Interferon Alfa-2a.
Ro 22-9000. Code designation for Alfaprostol.
Ro 23-0731/000. Code designation for Sedecamycin.
Ro 23-3544/000. Code designation for Ablukast.
Ro 23-3544/001. Code designation for Ablukast Sodium.
Ro 23-6019. Code designation for Teceleukin.
Ro 23-6240/000. Code designation for Fleroxacin.
Ro 24-2027/000. Code designation for Zalcitabine.
Ro 24-5913. Code designation for Cinalukast.
Ro 24-7375. Code designation for Daclizumab.
Ro 24-7472/000. Code designation for Edodekin Alfa.
Ro 25-8310/000. Code designation for Peginterferon Alfa-2a.
Ro-25-8315/000. Code designation for Pegnartograstim.
Ro27-2441/002. Code designation for Valategrast Hydrochloride.
Ro 31-2848/006. Code designation for Cilazapril.
Ro 31-3113. Code designation for Cilazaprilat.
Ro 31-3948/000. Code designation for Romazarit.
Ro 31-8959/000. Code designation for Saquinavir.
Ro 31-8959/003. Code designation for Saquinavir Mesylate.
Ro 32-3555/000. Code designation for Cipemastat.
Ro 40-5967/001. Code designation for Mibefradil Dihydrochloride.
Ro 40-7592. Code designation for Tolcapone.
Ro 42-1611. Code designation for Arteflene.
Ro 44-9883/000. Code designation for Lamifiban.
Ro 44-9883/023. Code designation for Lamifiban Hydrochloride.
Ro 45-2081. Code designation for Lenercept.
Ro 46-6240/010. Code designation for Napsagatran.
Ro 47-0203/029. Code designation for Bosentan.
Ro 48-3657/001. Code designation for Sibrafiban.
Ro 63-9141. Code designation for Ceftobiprole.
Ro 64-0796/002. Code designation for Oseltamivir Phosphate.
Ro 65-5788. Code designation for Ceftobiprole Medocaril.
Ro 67-3189/000. Code designation for Netupitant.
Ro 67-5930. Code designation for Befetupitant.
Ro 70-0001/001. Code designation for Semparatide Acetate.
Ro 106-6271/297. Code designation for Semparatide Acetate.
Ro107-9070/194. Code designation for Valganciclovir Hydrochloride.
RO115-1240/190. Code designation for Dabuzalgron Hydrochloride.
Ro 48347. Code designation for Trengestone.
RO76477. Code designation for Paliperidone.
RO92670. Code designation for Paliperidone Palmitate.
Ro0272441/002. Code designation for Valategrast Hydrochloride.
RO 640796. Code designation for Oseltamivir.
RO2052349-602. Code designation for Edaglitazone Sodium.
R.P. 20 578. Code designation for Bamnidazole.
RP 2254. Code designation for Glyprothiazol.
RP 2259. Code designation for Glybuthiazol.
RP 2512 [as isethionate]. Code designation for Pentamidine.
RP 2921. Code designation for Aminothiazole.
RP 2987. Code designation for Diethazine Hydrochloride.
RP 3854. Code designation for Melarsoprol.
RP 4763 [as sodium salt]. Code designation for Difetarsone.
RP 5171. Code designation for Proadifen Hydrochloride.
RP 5337. Code designation for Spiramycin.
RP 6484. Code designation for Etymemazine Hydrochloride.
RP 6847. Code designation for Oxomemazine.
RP 6870. Code designation for Inproquone.
RP-7044. Code designation for Levomepromazine.
RP 7044. Code designation for Methotrimeprazine.
RP 7204. Code designation for Cyamemazine.
RP 7293. Code designation for Pristinamycin.
RP 7891. Code designation for Glybuzole.
RP 8595. Code designation for Dimetridazole.
RP 8823. Code designation for Metronidazole.
RP 8909. Code designation for Periciazine.
RP 9159. Code designation for Perimetazine.
RP 9671. Code designation for Nosiheptide.
RP 9778. Code designation for Protionamide.
RP 9921. Code designation for Aprotinin.
RP 9955. Code designation for Melarsonyl Potassium.
RP 12222. Code designation for Penmesterol.
RP 13057 [as the base]. Code designation for Daunorubicin Hydrochloride.
RP 13607. Code designation for Clotioxone.
RP 14539. Code designation for Secnidazole.
RP 16091. Code designation for Metiazinic Acid.
RP 19552. Code designation for Pipotiazine Palmitate.
R.P. 19,583. Code designation for Ketoprofen.
RP 22,050 hydrochloride. Code designation for Zorubicin Hydrochloride.
RP 22410. Code designation for Glisoxepide.
RP 27267. Code designation for Zopiclone.
RP 31264. Code designation for Suriclone.
RP 54274. Code designation for Riluzole.
RP 54476. Code designation for Dalfopristin.
RP 54563. Code designation for Enoxaparin Sodium.
RP-54780. Code designation for Oxaliplatin.
RP 56976. Code designation for Docetaxel.
RP 57669. Code designation for Quinupristin.
RP 60475. Code designation for Intoplicine.
RP 62203. Code designation for Fananserin.
RP 62955. Code designation for Pagoclone.
RP 64305. Code designation for Ebastine.
RP 73401. Code designation for Piclamilast.
rPAF-AH. Code designation for Epafipase.
RPR251526. Code designation for Ciclesonide.
RR No. 32705. Code designation for Rutamycin.
R&S 218-M. Code designation for Alletorphine.
RS-1301. Code designation for Delmadinone Acetate.
RS-1320. Code designation for Flunisolide Acetate.
RS-2208. Code designation for Amadinone Acetate.
RS-2252. Code designation for Flucloronide.
RS-2362. Code designation for Procinonide.
RS-2386. Code designation for Ciprocinonide.
RS-3268R. Code designation for Nandrolone Cyclotate.
RS-3540. Code designation for Naproxen.
RS-3650. Code designation for Naproxen Sodium.
RS-3694R. Code designation for Cormethasone Acetate.
RS-3999. Code designation for Flunisolide.
RS-4034. Code designation for Naproxol.
RS-4464. Code designation for Triclonide.
RS-4691. Code designation for Cloprednol.
R&S 5205-M. Code designation for Homprenorphine.
RS-6245. Code designation for Tazolol Hydrochloride.
RS-6818. Code designation for Xanoxate Sodium.
RS-7337. Code designation for Tixanox.
RS-8858. Code designation for Oxfendazole.
RS-9390. Code designation for Prostalene.
RS-10085-197. Code designation for Moexipril Hydrochloride.
RS-11988. Code designation for Laidlomycin Propionate Potassium.
RS-15385-197. Code designation for Delequamine Hydrochloride.
RS-21361. Code designation for Imiloxan Hydrochloride.
RS-21592. Code designation for Ganciclovir.
RS-21592 sodium. Code designation for Ganciclovir Sodium.
RS-21607-197. Code designation for Azalanstat Dihydrochloride.
RS-25259-197. Code designation for Palonosetron Hydrochloride.

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RS-25560-197. Code designation for Nepicastat Hydrochloride.
RS-26306. Code designation for Ganirelix Acetate.
RS-35887. Code designation for Butoconazole Nitrate.
RS-35887-00-10-3. Code designation for Butoconazole Nitrate.
RS-35909-00-00-0. Code designation for Ticabesone Propionate.
RS-37326. Code designation for Anirolac.
RS-37449. Code designation for Temurtide.
RS-40584. Code designation for Flumoxonide.
RS-40974-00-00-0. Code designation for Tiopinac.
RS-43179. Code designation for Lonapalene.
RS-43285. Code designation for Ranolazine Hydrochloride.
RS-43285-003. Code designation for Ranolazine.
RS-44872. Code designation for Sulconazole Nitrate.
RS-44872-00-10-3. Code designation for Sulconazole Nitrate.
RS-49014. Code designation for Tazifylline Hydrochloride.
RS-61443. Code designation for Mycophenolate Mofetil.
RS-61443 [as mofetil]. Code designation for Mycophenolic Acid.
RS-61443-190. Code designation for Mycophenolate Mofetil Hydrochloride.
RS-66271-297. Code designation for Semparatide Acetate.
RS-68439. Code designation for Detirelix Acetate.
RS-69216. Code designation for Nicardipine Hydrochloride.
RS-69216-XX-07-0. Code designation for Nicardipine Hydrochloride.
RS-079070-194. Code designation for Valganciclovir Hydrochloride.
RS-82856. Code designation for Lixazinone Sulfate.
RS-82917-030. Code designation for Tifurac Sodium.
RS-84043. Code designation for Fenprostalene.
RS-84135. Code designation for Enprostil.
RS-85446-007. Code designation for Timobesone Acetate.
RS-87476-000. Code designation for Lifarizine.
RS-94991-298. Code designation for Nafarelin Acetate.
RS-100302-190. Code designation for Sulamserod Hydrochloride.
RSD1235. Code designation for Vernakalant Hydrochloride.
RSP58. Code designation for Delmitide Acetate.
RSR13. Code designation for Efaproxiral.
RSR13 sodium. Code designation for Efaproxiral Sodium.
R-tofisopam. Code designation for Dextofisopam.
rt-PA. Code designation for Alteplase.
RU-0211. Code designation for Lubiprostone.
RU 486. Code designation for Mifepristone.
RU 882. Code designation for Inocoterone Acetate.
RU 965. Code designation for Roxithromycin.
RU-1697. Code designation for Trenbolone Acetate.
RU-2267. Code designation for Altrenogest.
RU 2323. Code designation for Gestrinone.
RU 15060. Code designation for Tiaprofenic Acid.
Ru 15750. Code designation for Floctafenine.
RU-19110. Code designation for Halofuginone Hydrobromide.
Ru 23908. Code designation for Nilutamide.
RU 24756. Code designation for Cefotaxime Sodium.
RU 27987. Code designation for Trimegestone.
RU 28965. Code designation for Roxithromycin.
RU35926. Code designation for Milameline Hydrochloride.
RU 38486. Code designation for Mifepristone.
RU 38882. Code designation for Inocoterone Acetate.
RU 44570. Code designation for Trandolapril.
RUF 331. Code designation for Rufinamide.
RWJ 10131. Code designation for Norgestimate.
RWJ-10553. Code designation for Norelgestromin.
RWJ 15817. Code designation for Edoxudine.
RWJ 15927. Code designation for Rioprostil.
RWJ 16600. Code designation for Bemarinone Hydrochloride.
RWJ-17021. Code designation for Topiramate.
RWJ 17070. Code designation for Histrelin.
RWJ 18704. Code designation for Pelretin.
RWJ 20257. Code designation for Doretinel.
RWJ 20485. Code designation for Tepoxalin.
RWJ 21757. Code designation for Loxoribine.
RWJ 22164. Code designation for Atosiban.
RWJ 24517. Code designation for Carsatrin Succinate.
RWJ 24834. Code designation for Linarotene.
RWJ-25213. Code designation for Levofloxacin.
RWJ 26251. Code designation for Cladribine.
RWJ 28299. Code designation for Immune Globulin Intravenous Pentetate.
RWJ 37796. Code designation for Mazapertine Succinate.
RWJ 47428. Code designation for Prazarelix Acetate.
RWJ 49004. Code designation for Cedelizumab.
RWJ-53308. Code designation for Elarofiban.
RWJ-57504. Code designation for Tilmacoxib.
RWJ 60235. Code designation for Becaplermin.
RWJ-241947. Code designation for Netoglitazone.
RWJ-270201. Code designation for Peramivir.
RWJ-333369. Code designation for Carisbamate.
RX 6029-M HCl. Code designation for Buprenorphine Hydrochloride.
Rx 67408. Code designation for Fenclofenac.
RX77989. Code designation for Pentamorphone.
R-(-)-YM-12617. Code designation for Tamsulosin Hydrochloride.
S 7. Code designation for Fenticlor.
S-041. Code designation for Gadodiamide.
S-043. Code designation for Sprodiamide.
S.049. Code designation for Ecadotril.
S-59. Code designation for Amotosalen Hydrochloride.
S-62. Code designation for Chlorphentermine Hydrochloride.
S 73 4118. Code designation for Piretanide.
S 77 0777. Code designation for Prednicarbate.
S 77 1221 B [as sodium]. Code designation for Cefodizime.
S-210. Code designation for Morsuximide.
S-222. Code designation for Ditazole.
S-303 · 2HCl. Code designation for Amustaline Dihydrochloride.
S 314. Code designation for Fusafungine.
S-940. Code designation for Naftalofos.
S-1153. Code designation for Capravirine.
S-1210. Code designation for Bietaserpine.
S-1320. Code designation for Budesonide.
S 1530. Code designation for Nimetazepam.
S-2395. Code designation for Tertatolol.
S-2539F. Code designation for Phenothrin.
S-2620. Code designation for Almitrine Mesylate.
S 4105. Code designation for Medibazine.
S-4522. Code designation for Rosuvastatin Calcium.
S-4661. Code designation for Doripenem.
S 5614 HCl. Code designation for Dexfenfluramine Hydrochloride.
S-9490. Code designation for Perindopril.
S-9490-3. Code designation for Perindopril Erbumine.
S-9780. Code designation for Perindoprilat.
S 10036. Code designation for Fotemustine.
S-16820. Code designation for Prifelone.
S-25930. Code designation for Ibafloxacin.
S26308. Code designation for Imiquimod.
S-30594. Code designation for Sotirimod.
SA-267. Code designation for Dipenine Bromide.
SANORG34006. Code designation for Idraparinux Sodium.
SB-075 acetate. Code designation for Cetrorelix Acetate.
SB 7505. Code designation for Ibopamine.
SB-202026-A. Code designation for Sabcomeline Hydrochloride.
SB-204269-EO. Code designation for Carabersat.
SB 205312. Code designation for Pranlukast.
SB-207266-A. Code designation for Piboserod Hydrochloride.
SB 207499. Code designation for Cilomilast.
SB-209247. Code designation for Ticolubant.

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SB 209509-AX. Code designation for Frovatriptan Succinate.
SB 209763. Code designation for Felvizumab.
SB-214857-A. Code designation for Lotrafiban Hydrochloride.
SB-218842. Code designation for Tidembersat.
SB-220453. Code designation for Tonabersat.
SB-223030. Code designation for Idoxifene.
SB-223412-A. Code designation for Talnetant Hydrochloride.
SB-240563. Code designation for Mepolizumab.
SB-240683. Code designation for Pascolizumab.
SB-251353. Code designation for Garnocestim.
SB-265805-S. Code designation for Gemifloxacin Mesylate.
SB-275833. Code designation for Retapamulin.
SB-408075. Code designation for Cantuzumab Mertansine.
SB-462795. Code designation for Relacatib.
SB-480848. Code designation for Darapladib.
SB-485232. Code designation for Iboctadekin.
SB-497115-GR. Code designation for Eltrombopag Olamine.
SB-659032. Code designation for Rilapladib.
SB-683699. Code designation for Firategrast.
SB-715992-S. Code designation for Ispinesib Mesylate.
SBI-0067. Code designation for Galasomite.
SBW-22. Code designation for Ketorfanol.
SC103. Code designation for Ascorbyl Gamolenate.
SC-0735. Code designation for Nitisinone.
SC 1749 [as sodium salt]. Code designation for Menbutone.
SC-4642. Code designation for Norethynodrel.
SC-7031. Code designation for Disopyramide.
SC-7294. Code designation for Propetandrol.
SC-7525. Code designation for Bolandiol Dipropionate.
SC-9376. Code designation for Canrenone.
SC-9880. Code designation for Flurogestone Acetate.
SC 10363. Code designation for Megestrol Acetate.
SC 11585. Code designation for Oxandrolone.
SC 11800. Code designation for Ethynodiol Diacetate.
SC-12350. Code designation for Nitralamine Hydrochloride.
SC-12937. Code designation for Azacosterol Hydrochloride.
SC-13504. Code designation for Ropizine.
SC-13957. Code designation for Disopyramide Phosphate.
SC-14207. Code designation for Metogest.
SC-14266. Code designation for Canrenoate Potassium.
SC-16148. Code designation for Silandrone.
SC-18862. Code designation for Aspartame.
SC-19198. Code designation for Methynodiol Diacetate.
SC-21009. Code designation for Norgestomet.
SC-23992. Code designation for Prorenoate Potassium.
SC-25469. Code designation for Pinadoline.
SC-26100. Code designation for Difenoximide Hydrochloride.
SC-26304. Code designation for Dicirenone.
SC-26438. Code designation for Pirolazamide.
SC-26714. Code designation for Mexrenoate Potassium.
SC-27123. Code designation for Octriptyline Phosphate.
SC-27166. Code designation for Nufenoxole.
SC-27761. Code designation for Pranolium Chloride.
SC-29333. Code designation for Misoprostol.
SC-31828. Code designation for Disobutamide.
SC-32642. Code designation for Metronidazole Hydrochloride.
SC-32840. Code designation for Oxagrelate.
SC-33643. Code designation for Bemitradine.
SC-33963. Code designation for Reclazepam.
SC-34301. Code designation for Enisoprost.
SC-35135. Code designation for Edifolone Acetate.
SC-36602. Code designation for Actisomide.
SC-37681. Code designation for Gemeprost.
SC-38390. Code designation for Zinoconazole Hydrochloride.
SC-39026. Code designation for Lodelaben.
SC-40230. Code designation for Bidisomide.
SC-47111. Code designation for Lomefloxacin Hydrochloride.
SC-47111A. Code designation for Lomefloxacin.
SC-47111B. Code designation for Lomefloxacin Mesylate.
SC-48834. Code designation for Remiprostol.
SC-52151. Code designation for Telinavir.
SC-52458. Code designation for Forasartan.
SC-54684A. Code designation for Xemilofiban Hydrochloride.
SC-55389A. Code designation for Droxinavir Hydrochloride.
SC-55494. Code designation for Daniplestim.
SC-57099B. Code designation for Orbofiban Acetate.
SC-58635. Code designation for Celecoxib.
SC-59046. Code designation for Deracoxib.
SC-59735. Code designation for Tifacogin.
SC-65872. Code designation for Valdecoxib.
SC-66110. Code designation for Eplerenone.
SC-69124. Code designation for Parecoxib.
SC-69124A. Code designation for Parecoxib Sodium.
SC-70935. Code designation for Leridistim.
SC-72325. Code designation for Imisopasem Manganese.
SCA-136. Code designation for Vabicaserin Hydrochloride.
SCE 963. Code designation for Cefotiam Hydrochloride.
SCE-1365 (Takeda) (base). Code designation for Cefmenoxime Hydrochloride.
Sch 1000-Br-monohydrate. Code designation for Ipratropium Bromide.
Sch 2544. Code designation for Cycliramine Maleate.
Sch 3444. Code designation for Parapenzolate Bromide.
Sch 4358. Code designation for Meprednisone.
Sch 4831. Code designation for Betamethasone.
Sch 4855. Code designation for Pseudoephedrine Sulfate.
Sch 6620. Code designation for Prednazate.
Sch 6673. Code designation for Acetophenazine Maleate.
Sch 6783. Code designation for Diazoxide.
Sch 7056. Code designation for Acrisorcin.
Sch 9384. Code designation for Oxymetazoline Hydrochloride.
Sch 9724. Code designation for Gentamicin Sulfate.
Sch 10144. Code designation for Tolnaftate.
Sch 10159. Code designation for Triclofos Sodium.
Sch 10304. Code designation for Clonixin.
Sch 10595. Code designation for Bupicomide.
Sch 10649. Code designation for Azatadine Maleate.
Sch 11460. Code designation for Betamethasone Dipropionate.
Sch 11572. Code designation for Meclorisone Dibutyrate.
Sch 11973. Code designation for Tosifen.
Sch 12041. Code designation for Halazepam.
Sch 12149. Code designation for Pazoxide.
Sch 12169. Code designation for Closiramine Aceturate.
Sch 12650. Code designation for Dazadrol Maleate.
Sch 12679. Code designation for Trepipam Maleate.
Sch 12707. Code designation for Clonixeril.
Sch 13166 D fumarate. Code designation for Domazoline Fumarate.
Sch 13430.2KH_2PO_4. Code designation for Megalomicin Potassium Phosphate.
Sch 13475 sulfate. Code designation for Sisomicin Sulfate.
Sch 13521. Code designation for Flutamide.
Sch 13949W Sulfate. Code designation for Albuterol Sulfate.
Sch 14342. Code designation for Betamicin Sulfate.
Sch 14714. Code designation for Flunixin.
Sch 14714 meglumine. Code designation for Flunixin Meglumine.
Sch 14947. Code designation for Rosaramicin.
Sch 14947 Stearate. Code designation for Rosaramicin Stearate.
Sch 14947.NaH_2PO_4. Code designation for Rosaramicin Sodium Phosphate.
Sch 15280. Code designation for Azanator Maleate.
Sch 15427. Code designation for Carmantadine.
Sch 15507. Code designation for Dopamantine.
Sch 15698. Code designation for Fletazepam.
Sch 15719W. Code designation for Labetalol Hydrochloride.
Sch 16134. Code designation for Quazepam.

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Sch 16524. Code designation for Repromicin.
Sch 17894. Code designation for Rosaramicin Propionate.
Sch 18020W. Code designation for Beclomethasone Dipropionate.
Sch 18667. Code designation for Rosaramicin Butyrate.
Sch 19741. Code designation for Picotrin Diolamine.
Sch 19927. Code designation for Dilevalol Hydrochloride.
Sch 20569. Code designation for Netilmicin Sulfate.
Sch 21420. Code designation for Isepamicin.
Sch 21480. Code designation for Tioxidazole.
Sch 22219. Code designation for Alclometasone Dipropionate.
Sch 22591. Code designation for Pentisomicin.
Sch 25298. Code designation for Florfenicol.
SCH 27899. Code designation for Evernimicin.
Sch 28316Z. Code designation for Indenolol.
Sch 29851. Code designation for Loratadine.
Sch 30500. Code designation for Interferon Alfa-2b.
Sch 31353. Code designation for Dexamethasone Acefurate.
Sch 32088. Code designation for Mometasone Furoate.
Sch 32481. Code designation for Netobimin.
Sch 33844. Code designation for Spirapril Hydrochloride.
Sch 33861. Code designation for Spiraprilat.
SCH 34117. Code designation for Desloratadine.
Sch 35852. Code designation for Cisconazole.
SCH 39166. Code designation for Ecopipam Hydrochloride.
Sch 39300. Code designation for Molgramostim.
SCH 39400. Code designation for Binetrakin.
Sch 39720. Code designation for Ceftibuten.
SCH 40054 HCl. Code designation for Nemazoline Hydrochloride.
SCH 52000. Code designation for Ilodecakin.
SCH 52365. Code designation for Temozolomide.
SCH 56592. Code designation for Posaconazole.
SCH57068 · HCl. Code designation for Acolbifene Hydrochloride.
SCH58235. Code designation for Ezetimibe.
SCH 66336. Code designation for Lonafarnib.
SCH 209579. Code designation for Maxacalcitol.
SCH351125. Code designation for Ancriviroc.
SCH 417690. Code designation for Vicriviroc Maleate.
SCH 417849. Code designation for Talibegron Hydrochloride.
SCH 446132. Code designation for Dasantafil.
Scha-306. Code designation for Cintazone.
SCL-70. Code designation for Alofilcon A.
SCTZ [as edisylate]. Code designation for Clomethiazole.
SD 25. Code designation for Dicarfen.
SD 149-01. Code designation for Feneritrol.
SD 270-07 [as succinate]. Code designation for Oxaprazine.
SD 270-31 [as disuccinate]. Code designation for Oxaflumazine.
SD 271-12. Code designation for Clobenzorex.
SD 286-03. Code designation for Cimemoxin.
SD 1223-01. Code designation for Trazitiline.
SD 1248-17 [as hydrochloride]. Code designation for Tropatepine.
SD 1750. Code designation for Dichlorvos.
SD 2102-18. Code designation for Acrocinonide.
SD 2124-01. Code designation for Procinolol.
SD 7859. Code designation for Clorfenvinfos.
SD 14112. Code designation for Sulclamide.
SD 15803. Code designation for Vincofos.
SD 17102. Code designation for Meticrane.
SD 27115 [as cyclamate]. Code designation for Furfenorex.
SDX-105. Code designation for Bendamustine Hydrochloride.
SDZ-212-713. Code designation for Rivastigmine.
SDZ 215-811. Code designation for Pentetreotide.
SDZ 215-811s. Code designation for Pentetreotide.
SDZ ASM 981. Code designation for Pimecrolimus.
SDZ DJN 608. Code designation for Nateglinide.
SDZ ILE 964. Code designation for Muplestim.
SDZ MSL 109. Code designation for Sevirumab.
SDZ OST 577. Code designation for Tuvirumab.
SDZ PSC 833. Code designation for Valspodar.
SDZ-CHI-621. Code designation for Basiliximab.
SDZ-ENA-713. Code designation for Rivastigmine.
SDZ-HTF-919. Code designation for Tegaserod.
SE 1702. Code designation for Gliclazide.
SeHCAT. Code designation for Tauroselcholic Acid.
SERM 3. Code designation for Arzoxifene Hydrochloride.
SF 86-327. Code designation for Terbinafine.
SF-R11. Code designation for Bovactant.
SG-75. Code designation for Nicorandil.
SGD 301-76. Code designation for Oxiconazole Nitrate.
SGP 3. Code designation for Unifocon A.
SH 2.1139/H 248 AB. Code designation for Ioxotrizoic Acid.
SH 3.1168. Code designation for Gliflumide.
SH 100. Code designation for Oxapium Iodide.
SH 213 AB. Code designation for Iotroxic Acid.
SH 240. Code designation for Moxnidazole.
SH 263. Code designation for Droxacin Sodium.
SH 567. Code designation for Methenolone Acetate.
SH 582. Code designation for Gestonorone Caproate.
SH 601. Code designation for Methenolone Enanthate.
SH 714. Code designation for Cyproterone Acetate.
SH 717. Code designation for Glymidine Sodium.
SH 723. Code designation for Mesterolone.
SH 741. Code designation for Clomegestone Acetate.
SH 742. Code designation for Fluocortolone.
SH 770. Code designation for Fluocortolone Caproate.
SH 818. Code designation for Clocortolone Acetate.
SH 863. Code designation for Clocortolone Pivalate.
SH 926. Code designation for Iodamide.
SH 968. Code designation for Diflucortolone Pivalate.
SH 1040. Code designation for Gestaclone.
SH 1051. Code designation for Glicetanile Sodium.
SH B 331. Code designation for Gestodene.
SH E 199. Code designation for Etoformin Hydrochloride.
SH G 318 AB. Code designation for Sermetacin.
SH H 200 AB. Code designation for Ioglicic Acid.
SH H 239 AB. Code designation for Ioseric Acid.
SH K 203. Code designation for Fluocortin Butyl.
SH L 451 *A*. Code designation for Gadopentetate Dimeglumine.
SIB-1508Y. Code designation for Altinicline Maleate.
SJ 1977. Code designation for Methixene Hydrochloride.
SK&F 51. Code designation for Octodrine.
SK&F 478. Code designation for Diphenidol.
SK&F 478-A. Code designation for Diphenidol Hydrochloride.
SK&F 478-J. Code designation for Diphenidol Pamoate.
SK&F 525-A. Code designation for Proadifen Hydrochloride.
SK&F 1340. Code designation for Dimefadane.
SK&F 1995. Code designation for Dicloralurea.
SK&F 2208. Code designation for Hetaflur.
SKF 2599. Code designation for Doxenitoin.
SK&F 3050. Code designation for Cortodoxone.
SK&F 5116. Code designation for Methotrimeprazine.
SK&F 6539. Code designation for Flurothyl.
SK&F 7690. Code designation for Benorterone.
SK&F 7988. Code designation for Virginiamycin.
SKF-8318. Code designation for Xenazoic Acid.
SK&F 8542. Code designation for Triamterene.
SKF 8898-A. Code designation for Moroxydine.
SKF 9976 [as citrate]. Code designation for Oxolamine.
SK&F 12866. Code designation for Clorethate.
SKF 13338. Code designation for Ampyrimine.
SK&F 13364-A. Code designation for Thyromedan Hydrochloride.
SK&F 14287. Code designation for Idoxuridine.
SK&F 14336. Code designation for Clomacran Phosphate.
SK&F 15601A. Code designation for Toliodium Chloride.
SKF 16046. Code designation for Anisacril.

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Page 12440

SK&F 18,667. Code designation for Poloxalene.
SKF 20716. Code designation for Periciazine.
SK&F 24529. Code designation for Lobendazole.
SK&F 28175. Code designation for Fluotracen Hydrochloride.
SK&F 29044. Code designation for Parbendazole.
SK&F 30310. Code designation for Oxibendazole.
SKF 33134-A. Code designation for Amiodarone.
SK&F 38094. Code designation for Dectaflur.
SK&F 38095. Code designation for Olaflur.
SK&F 39162. Code designation for Auranofin.
SK&F 39186. Code designation for Amicloral.
SK&F 40383. Code designation for Carbuterol Hydrochloride.
SK&F 41558. Code designation for Cefazolin Sodium.
SK&F 53705-A. Code designation for Sulfonterol Hydrochloride.
SK&F 59962. Code designation for Cefazaflur Sodium.
SK&F 61636. Code designation for Bromoxanide.
SK&F 62698. Code designation for Ticrynafen.
SK&F 62979. Code designation for Albendazole.
SK&F 63797. Code designation for Dribendazole.
SK&F 69634. Code designation for Clopipazan Mesylate.
SK&F 70230-A. Code designation for Pipazethate.
SK&F 72517. Code designation for Elfazepam.
SK&F 82526-J. Code designation for Fenoldopam Mesylate.
SK&F 88373-Z. Code designation for Ceftizoxime Sodium.
SK&F 92058. Code designation for Metiamide.
SK&F 92657-A_2. Code designation for Prizidilol Hydrochloride.
SK&F 92676-A_3. Code designation for Impromidine Hydrochloride.
SK&F 92994-A_2. Code designation for Oxmetidine Hydrochloride.
SK&F 92994-J_2. Code designation for Oxmetidine Mesylate.
SK&F 93319. Code designation for Icotidine.
SK&F 93479. Code designation for Lupitidine Hydrochloride.
SK&F 93574. Code designation for Donetidine.
SK&F 93944. Code designation for Temelastine.
SK&F 94836. Code designation for Siguazodan.
SK&F 95587. Code designation for Sulotroban.
SK&F 96022. Code designation for Pantoprazole.
SK&F 96148. Code designation for Daltroban.
SK&F 100814. Code designation for Ardacin.
SK&F 101468-A. Code designation for Ropinirole Hydrochloride.
SK&F 102,362. Code designation for Nilvadipine.
SK&F 104353-Q. Code designation for Pobilukast Edamine.
SK&F-105517-D. Code designation for Carvedilol Phosphate.
SK&F 105657. Code designation for Epristeride.
SK&F 106615-A2. Code designation for Atiprimod Dihydrochloride.
SKF-106615-A2. Code designation for Atiprimod Dihydrochloride.
SK&F 106615-I2. Code designation for Atiprimod Dimaleate.
SK&F 107647. Code designation for Glaspimod.
SK&F 108566. Code designation for Eprosartan.
SK&F 108566-J. Code designation for Eprosartan Mesylate.
SK&F D-39304. Code designation for Cephradine.
SK&F D-75073-Z. Code designation for Cefonicid Monosodium.
SK&F D-75073-Z_2. Code designation for Cefonicid Sodium.
SK&F S-104864-A. Code designation for Topotecan Hydrochloride.
SKI-606. Code designation for Bosutinib.
SL 75 177-10. Code designation for Cicloprolol Hydrochloride.
SL 75.212-10. Code designation for Betaxolol Hydrochloride.
SL 76 002. Code designation for Progabide.
SL 77 499-10. Code designation for Alfuzosin Hydrochloride.
SL 79.229-00. Code designation for Fengabine.
SL 80.0342-00. Code designation for Alpidem.
SL 80.0750-23N. Code designation for Zolpidem Tartrate.
SL 81.0142-00. Code designation for Tolgabide.
SL 501. Code designation for Chlophedianol Hydrochloride.
SM-50C. Code designation for Lubazodone Hydrochloride.
SM-1213 (free base). Code designation for Amiprilose Hydrochloride.
SM-3997. Code designation for Tandospirone Citrate.
SM-7338. Code designation for Meropenem.
SM-13496. Code designation for Lurasidone Hydrochloride.
SMP 68-40. Code designation for Pyrabrom.
SMP-78 Acid S. Code designation for Ambruticin.
Sms2PA. Code designation for Strontium Chloride Sr 89.
SMS-201-995. Code designation for Octreotide.
SMS 201-995 ac. Code designation for Octreotide Acetate.
SMS 201-995 pa. Code designation for Octreotide Pamoate.
SMS pa. Code designation for Octreotide Pamoate.
SMT 487. Code designation for Edotreotide.
S.N. 44. Code designation for Insulin, Dalanated.
SN-166 [as the sodium salt]. Code designation for Glucosulfone.
SN-263. Code designation for Sodium Amylosulfate.
SN 654. Code designation for Mepartricin.
SNAC. Code designation for Salcaprozate Sodium.
SND919CL2Y. Code designation for Pramipexole Dihydrochloride.
SND-5008. Code designation for Cevimeline Hydrochloride.
SnET2. Code designation for Rostaporfin.
SNI-2011. Code designation for Cevimeline Hydrochloride.
SNK-508. Code designation for Cevimeline Hydrochloride.
SNR 1804. Code designation for Clamidoxic Acid.
SNX-111. Code designation for Ziconotide.
SP54. Code designation for Pentosan Polysulfate Sodium.
SP63. Code designation for Otilonium Bromide.
SP-106. Code designation for Nabitan Hydrochloride.
SP-119. Code designation for Tinabinol.
SP-175. Code designation for Nabazenil.
SP-204. Code designation for Menabitan Hydrochloride.
SP-303. Code designation for Crofelemer.
SP-304. Code designation for Pirnabine.
SP-325. Code designation for Naboctate Hydrochloride.
SP924. Code designation for Lestaurtinib.
SPA-S-132. Code designation for Partricin.
SPA-S-160. Code designation for Mepartricin.
SPA-S-510. Code designation for Piroxicam Cinnamate.
SPA-S-565. Code designation for Rifametane.
SPC 297 D. Code designation for Azidocillin.
SPC-100270. Code designation for Safingol.
SPC-100271. Code designation for Safingol Hydrochloride.
SPC-101210. Code designation for Cedefingol.
SPI-77. Code designation for Mitopodozide.
SPM 925. Code designation for Moexipril Hydrochloride.
SPM 927. Code designation for Lacosamide.
SPM 962. Code designation for Rotigotine.
SPP100. Code designation for Aliskiren.
SPP100. Code designation for Aliskiren Fumarate.
SQ 1089. Code designation for Hydroxyurea.
SQ 1489. Code designation for Thiram.
SQ 2128. Code designation for Ethoxazene Hydrochloride.
SQ-6201. Code designation for Uracil.
SQ-7726. Code designation for Uracil.
SQ-8493. Code designation for Uracil.
SQ 9343. Code designation for Phytate Sodium.
SQ 9453. Code designation for Dimethyl Sulfoxide.
SQ 9538. Code designation for Testolactone.
SQ 9993. Code designation for Estradiol Undecylate.
SQ 10,269. Code designation for Carbiphene Hydrochloride.
SQ 10,496. Code designation for Thiazesim Hydrochloride.
SQ 10,643. Code designation for Cinanserin Hydrochloride.
SQ 11,302. Code designation for Epicillin.
SQ 11436. Code designation for Cephradine.
SQ 11725. Code designation for Nadolol.
SQ 13050. Code designation for Econazole Nitrate.

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SQ 13,396. Code designation for Iopamidol.
SQ 13847. Code designation for Pirquinozol.
SQ 14055. Code designation for Tiamulin.
SQ 14,225. Code designation for Captopril.
SQ 15,101. Code designation for Algestone Acetophenide.
SQ 15,102. Code designation for Amcinafal.
SQ 15,112. Code designation for Amcinafide.
SQ 15,659. Code designation for Rolitetracycline.
SQ 15,860. Code designation for Glyhexamide.
SQ 15,874. Code designation for Pipazethate.
SQ 16,123. Code designation for Methicillin Sodium.
SQ 16,150. Code designation for Estradiol Enanthate.
SQ 16360. Code designation for Fusidate Sodium.
SQ 16374. Code designation for Methenolone Enanthate.
SQ 16,401. Code designation for Halquinols.
SQ 16,423. Code designation for Oxacillin Sodium.
SQ 16496. Code designation for Methenolone Acetate.
SQ 16,603. Code designation for Fusidic Acid.
SQ 18566. Code designation for Halcinonide.
SQ 19844. Code designation for Sincalide.
SQ 20009. Code designation for Etazolate Hydrochloride.
SQ 20824. Code designation for Cicloprofen.
SQ 20881. Code designation for Teprotide.
SQ 21982. Code designation for Iodoxamic Acid.
SQ 21983. Code designation for Iopronic Acid.
SQ 22022 [dihydrate]. Code designation for Cephradine.
SQ 22947. Code designation for Tiamulin Fumarate.
SQ 26490. Code designation for Naflocort.
SQ 26,703. Code designation for Zofenoprilat Arginine.
SQ 26776. Code designation for Aztreonam.
SQ 26962. Code designation for Mebrofenin.
SQ 26991. Code designation for Zofenopril Calcium.
SQ 27,239. Code designation for Tipredane.
SQ 27,519. Code designation for Fosinoprilat.
SQ 28555. Code designation for Fosinopril Sodium.
SQ 29,852. Code designation for Ceronapril.
SQ 30217. Code designation for Technetium Tc 99m Teboroxime.
SQ 30836. Code designation for Tigemonam Dicholine.
SQ-31,000. Code designation for Pravastatin Sodium.
SQ 32,097. Code designation for Technetium Tc 99m Siboroxime.
SQ 32,692. Code designation for Gadoteridol.
SQ 32,756. Code designation for Sorivudine.
SQ 33,248. Code designation for Calteridol Calcium.
SQ 34,514. Code designation for Lobucavir.
SQ34676. Code designation for Entecavir.
SQ 65396. Code designation for Cartazolate.
SQ 82291. Code designation for Oximonam.
SQ 82531. Code designation for Gloximonam.
SQ 82629. Code designation for Oximonam Sodium.
SQ 83360. Code designation for Pirazmonam Sodium.
SR-202. Code designation for Mifobate.
SR 720-22. Code designation for Metolazone.
SR 2508. Code designation for Etanidazole.
SR-7037. Code designation for Belfosdil.
SR 25990C. Code designation for Clopidogrel Bisulfate.
SR29142. Code designation for Rasburicase.
SR 33557. Code designation for Fantofarone.
SR33598B. Code designation for Dronedarone Hydrochloride.
SR 41319. Code designation for Tiludronic Acid.
SR 41319B. Code designation for Tiludronate Disodium.
SR 47436. Code designation for Irbesartan.
SR 57746. Code designation for Xaliproden.
SR 90107A. Code designation for Fondaparinux Sodium.
SR 96225. Code designation for Adenosine.
SR-96669. Code designation for Oxaliplatin.
SR141716. Code designation for Rimonabant.
SRA-333. Code designation for Lecozotan Hydrochloride.
SRG 95213. Code designation for Diazoxide.
ST12. Code designation for Dexamethasone Dipropionate.
ST-155. Code designation for Clonidine Hydrochloride.
ST-155-BS. Code designation for Clonidine.
ST 261. Code designation for Levocarnitine Propionate Hydrochloride.
ST 375. Code designation for Tolonidine.
St 567-BR [as hydrobromide]. Code designation for Alinidine.
ST 600. Code designation for Flutonidine.
ST-813. Code designation for Oxiconazole Nitrate.
St 1085 [as the base]. Code designation for Midodrine Hydrochloride.
St 1411. Code designation for Dimepregnen.
ST1512/SO4. Code designation for Hexoprenaline Sulfate.
ST 9067. Code designation for Azintamide.
St. Peter 224. Code designation for Midodrine Hydrochloride.
STA-307. Code designation for Tiomesterone.
STA-5312. Code designation for Rosabulin.
STA-5326 mesylate. Code designation for Apilimod Mesylate.
sTNF-RI. Code designation for Pegsunercept.
STS 557. Code designation for Dienogest.
SU101. Code designation for Leflunomide.
Su-4885. Code designation for Metyrapone Tartrate.
SU5416. Code designation for Semaxanib.
Su-5864. Code designation for Guanethidine Sulfate.
Su-6518. Code designation for Dimethindene Maleate.
Su-8341. Code designation for Cyclopenthiazide.
Su-9064. Code designation for Metoserpate Hydrochloride.
SU010398. Code designation for Sunitinib Malate.
Su-10568. Code designation for Clortermine Hydrochloride.
SU011248 L-malate salt. Code designation for Sunitinib Malate.
Su-13437. Code designation for Nafenopin.
Su-18137. Code designation for Cyproquinate.
Su 21524. Code designation for Pirprofen.
SUM 3170. Code designation for Loxapine.
SUN-0588 (Shiratori). Code designation for Sapropterin Dihydrochloride.
SUN 4936. Code designation for Carperitide.
SUN 9216. Code designation for Lanoteplase.
SUR 2647. Code designation for Sumacetamol.
SYD-230. Code designation for Clioxanide.
Synthetic TRH. Code designation for Protirelin.
SYR-322. Code designation for Alogliptin Benzoate.
T2G1s. Code designation for Biciromab.
T20. Code designation for Enfuvirtide.
T67. Code designation for Batabulin.
T-1220. Code designation for Piperacillin Sodium.
T1401 (BioMarin). Code designation for Sapropterin Dihydrochloride.
T-1551. Code designation for Cefoperazone Sodium.
T-1982. Code designation for Cefbuperazone.
T-2636. Code designation for Sedecamycin.
T-2636A. Code designation for Sedecamycin.
T-3811ME. Code designation for Garenoxacin Mesylate.
T138067. Code designation for Batabulin.
T138067-sodium. Code designation for Batabulin Sodium.
T-168390. Code designation for Dexlansoprazole.
TA-1790. Code designation for Avanafil.
TA-3090. Code designation for Clentiazem Maleate.
TA 5901. Code designation for Cefempidone.
TAK-165. Code designation for Mubritinib.
TAK-375. Code designation for Ramelteon.
TAK-390. Code designation for Dexlansoprazole.
TAK 475. Code designation for Lapaquistat Acetate.
TALL-1. Code designation for Ardenermin.
TAP 031 (as the base). Code designation for Fertirelin Acetate.
TAP-144. Code designation for Leuprolide Acetate.
TAT-3. Code designation for Picoperine.
TATBA. Code designation for Triamcinolone Hexacetonide.

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TBC1269z. Code designation for Bimosiamose Disodium.
Tc 99m anti-SSEA-1. Code designation for Technetium Tc 99m Fanolesomab.
Tc99m RB5 IgM. Code designation for Technetium Tc 99m Fanolesomab.
Tc99m RP-30A. Code designation for Technetium Tc 99m Sestamibi.
Tc99m-MP 4006. Code designation for Technetium Tc 99m Albumin Aggregated.
Tc 924 (DPD). Code designation for Butedronate Tetrasodium.
TC-01734. Code designation for Ispronicline.
TC-02403-12. Code designation for Rivanicline Galactarate.
TCC. Code designation for Triclocarban.
Tc-MAG_3. Code designation for Technetium Tc 99m Mertiatide.
^{99m}TcN-NOET. Code designation for Technetium Tc 99m Nitridocade.
TCV-116. Code designation for Candesartan Cilexetil.
Td-6424. Code designation for Telavancin Hydrochloride.
TE-031. Code designation for Clarithromycin.
TE 114. Code designation for Tiemonium Iodide.
TEAB. Code designation for Tetrylammonium Bromide.
Tenite Butyrate Formula 264 H4. Code designation for Cabufocon B.
TER286. Code designation for Canfosfamide Hydrochloride.
αTGI. Code designation for Teroxirone.
Th-152. Code designation for Metaproterenol Sulfate.
Th 322. Code designation for Metrifudil.
TH 1165a [as hydrobromide salt]. Code designation for Fenoterol.
TH-1321. Code designation for Protionamide.
TH-2151. Code designation for Hydracarbazine.
TH-2180. Code designation for Propanidid.
TH9507. Code designation for Tesamorelin.
THANK. Code designation for Ardenermin.
THFES (HM). Code designation for Zeranol.
THQ. Code designation for Tetroquinone.
THR. Code designation for Troxerutin.
THR 221 [as sodium]. Code designation for Cefodizime.
TL7. Code designation for Ardenermin.
TL 057. Code designation for Batabulin.
TLK286. Code designation for Canfosfamide Hydrochloride.
TMB-4. Code designation for Trimedoxime Bromide.
TMC 114. Code designation for Darunavir.
TMC 125. Code designation for Etravirine.
TMI-005. Code designation for Apratastat.
TMX-67. Code designation for Febuxostat.
TNF MAb. Code designation for Nerelimomab.
TNFSBF13B. Code designation for Ardenermin.
TNFSF20. Code designation for Ardenermin.
TNK-tPA. Code designation for Tenecteplase.
TNO-6. Code designation for Spiroplatin.
TNX-901. Code designation for Talizumab.
(S)-tofisopam. Code designation for Levotofisopam.
TP-5. Code designation for Thymopentin.
TP-21. Code designation for Thioridazine.
TP 508. Code designation for Rusalatide Acetate.
TPGS. Code designation for Tocophersolan.
TPN-12. Code designation for Sulforidazine.
TPS-23. Code designation for Mesoridazine.
TR-495. Code designation for Methaqualone.
TR-2378. Code designation for Broperamole.
TR-2515. Code designation for Pelanserin Hydrochloride.
TR-2855. Code designation for Cromitrile Sodium.
TR-2985. Code designation for Ropitoin Hydrochloride.
TR-3369. Code designation for Indorenate Hydrochloride.
TR-4698. Code designation for Rioprostil.
TR-4979. Code designation for Butaprost.
TR-5109. Code designation for Conorphone Hydrochloride.
TR-5379M. Code designation for Xorphanol Mesylate.
TRAIL-R1 mAb. Code designation for Mapatumumab.
Trans AMCHA. Code designation for Tranexamic Acid.
TRAP-508. Code designation for Rusalatide Acetate.
TRK-100. Code designation for Beraprost Sodium.
TRK-820. Code designation for Nalfurafine Hydrochloride.
TRM-1. Code designation for Mapatumumab.
TS 408. Code designation for Hydrocortisone Probutate.
TSAA-291. Code designation for Oxendolone.
TTFD. Code designation for Fursultiamine.
TTI-237. Code designation for Cevipabulin Fumarate.
TV-1203. Code designation for Etilevodopa.
TV-1901. Code designation for Valrocemide.
TV-3326. Code designation for Ladostigil Tartrate.
TV-4710. Code designation for Edratide.
TVP-1012. Code designation for Rasagiline Mesylate.
TVX485. Code designation for Etofenamate.
TWSB. Code designation for Sodium Stibocaptate.
U-935. Code designation for Amiquinsin Hydrochloride.
U-2032. Code designation for Kethoxal.
U-4527. Code designation for Cycloheximide.
U-5956. Code designation for Filipin.
U-6013. Code designation for Isoflupredone Acetate.
U-6987. Code designation for Carbutamide.
U-7743. Code designation for Mercufenol Chloride.
U-7750. Code designation for Streptovarycin.
U-7800. Code designation for Fluprednisolone.
U-8344. Code designation for Uracil Mustard.
U-8471. Code designation for Medrysone.
U-9889. Code designation for Streptozocin.
U-10,136. Code designation for Alprostadil.
U-10,149. Code designation for Lincomycin.
U-10,858. Code designation for Minoxidil.
U-10,974. Code designation for Flumethasone.
U-10,997. Code designation for Mibolerone.
U-11100A. Code designation for Nafoxidine Hydrochloride.
U-12,019E. Code designation for Methylprednisolone Sodium Phosphate.
U-12,062. Code designation for Dinoprostone.
U-12,241. Code designation for Cirolemycin.
U-12898. Code designation for Bluensomycin.
U-13,933. Code designation for Asperlin.
U-14,583. Code designation for Dinoprost.
U-14,583E. Code designation for Dinoprost Tromethamine.
U-14,743. Code designation for Porfiromycin.
U-15167. Code designation for Nogalamycin.
U-15,614. Code designation for Trestolone Acetate.
U-15,965. Code designation for Lydimycin.
U-17312E. Code designation for Etryptamine Acetate.
U-17,323. Code designation for Fluorometholone Acetate.
U-17835. Code designation for Tolazamide.
U-18,409AE. Code designation for Spectinomycin Hydrochloride.
U-18,496. Code designation for Azacitidine.
U-18,573. Code designation for Ibuprofen.
U-18,573G. Code designation for Ibuprofen Aluminum.
U-19183. Code designation for Sparsomycin.
U-19,646. Code designation for Chlorphenesin Carbamate.
U-19,718. Code designation for Kalafungin.
U-19763. Code designation for Bolasterone.
U-19,920. Code designation for Cytarabine.
U-19920A. Code designation for Cytarabine Hydrochloride.
U-20,661. Code designation for Steffimycin.
U-21,251. Code designation for Clindamycin.
U-22020. Code designation for Indoxole.
U-22,550. Code designation for Calusterone.
U-22,559A. Code designation for Dexoxadrol Hydrochloride.
U-24,729A. Code designation for Mirincamycin Hydrochloride.
U-24,792. Code designation for Lomofungin.
U-24,973A. Code designation for Melitracen Hydrochloride.

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U-25,179 E. Code designation for Clindamycin Palmitate Hydrochloride.
U-25,873. Code designation for Ranimycin.
U-26,225A. Code designation for Tramadol Hydrochloride.
U-26,452. Code designation for Glyburide.
U-27,182. Code designation for Flurbiprofen.
U-28,009. Code designation for Denofungin.
U-28,288D. Code designation for Guanadrel Sulfate.
U-28,508. Code designation for Clindamycin Phosphate.
U-28,774. Code designation for Ketazolam.
U-29,479. Code designation for Scopafungin.
U-30,604. Code designation for Zorbamycin.
U-31,889. Code designation for Alprazolam.
U-31,920. Code designation for Uldazepam.
U-32,070E. Code designation for Calcifediol.
U-32,921. Code designation for Carboprost.
U-32,921E. Code designation for Carboprost Tromethamine.
U-33,030. Code designation for Triazolam.
U-34,865. Code designation for Diflorasone Diacetate.
U-36,059. Code designation for Amitraz.
U-36,384. Code designation for Carboprost Methyl.
U-41,123. Code designation for Adinazolam.
U-41,123F. Code designation for Adinazolam Mesylate.
U-42,126. Code designation for Acivicin.
U-42,585E. Code designation for Lodoxamide Tromethamine.
U-42,718. Code designation for Lodoxamide Ethyl.
U 42,842. Code designation for Arbaprostil.
U-43,120. Code designation for Paulomycin.
U-46,785. Code designation for Meteneprost.
U-47,931E. Code designation for Bromadoline Maleate.
U-48,753E. Code designation for Eclanamine Maleate.
U-52,047. Code designation for Menogaril.
U-53,059. Code designation for Itazigrel.
U-53,217. Code designation for Epoprostenol.
U-53,217A. Code designation for Epoprostenol Sodium.
U-53,996H. Code designation for Tazadolene Succinate.
U-54,461. Code designation for Bropirimine.
U-54,555. Code designation for Metronidazole Phosphate.
U-54,669F. Code designation for Losulazine Hydrochloride.
U-56,321. Code designation for Timefurone.
U-57,930E. Code designation for Pirlimycin Hydrochloride.
U-60,257. Code designation for Piriprost.
U-60,257B. Code designation for Piriprost Potassium.
U-61,431F. Code designation for Ciprostene Calcium.
U-62066E. Code designation for Spiradoline Mesylate.
U-63,196. Code designation for Cefpimizole.
U-63,196E. Code designation for Cefpimizole Sodium.
U-63287. Code designation for Ciglitazone.
U-63,366F. Code designation for Trospectomycin Sulfate.
U-63,557A. Code designation for Furegrelate Sodium.
U-64279A. Code designation for Ceftiofur Hydrochloride.
U-64279E. Code designation for Ceftiofur Sodium.
U-66858. Code designation for Bunaprolast.
U-67,590A. Code designation for Methylprednisolone.
U-67,590A. Code designation for Methylprednisolone Suleptanate.
U-68,553B. Code designation for Alentemol Hydrobromide.
U-69689E. Code designation for Fertirelin Acetate.
U-70138. Code designation for Paldimycin.
U-70226E. Code designation for Ibutilide Fumarate.
U-71038. Code designation for Ditekiren.
U-72107A. Code designation for Pioglitazone Hydrochloride.
U-72791. Code designation for Cefmetazole.
U-72791A. Code designation for Cefmetazole Sodium.
U-73,975. Code designation for Adozelesin.
U-74006F. Code designation for Tirilazad Mesylate.
U-75630. Code designation for Ibuprofen Piconol.
U-76252. Code designation for Cefpodoxime Proxetil.
U-77,233. Code designation for Ormaplatin.
U-77779. Code designation for Bizelesin.
U-78875. Code designation for Panadiplon.
U-78,938. Code designation for Dexormaplatin.
U-80244. Code designation for Carzelesin.
U-82127. Code designation for Alexomycin.
U-85,855. Code designation for Alvircept Sudotox.
U-87201E. Code designation for Atevirdine Mesylate.
U-88943E. Code designation for Artilide Fumarate.
U-90152S. Code designation for Delavirdine Mesylate.
U-95376. Code designation for Premafloxacin.
U-98079A. Code designation for Itasetron.
U-98528E; SUD919CL2Y. Code designation for Pramipexole.
U-100,592. Code designation for Eperezolid.
U-100,766. Code designation for Linezolid.
U-101,440E. Code designation for Irinotecan Hydrochloride.
U-108342E. Code designation for Trecetilide Fumarate.
UCB 1402. Code designation for Decloxizine.
UCB 1474. Code designation for Chlorbenzoxamine Hydrochloride.
UCB 1549. Code designation for Minepentate.
UCB 1967. Code designation for Dropropizine.
UCB 2073. Code designation for Etoxeridine.
UCB 3928. Code designation for Fedrilate.
UCB 4445. Code designation for Buclizine Hydrochloride.
ucb 22059. Code designation for Levetiracetam.
ucb 28754. Code designation for Efletirizine Dihydrochloride.
ucb 34714. Code designation for Brivaracetam.
ucb 44212. Code designation for Seletracetam.
ucb L059. Code designation for Levetiracetam.
UDCG-115. Code designation for Pimobendan.
UH-AC 62XX. Code designation for Meloxicam.
UK-738. Code designation for Ethybenztropine.
UK-2054. Code designation for Famotine Hydrochloride.
UK-2371. Code designation for Memotine Hydrochloride.
UK-3540-1. Code designation for Amedalin Hydrochloride.
UK-3557-15. Code designation for Daledalin Tosylate.
UK-4271. Code designation for Oxamniquine.
UK-11,443. Code designation for Primidolol.
UK-14304-18. Code designation for Brimonidine Tartrate.
UK-18,892. Code designation for Butikacin.
UK-20,349. Code designation for Tioconazole.
UK-25,842. Code designation for Oxfenicine.
UK-31,214. Code designation for Propikacin.
UK-31,557. Code designation for Carbazeran.
UK-33,274-27. Code designation for Doxazosin Mesylate.
UK-37,248-01. Code designation for Dazoxiben Hydrochloride.
UK-38,485. Code designation for Dazmegrel.
UK-48,340-11. Code designation for Amlodipine Maleate.
UK-48,340-26. Code designation for Amlodipine Besylate.
UK-49,858. Code designation for Fluconazole.
UK-61260-27. Code designation for Nanterinone.
UK-61,689. Code designation for Semduramicin.
UK-61,689-2. Code designation for Semduramicin Sodium.
UK-67,994. Code designation for Doramectin.
UK-68,798. Code designation for Dofetilide.
UK-73,967. Code designation for Candoxatrilat.
UK-76654-2 [as fumarate]. Code designation for Zamifenacin.
UK-79,300. Code designation for Candoxatril.
UK-80067. Code designation for Modipafant.
UK-81,252. Code designation for Sampatrilat.
UK-88060. Code designation for Espatropate.
UK-88525. Code designation for Darifenacin.
UK-88525-04 (hydrobromide). Code designation for Darifenacin Hydrobromide.
UK-92,480-10. Code designation for Sildenafil Citrate.
UK-109,496. Code designation for Voriconazole.
UK-112,166. Code designation for Revatropate.

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UK-112,166-04 [as hydrobromide]. Code designation for Revatropate.
UK-116,044. Code designation for Eletriptan.
UK-116,044-04. Code designation for Eletriptan Hydrobromide.
UK-116,044-04 [as hydrobromide]. Code designation for Eletriptan.
UK-124,114. Code designation for Selamectin.
UK-287,074-02. Code designation for Cefovecin Sodium.
UK-292,663. Code designation for Fosfluconazole.
UK-338,003. Code designation for Taprizosin.
UM 952. Code designation for Buprenorphine Hydrochloride.
UP 74. Code designation for Nixylic Acid.
UP 83. Code designation for Niflumic Acid.
UP 106. Code designation for Propizepine.
UP 107. Code designation for Bepiastine.
UP 164. Code designation for Morniflumate.
UR-4056. Code designation for Flutrimazole.
USV 3659-(S). Code designation for Pivopril.
UT-15. Code designation for Treprostinil.
V-C 13. Code designation for Dichlofenthion.
VER001. Code designation for Dalbavancin.
VI-21,497. Code designation for Merimepodib.
VK-57. Code designation for Glyprothiazol.
VM-26. Code designation for Teniposide.
VML 251. Code designation for Frovatriptan Succinate.
VP-16-213. Code designation for Etoposide.
VP 63843. Code designation for Pleconaril.
VUAB6453 (SPOFA). Code designation for Metipranolol.
VX-478. Code designation for Amprenavir.
VX-497. Code designation for Merimepodib.
VX-710-3. Code designation for Biricodar Dicitrate.
VX-740. Code designation for Pralnacasan.
VX-853-2. Code designation for Timcodar Dimesylate.
W 37. Code designation for Buformin.
W-554. Code designation for Felbamate.
W-583. Code designation for Mebutamate.
W 713. Code designation for Tybamate.
W-1015. Code designation for Nisobamate.
W-1372. Code designation for Beloxamide.
W 1655. Code designation for Phenazopyridine Hydrochloride.
W 1760A. Code designation for Namoxyrate.
W 1929. Code designation for Colistimethate Sodium.
W 2180. Code designation for Suxemerid Sulfate.
W 2197. Code designation for Pentrinitrol.
W 2291A. Code designation for Mimbane Hydrochloride.
W-2354. Code designation for Seclazone.
W 2394A. Code designation for Pemerid Nitrate.
W-2395. Code designation for Meseclazone.
W 2426. Code designation for Chlorphentermine Hydrochloride.
W 2900A. Code designation for Etozolin.
W-2946M. Code designation for Reproterol Hydrochloride.
W-2964M. Code designation for Flupirtine Maleate.
W 2965 A. Code designation for Acetryptine.
W-2979M. Code designation for Azelastine Hydrochloride.
W 3207B. Code designation for Modaline Sulfate.
W 3366A. Code designation for Quindonium Bromide.
W3395. Code designation for Algestone Acetonide.
W 3399. Code designation for Quingestrone.
W 3566. Code designation for Quinestrol.
W 3580B. Code designation for Ampyzine Sulfate.
W 3623. Code designation for Cyprazepam.
W 3676. Code designation for Sulazepam.
W 3699. Code designation for Piprozolin.
W 3746. Code designation for Cetophenicol.
W 3976B. Code designation for Triampyzine Sulfate.
W 4020. Code designation for Prazepam.
W 4425. Code designation for Almadrate Sulfate.
W 4454A. Code designation for Estrazinol Hydrobromide.
W 4540. Code designation for Quingestanol Acetate.
W 4565. Code designation for Oxolinic Acid.
W 4600. Code designation for Algeldrate.
W 4701. Code designation for Hexedine.
W 4744. Code designation for Mecloqualone.
W 4869. Code designation for Prednival.
W-5219. Code designation for Proglumide.
W 5494A. Code designation for Naranol Hydrochloride.
W 5733. Code designation for Atolide.
W 5759A. Code designation for Tilidine Hydrochloride.
W 5975. Code designation for Betamethasone Benzoate.
W 6309. Code designation for Difluprednate.
W 6412A. Code designation for Bunolol Hydrochloride.
W 6439A. Code designation for Suloxifen Oxalate.
W 6495. Code designation for Oxisuran.
W 7000A. Code designation for Levobunolol Hydrochloride.
W 7320. Code designation for Alclofenac.
W7783. Code designation for Ambruticin.
W 8495. Code designation for Isoxicam.
W 10168. Code designation for Vifilcon A.
W-19053 [as hydrochloride]. Code designation for Etidocaine.
W-36095. Code designation for Tocainide.
W 42782. Code designation for Iproxamine Hydrochloride.
W 43026A. Code designation for Ciclafrine Hydrochloride.
WA 184. Code designation for Sitogluside.
W-A 335. Code designation for Danitracen.
WAL 2014 FU. Code designation for Talsaclidine Fumarate.
WAY-140424. Code designation for Bazedoxifene Acetate.
WAY 164339. Code designation for Torapsel.
WAY-207294. Code designation for Inotuzumab Ozogamicin.
WAY-ACA-147. Code designation for Eldacimibe.
WAY-ANA-756. Code designation for Tasosartan.
WAY-ARI-509. Code designation for Minalrestat.
WAY-CMA-676. Code designation for Gemtuzumab Ozogamicin.
WAY-GAR-936. Code designation for Tigecycline.
WAY-GPA-748. Code designation for Pralmorelin Dihydrochloride.
WAY-PDA-641. Code designation for Filaminast.
WAY-PEM-420. Code designation for Dexpemedolac.
WAY-SEC-579. Code designation for Mirisetron Maleate.
WAY-VPA-985. Code designation for Lixivaptan.
WE352. Code designation for Triflubazam.
We 941. Code designation for Brotizolam.
We 973-BS. Code designation for Ciclotizolam.
WEB 2086 BS. Code designation for Apafant.
WG-253. Code designation for Rimiterol Hydrobromide.
WG 537 [as acetate]. Code designation for Flumedroxone.
WH 5668. Code designation for Propanidid.
WHR-539. Code designation for Fenclorac.
WHR-1051B. Code designation for Biclodil Hydrochloride.
WHR-1142A. Code designation for Lidamidine Hydrochloride.
WHR-2908A. Code designation for Lofepramine Hydrochloride.
WHR-5020. Code designation for Etofenamate.
Win 771. Code designation for Hydroxypethidine.
Win 1344. Code designation for Gamfexine.
Win 1783. Code designation for Isomethadone.
Win 3406. Code designation for Isoetharine.
Win 5063. Code designation for Racephenicol.
Win 5063-2. Code designation for Thiamphenicol.
Win 5563-3. Code designation for Colterol Mesylate.
Win 8851-2. Code designation for Tyropanoate Sodium.
Win 9154. Code designation for Inositol Niacinate.
Win 9317. Code designation for Propatyl Nitrate.
Win 11,318. Code designation for Bupivacaine Hydrochloride.
Win 11450. Code designation for Benorilate.
Win 11,464. Code designation for Fludorex.
Win 11,530. Code designation for Menoctone.
Win 11831. Code designation for Lorajmine Hydrochloride.

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Win 13,146. Code designation for Teclozan.
Win 13820. Code designation for Becanthone Hydrochloride.
Win 14833. Code designation for Stanozolol.
Win 17625. Code designation for Azastene.
Win 17665. Code designation for Topterone.
Win 17,757. Code designation for Danazol.
Win 18,320. Code designation for Nalidixic Acid.
Win 18,320-3. Code designation for Nalidixate Sodium.
Win 18,413-2. Code designation for Solypertine Tartrate.
Win 18,501-2. Code designation for Oxypertine.
Win 18,935. Code designation for Milipertine.
Win 19356. Code designation for Clorindanic Acid.
Win 20,228. Code designation for Pentazocine.
Win 20,740. Code designation for Cyclazocine.
Win 21,904. Code designation for Alexidine.
WIN 22118. Code designation for Pegorgotein.
Win 23,200. Code designation for Volazocine.
Win 24,540. Code designation for Trilostane.
Win 24,933. Code designation for Hycanthone.
Win 25,347. Code designation for Nimazone.
Win 25,978. Code designation for Amfonelic Acid.
Win 27147-2. Code designation for Cyclindole.
Win 27,914. Code designation for Nivazol.
Win 29194-6. Code designation for Carbantel Lauryl Sulfate.
Win 31,665. Code designation for Alpertine.
Win 32,729. Code designation for Epostane.
Win 32,784. Code designation for Bitolterol Mesylate.
Win 34,276. Code designation for Ketazocine.
Win 34284. Code designation for Oxarbazole.
Win 34886. Code designation for Nisbuterol Mesylate.
Win 35150. Code designation for Flucindole.
Win 35,213. Code designation for Rosoxacin.
Win 35833. Code designation for Ciprofibrate.
Win 38020. Code designation for Arildone.
Win 38770. Code designation for Azarole.
Win 39103. Code designation for Metrizamide.
Win 39424. Code designation for Iohexol.
Win 40014. Code designation for Quinfamide.
Win 40350. Code designation for Durapatite.
Win 40680. Code designation for Inamrinone.
Win 40808-7. Code designation for Sulfinalol Hydrochloride.
Win 41464-2. Code designation for Octenidine Hydrochloride.
Win 41,464-6. Code designation for Octenidine Saccharin.
Win 41528-2. Code designation for Fezolamine Fumarate.
Win 42156-2. Code designation for Tonazocine Mesylate.
Win 42,202. Code designation for Fosarilate.
Win 42964-4. Code designation for Zenazocine Mesylate.
Win 44,441-3. Code designation for Quadazocine Mesylate.
Win 47,203-2. Code designation for Milrinone.
Win 48,049. Code designation for Ofornine.
Win 48,098-6. Code designation for Pravadoline Maleate.
Win 49,016. Code designation for Medorinone.
Win 49,375. Code designation for Amifloxacin.
Win 49,375-3. Code designation for Amifloxacin Mesylate.
Win 49,596. Code designation for Zanoterone.
Win 51,181-2. Code designation for Napamezole Hydrochloride.
Win 51,711. Code designation for Disoxaril.
WIN 52,172-2. Code designation for Pirtenidine Hydrochloride.
Win 54,177-4. Code designation for Ipazilide Fumarate.
WIN 59010. Code designation for Mangafodipir Trisodium.
WIN 59075. Code designation for Tirapazamine.
WIN 63843. Code designation for Pleconaril.
Win 90,000. Code designation for Cicletanine.
Wl 140. Code designation for Calcium Polycarbophil.
Wl 287. Code designation for Euprocin Hydrochloride.
Wl 291. Code designation for Zolamine Hydrochloride.
WP-973. Code designation for Chlorhexidine Phosphanilate.
WR-2721. Code designation for Amifostine.
WR 6026. Code designation for Sitamaquine.
WR 142,490. Code designation for Mefloquine.
WR-171669. Code designation for Halofantrine Hydrochloride.
WR 180,409. Code designation for Enpiroline Phosphate.
WR-228,258. Code designation for Tebuquine.
WR 238605. Code designation for Tafenoquine.
WV 569 [as hydrochloride]. Code designation for Norfenefrine.
WX 2412. Code designation for Fungimycin.
WX 14812. Code designation for Alofilcon A.
WX 14822. Code designation for Hydrofilcon A.
WY-460E. Code designation for Thiazinamium Chloride.
Wy-806. Code designation for Oxethazaine.
Wy-1359. Code designation for Propiomazine.
Wy-2039. Code designation for Etoxeridine.
Wy-2445. Code designation for Carphenazine Maleate.
Wy-2837. Code designation for Potassium Aspartate and Magnesium Aspartate.
Wy-2838. Code designation for Potassium Aspartate and Magnesium Aspartate.
Wy-3263. Code designation for Iprindole.
Wy-3277. Code designation for Nafcillin Sodium.
Wy-3467. Code designation for Diazepam.
Wy-3475. Code designation for Norbolethone.
Wy-3478. Code designation for Sodium Oxybate.
Wy-3498. Code designation for Oxazepam.
Wy-3707. Code designation for Norgestrel.
Wy-3917. Code designation for Temazepam.
Wy-4036. Code designation for Lorazepam.
WY-4082. Code designation for Lormetazepam.
Wy-4508. Code designation for Cyclacillin.
WY-5104. Code designation for Levonorgestrel.
Wy-8138. Code designation for Bisoxatin Acetate.
Wy-8678. Code designation for Guanabenz.
WY-8678 acetate. Code designation for Guanabenz Acetate.
WY-15,705. Code designation for Ciramadol.
WY-15,705 HCl. Code designation for Ciramadol Hydrochloride.
WY-16,225. Code designation for Dezocine.
WY-18,251. Code designation for Tilomisole.
WY-20,788. Code designation for Penamecillin.
WY-21,743. Code designation for Oxaprozin.
WY-21,894. Code designation for Fentiazac.
Wy 21901. Code designation for Indoramin.
WY-21,901 HCl. Code designation for Indoramin Hydrochloride.
WY 22811 HCl. Code designation for Meptazinol Hydrochloride.
WY-23,409. Code designation for Ciclazindol.
WY-24,081 HCl. Code designation for Tiquinamide Hydrochloride.
WY-24,377. Code designation for Isotiquimide.
WY-25,021. Code designation for Rolgamidine.
WY-40,972. Code designation for Lutrelin Acetate.
WY-42,362 HCl. Code designation for Recainam Hydrochloride.
WY-42,362 tosylate. Code designation for Recainam Tosylate.
WY-44,417 sodium. Code designation for Apalcillin Sodium.
WY-44,635. Code designation for Cefpiramide.
WY-44,635 sodium. Code designation for Cefpiramide Sodium.
WY-45,030. Code designation for Venlafaxine Hydrochloride.
Wy-45233. Code designation for Desvenlafaxine Succinate.
WY-47384. Code designation for Gevotroline Hydrochloride.
WY-47,663 acetate. Code designation for Anaritide Acetate.
WY-47791 HCl. Code designation for Carvotroline Hydrochloride.
WY-47846HCl. Code designation for Zalospirone Hydrochloride.
WY-48252. Code designation for Ritolukast.
Wy-48314. Code designation for Lexithromycin.
WY-48624. Code designation for Enciprazine Hydrochloride.
WY-48986. Code designation for Risotilide Hydrochloride.
WY-50324 HCl. Code designation for Adatanserin Hydrochloride.
WY-090217. Code designation for Sirolimus.
WY-90493 RD. Code designation for Ardeparin Sodium.

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X-1497. Code designation for Methicillin Sodium.
XA41. Code designation for Latanoprost.
XI-921. Code designation for Iron Sucrose.
XL119. Code designation for Becatecarin.
XLG. Code designation for Polyglactin 910.
XM-72. Code designation for Polybutester.
XP03. Code designation for Levomepromazine.
XR9576. Code designation for Tariquidar.
XU 62-320. Code designation for Fluvastatin Sodium.
XZ-450. Code designation for Azithromycin.
Y 3642. Code designation for Tinoridine.
Y 4153 [as hydrochloride]. Code designation for Clocapramine.
Y 6124 [as hydrochloride]. Code designation for Bufetolol.
YC-93. Code designation for Nicardipine Hydrochloride.
^{90}Y-DOTA-hLL2. Code designation for Yttrium Y 90 Epratuzumab Tetraxetan.
^{90}Y-DOTA-hMN14. Code designation for Yttrium Y 90 Labetuzumab Tetraxetan.
YH1885. Code designation for Revaprazan Hydrochloride.
^{90}Y-hLL2. Code designation for Yttrium Y 90 Epratuzumab.
^{90}Y-hMN-14. Code designation for Yttrium Y 90 Labetuzumab.
YKP-509. Code designation for Carisbamate.
YM087. Code designation for Conivaptan Hydrochloride.
YM337. Code designation for Tadocizumab.
YM617. Code designation for Tamsulosin Hydrochloride.
YM872. Code designation for Zonampanel.
YM905. Code designation for Solifenacin Succinate.
YM992. Code designation for Lubazodone Hydrochloride.
YM-08316. Code designation for Formoterol Fumarate.
YM-09330. Code designation for Cefotetan Disodium.
YM-12617-1. Code designation for Tamsulosin Hydrochloride.
YM-35992. Code designation for Lubazodone Hydrochloride.
YM-67905. Code designation for Solifenacin Succinate.
YM67905. Code designation for Solifenacin Succinate.
YN-72. Code designation for Sorivudine.
YTR-830H. Code designation for Tazobactam.
YZ-817. Code designation for Dexelvucitabine.
Z 326. Code designation for Fentonium Bromide.
Z 424. Code designation for Viminol.
Z 1282. Code designation for Fosfomycin Tromethamine.
Z-4828. Code designation for Trofosfamide.
Z4942. Code designation for Ifosfamide.
Z 6000. Code designation for Troxerutin.
ZAL-846. Code designation for Zaleplon.
ZCE025. Code designation for Indium In 111 Altumomab Pentetate.
ZD0473. Code designation for Picoplatin.
ZD1033. Code designation for Anastrozole.
ZD1694. Code designation for Raltitrexed.
ZD1839. Code designation for Gefitinib.
ZD2079. Code designation for Talibegron Hydrochloride.
ZD4522 (calcium salt). Code designation for Rosuvastatin Calcium.
ZD5077. Code designation for Quetiapine Fumarate.
ZD6474. Code designation for Vandetanib.
ZD9238. Code designation for Fulvestrant.
ZD9331. Code designation for Plevitrexed.
ZK 10 720. Code designation for Ioprocemic Acid.
ZK 39 482. Code designation for Iotrolan.
ZK 57 671. Code designation for Sulprostone.
ZK 62 711. Code designation for Rolipram.
ZK 71 630. Code designation for Iotetric Acid.
ZK 76 604. Code designation for Pirazolac.
ZK 79 112. Code designation for Iotasul.
ZK 30595. Code designation for Drospirenone.
ZK 35760. Code designation for Iopromide.
ZK 00036374. Code designation for Iloprost.
ZK 37659. Code designation for Dienogest.
ZK 62498. Code designation for Azelaic Acid.
ZK 00091106. Code designation for Clodronate Disodium.
ZK 132281. Code designation for Ferucarbotran.
ZK 139834. Code designation for Gadoxetate Disodium.
ZK 156942. Code designation for Tisocalcitate.
ZK 807834. Code designation for Fidexaban.
ZM 204,636. Code designation for Quetiapine Fumarate.
(S)-Zopiclone. Code designation for Eszopiclone.
ZP-123 (Zealand). Code designation for Rotigaptide.
zTNF4. Code designation for Ardenermin.
ZYC101a. Code designation for Amolimogene Bepiplasmid.
2-5410-3A. Code designation for Iodixanol.
2-HMHBG. Code designation for Omaciclovir.
2-PAM. Code designation for Pralidoxime Chloride.
2-PAM Chloride. Code designation for Pralidoxime Chloride.
3-01003. Code designation for Guanoxan Sulfate.
3-01029. Code designation for Guanoclor Sulfate.
3 MS. Code designation for Hydroxytoluic Acid.
4A65. Code designation for Imidocarb Hydrochloride.
4-C-32. Code designation for Ticlopidine Hydrochloride.
4-HC. Code designation for Perfosfamide.
4-MP. Code designation for Fomepizole.
4-OHT. Code designation for Afimoxifene.
5-1 Ukima 5 Chome. Code designation for Mitemcinal Fumarate.
5-azacytosine arabinoside. Code designation for Fazarabine.
5-FU. Code designation for Fluorouracil.
5IUDR. Code designation for Idoxuridine.
8-Cl-cAMP. Code designation for Tocladesine.
10 80 07. Code designation for Omoconazole Nitrate.
12C. Code designation for Velaresol.
15AU81. Code designation for Treprostinil.
17-AAG. Code designation for Tanespimycin.
17-DMAG.HCl. Code designation for Alvespimycin Hydrochloride.
22-708. Code designation for Endralazine Mesylate.
26P. Code designation for Aliflurane.
27-400. Code designation for Cyclosporine.
32-046. Code designation for Edetate Dipotassium.
36-801. Code designation for Etifoxine.
37 162 R.P. Code designation for Suproclone.
40 045. Code designation for Articaine Hydrochloride.
40 045. Code designation for Articaine.
41-123. Code designation for Clazolam.
41 982 RP. Code designation for Pefloxacin Mesylate.
42-348. Code designation for Lifibrate.
42-548. Code designation for Mazindol.
43-663. Code designation for Guanoxabenz.
43-715. Code designation for Proquazone.
46-790. Code designation for Fluproquazone.
46 R.P. Code designation for Benzylsulfamide.
47-210 [as sodium]. Code designation for Tetriprofen.
48-674. Code designation for Furacrinic Acid.
51W89. Code designation for Cisatracurium Besylate.
53-32C. Code designation for Ticlopidine Hydrochloride.
57C65. Code designation for Cloguanamil.
65-318. Code designation for Bidimazium Iodide.
66-269. Code designation for Pretamazium Iodide.
79 T61. Code designation for Lucanthone Hydrochloride.
88BV59H21-2V67-66. Code designation for Votumumab.
115-8543 Japan. Code designation for Mitemcinal Fumarate.
125 I NM-113. Code designation for Iomethin I 125.
129Y83. Code designation for Colfosceril Palmitate.
131 I NM-113. Code designation for Iomethin I 131.
141W94. Code designation for Amprenavir.
177 J.D. Code designation for Aminocaproic Acid.
194-B. Code designation for Zolamine Hydrochloride.
205 E. Code designation for Calcium Dobesilate.
249-16. Code designation for Deditonium Bromide.

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256U87 hydrochloride. Code designation for Valacyclovir Hydrochloride.
311C90. Code designation for Zolmitriptan.
349 C59. Code designation for Moxipraquine.
403. Code designation for Imisopasem Manganese.
506U. Code designation for Nelarabine.
506U. Code designation for Nelzarabine.
516 MD. Code designation for Cinnarizine.
524W91. Code designation for Emtricitabine.
546C88. Code designation for Tilarginine.
566C. Code designation for Atovaquone.
566C80. Code designation for Atovaquone.
589C. Code designation for Tucaresol.
611 C 65. Code designation for Thenium Closylate.
619C89. Code designation for Sipatrigine.
640/1. Code designation for Cefuracetime.
640/359. Code designation for Cefuroxime.
673-082. Code designation for Nexeridine Hydrochloride.
711 SE. Code designation for Pipratecol.
776C85. Code designation for Eniluracil.
786-723. Code designation for Anilopam Hydrochloride.
882C87. Code designation for Netivudine.
935U83. Code designation for Raluridine.
1263W94. Code designation for Maribavir.
1314 TH. Code designation for Ethionamide.
1380U. Code designation for Baquiloprim.
1589 RB. Code designation for Pefloxacin.
1592U89. Code designation for Abacavir Succinate.
1592U89. Code designation for Abacavir Sulfate.
1709 CERM. Code designation for Niaprazine.
1875 CERM. Code designation for Fepromide.
2936. Code designation for Proscillaridin.
3123L. Code designation for Puromycin.
4091 C.B. Code designation for Benfurodil Hemisuccinate.
4306 CB. Code designation for Clorazepate Dipotassium.
4311 CB. Code designation for Clorazepate Monopotassium.
4909 RP. Code designation for Chlorproethazine Hydrochloride.
5048. Code designation for Dimethisterone.
5052. Code designation for Acetylcysteine.
5054. Code designation for Prodilidine Hydrochloride.
5058. Code designation for Oxybutynin Chloride.
5071. Code designation for Megestrol Acetate.
5107. Code designation for Chloral Betaine.
5190. Code designation for Amidephrine Mesylate.
5373. Code designation for Melengestrol Acetate.
6366A. Code designation for Imidaprilat.
7162 RP. Code designation for Trimipramine.
7432-S. Code designation for Ceftibuten.
8088 C.B. Code designation for Benfotiamine.
8102 CB. Code designation for Bamifylline Hydrochloride.
8599 R.P. mesylate. Code designation for Fonazine Mesylate.
10275-S. Code designation for Epitiostanol.
16726. Code designation for Symetine Hydrochloride.
16842. Code designation for Bitoscanate.
18894. Code designation for Nifungin.
20025. Code designation for Clorprenaline Hydrochloride.
21401-Ba. Code designation for Tribenoside.
21679-CH. Code designation for Malethamer.
24281. Code designation for Mitocarcin.
26383. Code designation for Thiphencillin Potassium.
27165. Code designation for Temefos.
28002. Code designation for Epipropidine.
29060-LE. Code designation for Vinblastine Sulfate.
29866. Code designation for Levopropoxyphene Napsylate.
30038CB. Code designation for Minaprine Hydrochloride.
30109. Code designation for Noracymethadol Hydrochloride.
30639. Code designation for Polyethadene.
31518. Code designation for Pyrroliphene Hydrochloride.
31595C. Code designation for Mitosper.
31814. Code designation for Heteronium Bromide.
32379. Code designation for Dromostanolone Propionate.
32645. Code designation for Vinleurosine Sulfate.
33006. Code designation for Acetohexamide.
33355. Code designation for Mestranol.
33379. Code designation for Flurandrenolide.
33876. Code designation for Anthelmycin.
34977. Code designation for Capreomycin Sulfate.
35483. Code designation for Cyclothiazide.
36781. Code designation for Vinrosidine Sulfate.
37231. Code designation for Vincristine Sulfate.
38000. Code designation for Clometherone.
38253. Code designation for Cephalothin Sodium.
38389. Code designation for Levopropylcillin Potassium.
38489. Code designation for Nortriptyline Hydrochloride.
38851. Code designation for Bolmantalate.
39435. Code designation for Cephaloglycin.
40045. Code designation for Trimetazidine.
40602. Code designation for Cephaloridine.
41071. Code designation for Cefalonium.
42406. Code designation for Metoquizine.
43853. Code designation for Clobenoside.
44089. Code designation for Valproic Acid.
44106. Code designation for Toquizine.
44328. Code designation for Dexproxibutene.
46083. Code designation for Cefazolin Sodium.
46236. Code designation for Dobutamine Hydrochloride.
47599. Code designation for Pyrazofurin.
47657. Code designation for Apramycin.
47663. Code designation for Tobramycin.
49040. Code designation for Vinglycinate Sulfate.
49825. Code designation for Nylestriol.
52230. Code designation for Pyrrolnitrin.
53183. Code designation for Aranotin.
53858. Code designation for Fenoprofen.
59156. Code designation for Enpromate.
60231/4. Code designation for Rufinamide.
60284. Code designation for Cyclophenazine Hydrochloride.
64716. Code designation for Cinoxacin.
66873. Code designation for Cephalexin.
67314. Code designation for Monensin.
68618. Code designation for Mycophenolic Acid.
69323. Code designation for Fenoprofen Calcium.
79907. Code designation for Lergotrile.
80066. Code designation for Bufilcon A.
83636. Code designation for Lergotrile Mesylate.
106223. Code designation for Cefamandole Nafate.
110264. Code designation for Cefaparole.
177501. Code designation for Clodronate Disodium.

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218791-21-0. Imisopasem Manganese
218949-48-5. Tesamorelin
219311-43-0. Dabuzalgron Hydrochloride
(See also *219311-44-1*)
219311-44-1. Dabuzalgron Hydrochloride [dabuzalgron]
(See also *219311-43-0*)
219527-63-6. Repifermin
219581-36-9. Alvameline Maleate
219649-07-7. Labetuzumab
219680-11-2. Zabofloxacin
219685-50-4. Eculizumab
219685-93-5. Pexelizumab
219716-33-3. Visilizumab
219810-59-0. Neramexane Mesylate [neramexane]
(See also *457068-92-7*)
219846-21-8. Resequinil
219861-08-2. Escitalopram Oxalate
219923-85-0. Pramiconazole
219989-84-1. Ixabepilone
220201-34-3. Talaporfin Sodium
(See also *110230-98-3*)
220322-05-4. Elzasonan Hydrochloride
220578-59-6. Gemtuzumab Ozogamicin
220620-09-7. Tigecycline
220641-11-2. Naminidil
220651-94-5. Ruplizumab
220712-29-8. Tadekinig Alfa
220847-86-9. Valategrast Hydrochloride [valategrast]
(See also *828271-96-1*)
220984-26-9. Detiviciclovir
220991-20-8. Lumiracoxib
220991-32-2. Robenacoxib
220997-97-7. Diflomotecan
220998-10-7. Elomotecan
221005-96-5. Elarofiban
(See also *198958-88-2*)
221241-63-0. Fandosentan Potassium [fandosentan]
(See also *221246-12-4*)
221246-12-4. Fandosentan Potassium
(See also *221241-63-0*)
221373-18-8. Olanzapine Pamoate
221877-54-9. Zotarolimus
222400-20-6. Tomopenem
222535-22-0. Alefacept
222716-86-1. Pegaptanib Sodium
222732-94-7. Asoprisnil Ecamate
222834-30-2. Ragaglitazar
223420-20-0. Cipralisant Maleate
223537-30-2. Rupintrivir
223577-45-5. Aviscumine
223652-90-2. Garenoxacin Mesylate
(See also *194804-75-6*)
223661-25-4. Bulaquine
224452-66-8. Retapamulin
224785-90-4. Vardenafil
224789-15-5. Vardenafil Dihydrochloride
225239-31-6. Technetium Tc 99m Fanolesomab
225367-66-8. Efletirizine Dihydrochloride
226256-56-0. Cinacalcet
226700-79-4. Fosamprenavir Sodium [fosamprenavir]
(See also *226700-80-7*)
226700-80-7. Fosamprenavir Sodium
(See also *226700-79-4*)
226700-81-8. Fosamprenavir Calcium
226954-04-7. Emapunil
227318-75-4. Sotirimod
227622-74-4. Gadomelitol
227940-00-3. Adekalant
228266-40-8. Taltobulin
229614-55-5. Peramivir (monohydrate)
229975-97-7. Atazanavir Sulfate
(See also *198904-31-3*)
230949-16-3. Esoxybutynin Chloride
(See also *119618-22-3*)
231277-92-2. Lapatinib Ditosylate [lapatinib]
(See also *388082-78-8*)
233254-24-5. Tomeglovir
234096-34-5. Cefovecin Sodium [cefovecin]
(See also *141195-77-9*)
235114-32-6. Micafungin Sodium [micafungin]
(See also *208538-73-2*)
235428-87-2. Taplitumomab Paptox
237068-57-4. Oglufanide Disodium
(See also *38101-59-6*)
239101-33-8. Deferitrin
241473-69-8. Reslizumab
241800-98-6. Zoniporide
242138-07-4. Omalizumab
242148-62-5. Hofocon A
242478-37-1. Solifenacin Succinate [solifenacin]
(See also *242478-38-2*)
242478-38-2. Solifenacin Succinate
(See also *242478-37-1*)
243835-65-6. Lamifiban Hydrochloride
244015-05-2. Iseganan Hydrochloride
(See also *257277-05-7*)
244081-42-3. Rafabegron
244096-20-6. Gavilimomab
244130-01-6. Mirostipen
244767-67-7. Dapivirine
245116-90-9. Lidorestat [anhydrous]
246527-99-1. Mureletecan
246539-15-1. Dibotermin Alfa
246861-96-1. Garnocestim
247046-52-2. Dilopetine
247207-64-3. Leconotide
247257-48-3. Fimasartan
248281-84-7. Laquinimod
248282-01-1. Paquinimod
248919-64-4. Linaprazan
249296-44-4. Varenicline Tartrate [varenicline]
(See also *375815-87-5*)
250242-54-7. Lemalesomab
250386-15-3. Apadenoson
250601-04-8. Imiglitazar
250694-07-6. Teglicar
250710-65-7. Adargileukin Alfa
251303-04-5. Ertiprotafib
251562-00-2. Tifuvirtide
251565-85-2. Tesaglitazar
252188-71-9. Ceftobiprole Medocaril
(See also *376653-43-9*)
252260-06-3. Posizolid
252555-01-4. Acolbifene Hydrochloride
(See also *182167-02-8*)
252662-47-8. Toralizumab
252870-53-4. Ispronicline
252920-94-8. Solabegron Hydrochloride [solabegron]
(See also *451470-34-1*)
253450-09-8. Besonprodil
254877-67-3. Ataciguat
254964-60-8. Tasquinimod
255730-18-8. Artemisone
255734-04-4. Ritobegron
256382-08-8. Rivenprost
256411-32-2. Belotecan Hydrochloride [belotecan]
(See also *213819-48-8*)
257277-05-7. Iseganan Hydrochloride [iseganan]
(See also *244015-05-2*)
257933-82-7. Pelitinib
258516-87-9. Fospropofol Disodium
(See also *258516-89-1*)
258516-89-1. Fospropofol Disodium [fospropofol]
(See also *258516-87-9*)
259074-76-5. Alfimeprase
259188-38-0. Rebimastat
259525-01-4. Enecadin
260980-89-0. Topilutamide
261356-80-3. Epoetin Delta
261944-46-1. Soraprazan
262352-17-0. Torcetrapib
263351-82-2. Paclitaxel Poliglumex
263547-71-3. Epitumomab Cituxetan
263562-28-3. Barixibat
264609-13-4. Edonentan
(See also *210891-04-6*)
265114-23-6. Cimicoxib
265121-04-8. Fosaprepitant Dimeglumine
(See also *172673-20-0*)
266359-83-5. Reparixin
267227-08-7. Apolizumab
267243-28-7. Canertinib Dihydrochloride [canertinib]
(See also *289499-45-2*)
268203-93-6. Udenafil
269055-15-4. Etravirine
269062-93-3. Omiganan Pentahydrochloride
(See also *204248-78-2*)
269079-62-1. Isalmadol
272780-74-2. Metelimumab
274679-00-4. Padoporfin
274693-27-5. Ticagrelor
274901-16-5. Vildagliptin
274925-86-9. Nebicapone
276690-58-5. Iroxanadine
279215-43-9. Tifenazoxide
279253-83-7. Vapitadine Dihydrochloride
(See also *793655-64-8*)
280585-34-4. Oxeglitazar
280755-12-6. Tulathromycin (component B)
(See also *217500-96-4*)
280776-87-6. Gadocoletic Acid
282526-98-1. Cetilistat

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Appendix VII

Guiding Principles for Coining United States Adopted Names for Drugs

By definition, nonproprietary names are not subject to proprietary trademark rights but are entirely in the public domain. This distinguishes them from the trademarked names that have been registered for private use. A United States Adopted Name (USAN) is a nonproprietary name selected by the USAN Council according to principles developed to assure safety, consistency, and logic in the choice of names. These principles take into account practical considerations, such as the existence of trademarks and the fact that the intended uses of substances for which names are being selected may change. These guidelines are and must be sufficiently flexible to be revised if this is considered to be desirable and/or necessary.

General Rules

1. A nonproprietary name should be useful primarily to health practitioners, especially physicians, pharmacists, nurses, educators, dentists, and veterinarians.
   a. The primary criterion for judging usefulness is suitability, including safety for use in the routine processes of prescribing, ordering, dispensing, and administering drugs throughout the United States.
   b. The second criterion is suitability for use in educational programs for students in medically oriented professions and for use in scientific and lay publications.
   c. The third criterion is suitability for use internationally for drug identification, for the exchange of information and translation into different languages.
2. Attributes that contribute to usefulness are simplicity (brevity and ease of pronunciation), euphony, and ready recognition and recall.
   a. The name for the active moiety of a drug should be a single word, preferably with no more than four syllables.
   b. The name for the active moiety may be modified by a single term, preferably with no more than four syllables, to show a chemical modification, such as salt or ester formation (e.g., cortisone acetate from cortisone, cefamandole sodium from cefamandole, erythromycin acistrate from erythromycin).
   c. Only under compelling circumstances is a name with more than one modifying term acceptable (e.g., pharmaceuticals containing radioactive isotopes, the different classes of interferons).
   d. Acronyms, initials, and condensed words may be acceptable in otherwise appropriate terminology.
3. A name should reflect characteristics and relationships that will be of practical value to the users.
   a. A common, simple word element (a "stem") should be incorporated in the names of all members of a group of related drugs when pertinent, common characteristics can be identified (e.g., similarity of pharmacological action). When pharmacological similarity is found in drugs of distinctly different chemical nature, stems should differ (e.g., the antipsychotics, promazine and haloperidol; the nonsteroidal anti-inflammatory agents [NSAID], ibuprofen, etodolac, and isoxicam).
   b. Distinctive terminology should be used for specific drugs or groups (e.g., insulin I 131, dextran 40, interferon alfa-2a and interferon alfa-n1; licryfilcon A and licryfilcon B; epoetin alfa and epoetin beta).
4. A name should be free from conflict with other nonproprietary names and with established trademarks and should be neither confusing nor chemically misleading.
   a. Prefixes that imply "better," "newer," or "more effective," or evoke the name of the manufacturer, dosage form, duration of action or rate of drug release should not be used.
   b. Prefixes that refer to an anatomical connotation or medical condition are not acceptable.
   c. Prefixes that indicate a chemical element or compound (Ca, Ni, and Stannous) are not acceptable.
5. Preference should be given to names of established usage provided they conform to these guiding principles and are determined to be free from conflict with existing nonproprietary names and trademarks.
6. Identical negotiations submitted by two or more manufacturers will be conducted in accordance with the Council's practice of maintaining confidentiality. The applicants involved will not be notified of the multiple sources of the submission. However, the name selected by the USAN Council will need to be accepted by each manufacturer involved in the negotiation process.
7. A request for a USAN should be made after the drug manufacturer or sponsor has submitted an Investigational New Drug (IND) application to the Food and Drug Administration (FDA) to obtain permission to initiate studies on humans.
8. Deferred Negotiations:
   a. The USAN Council Secretariat will defer an ongoing negotiation for six (6) months plus one additional three-month extension upon receipt of a written request from the manufacturer. If the USAN Council has selected a name candidate and recommended this name to the manufacturer, the maximum deferral is one six-month period.
   b. The negotiation will be canceled after the maximum nine-month deferral has lapsed.
   c. If the negotiation is to be reopened at a later time, it will receive a new USAN file number and will be treated as a new application. The manufacturer will be expected to submit a new USAN negotiation form, update the background information, and submit the appropriate user's fee.

Specific Rules

1. Because of the international exchange of drug information, specific guidelines have been formulated to ensure appropriate translation of nonproprietary names into other languages. The following rules of preferred spelling should be used when coining USAN designations:
   a. the letter "f" should be used instead of "ph"
   b. the letter "t" should be used instead of "th"

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Samsung Bioepis Exhibit No. 1002
Page 12450

c. the letter "e" should be used instead of "ae" or "oe"
d. the letter "i" should be used instead of "y"
e. the letter "h" should be avoided
f. the letter "k" should be avoided.
g. the letter "j" should be avoided.
h. the letter "w" should be avoided.
i. "ar", "rac", "lev", "dex", or "es" are reserved for stereochemical configurations

2. Additionally, these letter combinations are restricted until further notice. Please avoid the following prefixes:
   a. the beginning letter combination of "me"
   b. the beginning letter combination of "str"
   c. chemical connotations such as "ben", "bu", "cat", "cel", "fen", "flu", "piro"
   d. chemical symbols unless present in the compound, "al", "ba", "ca", "li", "ni"

   In order to facilitate the development of names that will be accepted on an international level please note:
   A. The following letter combinations pose pronunciation problems in several languages:
      -ch-
      -rs-
      -xn
   B. The letter sequence "-m" and "-n" followed by consonants may be regarded as difficult.
      (1) "-m" before a consonant other than "p", "n", or "b"
      (2) -nb-, and -np- should be avoided
   C. The letter sequence "-vr" should be avoided.
   D. In addition, it should be kept in mind that there is, in some languages, no distinction between:
      "b" and "v" or "p"
      "l" and "r"
      "z" and "g"
3. Isolated letters, numbers, or hyphenations are restricted to those groups of substances for which such usage fulfills a clearly demonstrable purpose (e.g., interferon alfa-2b, paflufocon A, technetium Tc 99m siboroxime).
4. Group relationships in a name preferably should be indicated by use of syllables or stems; conversely, use of the stem for other than the appropriate group should be avoided. When multiple stems are available, the stem conveying the most information should be used.
5. Esters, salts, chelates, and complexes ordinarily require a two-word name to indicate the inactive as well as the active portion.
6. The preferred order for the name of an inorganic salt is cation-anion (e.g., sodium bromide). The same order is preferred for well-known salts of simple organic acids (e.g., sodium lactate, magnesium citrate, potassium acetate). However, for more complex organic compounds, the pharmacologically active portion should be identified first (e.g., oxacillin sodium, ibuprofen piconol, dexibuprofen lysine).
7. A name for a salt or ester generally should be derived from the name of the pharmacologically active moiety or corresponding acid (e.g., sodium acetate or ethyl acetate, derived from acetic acid). When a nonacid suffix is used, as in the penicillin series, a salt should be named without modification of the parent acid name (e.g., oxacillin sodium, derived from oxacillin). Names for different salts or esters of the same active moiety should differ only in the name of the inactive portion; exceptions are permissible when the salt and ester forms possess pharmacologic activity.
8. A name for the salt form of the pharmacologically active moiety is specific to the number of molecules used to react with the active moiety (e.g., balsalazide disodium, gusperimus trihydrochloride). If only one molecule is used to react with the active moiety, the designation for the salt name is used without reference to the mono-prefix (e.g., besipirdine hydrochloride, afovirsen hydrochloride). [This rule was formulated and approved in January 1993; different requirements were applied prior to this date.]
9. A name for a quaternary ammonium substance should designate the cation and anion separately (e.g., octonium bromide, not octonine methylbromide). The name assigned to the cation must contain the *-ium* suffix stem.
10. A name for a complex of two or more components should list the name of the principal active ingredient followed by a coined designation for the second component ending with an *-ex* suffix to indicate "complex" (e.g., bisacodyl tannex, doxycycline fosfatex). Complexes formed from sulfonated diethenylbenzene-ethenylbenzene copolymers and an active ingredient should list the name of the principal active ingredient followed by "polistirex" (e.g., chlorpheniramine polistirex, codeine polistirex).
11. A name for a drug containing a radioactive atom should list, in the order given: (1) the name of the drug containing the radioactive atom, (2) the element symbol, (3) the isotope number, and (4) the name of the carrier agent, if any (e.g., rose bengal sodium I 131, cyanocobalamin Co 60, potassium bromide Br 82, technetium Tc 99m butilfenin, technetium Tc 99m medronate, indium In 111 oxyquinoline, indium In 111 satumomab pendetide).
12. A name for a substance generally should not indicate the state of hydration, the morphology, or the mode of preparation. Reference to the water of hydration is retained in the chemical information (chemical names, formulas, weight) but is excluded from the nonproprietary name. The degree of hydration becomes a part of the chemical entity identified by the USAN.
13. Under the terms of the Orphan Drug Act of 1983, the development and marketing of drug products that are of limited commercial application but that are potentially useful in relatively rare disease conditions are encouraged. The selection of a name for an orphan drug may be based on special considerations. Therefore, when the name for an orphan drug appears to follow a more chemically oriented terminology style than is customary for drug nomenclature generally, this is not to be regarded as a basis or a precedent for a future selection of a USAN.
14. A name coined for a new chemical entity routinely does not specify the stereoisomeric form of the molecule in the nonproprietary name. If the stereochemical configuration has been determined, this information is presented in the chemical name(s) and is reflected in the structural formula. A USAN can, therefore, identify the racemic mixture (e.g., carnitine, ibuprofen, tetramisole), the levo isomer (e.g., remoxipride, quadazocine), or the dextro form (e.g., butopamine). Subsequently, if a name is needed for a different enantiomer or for the racemic form, the following prefixes should be added to the existing name:
   a. For the racemate, the rac-/race- prefix is used (e.g., racemethionine, racepinephrine, ractopamine).
   b. For the levo rotatory form, the "(S)" isomer, the lev-/levo- prefix is used (e.g., levocarnitine, levamisole, levcromakalim, levdobutamine).
   c. For the levo rotatory form but for the "(R)" isomer, ["R(-)"-isomer], the "ar-" prefix is added to the base name.
   d. For the dextro rotatory form, the "(R)" isomer, the dex-/dextro- prefix is used (e.g., dexamisole, dexibuprofen, dextroamphetamine, dexverapamil, dexrazoxane, dexfosfoserine, dexniguldipine).
   e. For the dextro rotatory form but for the "(S)" isomer ["S(+)"-isomer], the "es-" prefix is added to the base name.

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Samsung Bioepis Exhibit No. 1002
Page 12451

15. Official names have been selected for a number of radicals and adducts used to form salts or esters of the pharmacologically active moiety. In a majority of cases, these names represent contractions of the chemical name assigned to the radical or adduct. In four specific cases, the official name identifies a multicomponent adduct:
    - *acistrate* identifies the 2′-acetate (ester) **and** octadecanoate (salt) (e.g., erythromycin acistrate).
    - *probutate* identifies the double ester—1-oxobutoxy **and** 1-oxopropoxy (e.g., hydrocortisone probutate).
    - *estolate* identifies the double salt—propanoate **and** dodecyl sulfate (e.g., erythromycin estolate).
    - *hyclate* identifies the monohydrochloride salt, hemiethanolate, hemihydrate combination (e.g., doxyclin hyclate).
    - For the complete list of official names for radicals, see the end of this Appendix.

Nomenclature for Biological Products

The USAN Council has been involved in coining names for various biological products: the insulins, interferons, interleukins, growth hormones, colony-stimulating factors, cytokines, and monoclonal antibodies. With increasing development of highly purified biological extracts and recombinant materials, the Council expects to have an increasingly greater role in assigning names and developing nomenclature rules for these agents.

Listed below are specific guidelines created by the USAN Council, in conjunction with the Food and Drug Administration (FDA), the US FDA Center for Biologics Evaluation and Research (CBER), and the World Health Organization (WHO) International Nonproprietary Names (INN) Committee.

Interferons

The following multitiered style for creating nonproprietary names for interferons was adopted by the USAN Council:

(1) The word interferon is the first element in the name. Interferon is defined as the class name for a family of species-specific proteins (or glycoproteins) that are produced according to information encoded by species of interferon genes and exert complex antineoplastic, antiviral, and immunomodulating effects. The three main forms of interferon used in therapy are interferon alfa (formerly leukocyte or lymphoblastoid interferon), interferon beta (formerly fibroblast interferon), and interferon gamma (formerly immune interferon).

(2) The appropriate Greek letter (spelled out) is the second word of the name:

alfa, beta, gamma.

(3) An appropriate Arabic numeral and letter are appended to the Greek letter by a hyphen (no space) to delineate subcategories. The numbers conform to the recommendation of the Interferon Nomenclature Committee. The lowercase letter is assigned by the drug nomenclature agencies to differentiate one manufacturer's interferon from another's. Examples of pure interferon substances are:

interferon alfa-2a
interferon alfa-2b
interferon beta-1a
interferon beta-1b
interferon gamma-1a

(4) For mixtures of naturally occurring interferons, the lower case letter "n" precedes the number. Examples of names of mixtures of interferons obtained from a natural source, whether the exact percentage of a mixture is known or not, are:

interferon alfa-n1
interferon alfa-n2

Interleukins

The suffix *-kin* is used in naming interleukin-type substances except for interleukin 3 (IL-3) which was classified as a pleiotropic colony-stimulating factor and assigned the "plestim" stem (e.g., daniplestim). The "kin" nomenclature series was divided into subgroups with an adjuvant stem representing the numerical class of the interleukin followed by the kin suffix. The subgroups are:

-nakin	interleukin 1 derivatives
-onakin	interleukin 1α derivatives
-benakin	interleukin 1β derivatives
-leukin	interleukin 2 derivatives
-trakin	interleukin 4 derivatives
-penkin	interleukin 5 derivatives
-exakin	interleukin 6 derivatives
-eptakin	interleukin 7 derivatives
-octakin	interleukin 8 derivatives
-nonakin	interleukin 9 derivatives
-decakin	interleukin 10 derivatives
-elvekin	interleukin 11 derivatives
-dodekin	interleukin 12 derivatives

Somatotropins

The following guidelines have been developed for somatotropin analogs:

(1) The *som-* prefix is used for growth hormone derivatives, e.g.,
somatropin for human growth hormone
somatrem for methionyl human growth hormone

(2) The *som-* prefix and the *-bove* suffix are required for bovine somatotropin derivatives, e.g.,
somidobove
sometribove
somagrebove

(3) The *som-* prefix and the *-por* suffix are required for porcine somatotropin derivatives, e.g.,
somalapor
somenopor
sometripor
somfasepor

Colony-Stimulating Factors

The following guidelines have been developed for recombinant colony-stimulating factors:

(1) The suffix *-grastim* is used for granulocyte colony-stimulating factors (G-CSF), e.g.,
lenograstim
filgrastim

(2) The suffix *-gramostim* is used for granulocyte macrophage colony-stimulating factors (GM-CSF), e.g.,
molgramostim
regramostim
sargramostim

(3) The suffix *-mostim* is used for macrophage colony-stimulating factors (M-CSF), e.g.,
mirimostim

(4) The suffix *-plestim* is used for interleukin 3 (IL-3) factors classified as pleiotropic colony-stimulating factors, e.g.,
muplestim
daniplestim

(5) The suffix *-distim* is used for conjugates of two different types of colony-stimulating factors, e.g.,
milodistim

(6) The suffix *-cestim* is used for stem cell stimulating factors, e.g., ancestim.

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Erythropoietins

The word *epoetin* is used for recombinant human erythropoietin, followed by the appropriate Greek letter (spelled out). "Epoetin" describes erythropoietin preparations that have an amino acid sequence identical to the endogenous cytokine; the words alfa, beta, gamma, etc. are added to designate preparations that differ in the composition and the nature of the carbohydrate moieties. Erythropoietins assigned a USAN are:

epoetin alfa
epoetin beta
epoetin gamma

Monoclonal Antibodies

The following guidelines have been developed for monoclonal antibodies:

(1) The suffix *-mab* is used for monoclonal antibodies and fragments.

(2) Identification of the animal source of the product is an important safety factor based on the number of products that may cause source-specific antibodies to develop in patients. The following letters were approved as product source identifiers:

u = human	e = hamster
o = mouse	i = primate
a = rat	xi = chimera
zu = humanized	

These identifiers are used as infixes preceding the *-mab* suffix stem, e.g.,

-umab (human)
-omab (mouse)
-ximab (chimera)
-zumab (humanized)

(3) The general disease state subclass must be incorporated into the name by use of a code syllable. The following disease state subclasses were approved based on products currently before the Council. Additional subclasses will be added as necessary.

Disease or Target Class:	
Viral	*-vir-*
Bacterial	*-bac-*
Immune	*-lim-*
Infectious Lesions	*-les-*
Tumors	
colon	*-col-*
melanoma	*-mel-*
mammary	*-mar-*
testis	*-got-*
ovary	*-gov-*
prostate	*-pr(o)-*
miscellaneous	*-tum-*

(4) In order to create a unique name, a distinct, compatible syllable should be selected as the starting prefix.

(5) Sequence of stems. The order for combining the key elements is as follows: Infix representing the target disease state, the source of the product, the monoclonal root *-mab* used as a suffix (e.g., bi*ciromab*, sa*tumomab*, ne*bacumab*, se*virumab*, tu*virumab*). When combining a target or disease infix stem with the source stem for chimeric monoclonal antibody, the last consonant of the target/disease syllable is dropped, e.g.:

target	*source*	*-mab stem*	*USAN*
-cir-	-xi	-mab	abciximab
-lim-	-zu	-mab	daclizumab

These modifications were deemed necessary to facilitate pronunciation of the resultant designation.

(6) If the product is radiolabeled or conjugated to another chemical such as a toxin, identification of this conjugate is accomplished by use of a separate, second word or other acceptable chemical designation. For monoclonals conjugated to a toxin, the "*-tox*" stem must be included as part of the name selected for the toxin (e.g., zolimomab *aritox*, the designation *aritox* was selected to identify ricin A-chain). For radiolabeled products, the word order is: name of the isotope, element symbol, isotope number, and name of the monoclonal antibody: e.g., *technetium Tc 99m biciromab indium In 111 altumomab pentetate*.

(7) A separate, distinct name must be assigned to any linker/chelator used to conjugate the monoclonal antibody to a toxin, isotope, or for pegylated monoclonal antibodies, e.g.,

telimomab aritox
indium In 111 satumomab pendetide
enlimomab pegol.

For the USAN Council to initiate the selection of a nonproprietary name for a monoclonal antibody or fragment, the nomenclature application must provide the following relevant information:

(1) The immunoglobulin class and subclass and the type of associated light chain.

(2) Identity of the fragment of the immunoglobulin used (if applicable).

(3) Species source from which the coding region for the immunoglobulin originated and specific, complete origin of all parts of chimeric, humanized, or semisynthetic immunoglobulins.

(4) The antigen specificity of the immunoglobulin, including its source.

(5) The clone designation (specify if vector or vector-cell combination).

(6) For conjugated monoclonal antibodies, the identity of any linkers, chelators, toxins, and/or isotopes present in the product.

(7) Identity of other modifications to the antibody, e.g., reduction of disulfide bonds, glycosylation or deglycosylation, amino acid modification, or substitution.

List of Stems Used by the USAN Council

This list represents common stems for which chemical and/or pharmacologic parameters have been established. These stems and their definitions have been approved by the USAN Council and are recommended for use in coining new nonproprietary names for drugs that belong to an established series of related agents. The list is not exhaustive in that it does not include all stems used by the Council and other national or international nomenclature groups. It is the nature of the nomenclature process that new, potential stems are constantly being created and that definitions of older stems may need to be modified as new information becomes available. (Updated August 2006)

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Stem	*Definition*	*Examples*
-abine	(see -arabine, -citabine)	
-ac	anti-inflammatory agents (acetic acid derivatives)	bromfen*ac* dexpemedol*ac*
-acetam	(see -racetam)	
-actide	synthetic corticotropins	ser*actide*
-adol or -adol-	analgesics (mixed opiate receptor agonists/antagonists)	taz*adol*ene spir*adol*ene levonantr*adol*
-adox	antibacterials (quinoline dioxide derivatives)	carb*adox*
-afenone	antiarrhythmics (propafenone derivatives)	alpr*afenone* dipra*fenonex*
-afil	PDE5 inhibitors	tadal*afil*
-aj-	antiarrhythmics (ajmaline derivatives)	lor*aj*mine
-aldrate	antacid aluminum salts	mag*aldrate*
-algron	alpha$_1$ and alpha$_2$-adrenoreceptor agonists	dabuz*algron*
-alol	combined alpha and beta blockers	labet*alol* medrox*alol*
-amivir	(see -vir)	
-ampa	ionotropic non-NMDA glutamate receptors (AMPA and/or KA receptors)	
-ampanel	antagonists	bec*ampanel*
-ampator	modulators	for*ampator*
-andr-	androgens	n*andr*olone
-anib	angiogenesis inhibitors	semax*anib*
-anserin	serotonin 5-HT$_2$ receptor antagonists	alt*anserin* trop*anserin* adat*anserin*
-antel	anthelmintics (undefined group)	carb*antel*
-antrone	antineoplastics; anthraquinone derivatives	pix*antrone*
-apsel	P-selectin antagonists	tor*apsel*
-arabine	antineoplastics (arabinofuranosyl derivatives)	faz*arabine* flud*arabine*
aril-, -aril, -aril-	antiviral (arildone derivatives)	pleco*naril* *aril*done fos*aril*ate
-arit	antirheumatics (lobenzarit type)	lobenz*arit* clobuz*arit*
-arol	anticoagulants (dicumarol type)	dicum*arol*
-arone	antiarrhythmics	amiod*arone* droned*arone*
-arot-	arotinoids	et*arot*ene sum*arot*ene taz*arot*ene
-arotene	arotinoid derivatives	bex*arotene* lin*arotene* taz*arotene*
arte-	antimalarials (artemisin derivatives)	*arte*flene
-ase	enzymes	alglucer*ase* dorn*ase* alfa
	subgroup:	
-dismase	superoxide dismutase activity (exception: orgotein)	su*dismase*
-teplase	tissue-type plasminogen activators	al*teplase* du*teplase* sil*teplase*
-uplase	urokinase-type plasminogen activators	sar*uplase* nasar*uplase*
-ast	antiasthmatics/antiallergics (not acting primarily as antihistamines; leukotriene biosynthesis inhibitors)	
	subgroup:	
-lukast	leukotriene receptor antagonists	cina*lukast* pobi*lukast*
-milast	type IV phosphodiesterase inhibitors	picla*milast*
-trodast	thromboxane A$_2$ receptor antagonists	sera*trodast*
-zolast	benzoxazole derivatives	eclaz*olast* ontaz*olast*
-tegr-	integrin antagonists	vala*tegrast*
-(a)tadine	tricyclic histaminic-H$_1$ receptor antagonists, loratadine derivatives	deslor*atadine* rup*atadine* soman*tadine*
-astine	antihistaminics (histamine H$_1$ receptor antagonists)	eb*astine*
-atadine	tricyclic antiasthmatics	olop*atadine* lor*atadine*
-axine	antianxiety, antidepressant inhibitor of norepinephrine and dopamine re-uptake	
-(f)axine		rada*faxine*
-azenil	benzodiazepine receptor agonists/antagonists	bret*azenil* flum*azenil*
-azepam	antianxiety agents (diazepam type)	lor*azepam*
-azepide	cholecystokinin receptor antagonists	dev*azepide*
-azocine	narcotic antagonists/agonists (6,7-benzomorphan derivatives)	quad*azocine* ket*azocine*
-azoline	antihistamines/local vasoconstrictors (antazoline type)	ant*azoline*
-azosin	antihypertensives (prazosin type)	dox*azosin*
-bactam	beta-lactamase inhibitors	sul*bactam*
-bamate	tranquilizers/antiepileptics (propanediol and pentanediol groups)	meprob*amate* fel*bamate*
-barb or -barb-	barbituric acid derivatives	pheno*barb*ital seco*barb*ital etero*barb*
-begron	beta 3 adrenoreceptor agonist	tali*begron*
-bendazole	anthelmintics (tibendazole type)	cam*bendazole*
-berel	beta estrogen receptor agonist	prina*berel*
-bersat	anticonvulsants; antimigraine (benzoylamino-benzpyran derivatives)	cara*bersat* tidem*bersat*
bol- or -bol-	anabolic steroids	*bol*andiol mi*bol*erone
-bufen	non-steroidal anti-inflamınatory agents, fenbufen derivatives	indo*bufen*
-bulin	antineoplastics (mitotic inhibitors; tubulin binders)	mivo*bulin*
-butan	antiseptics (dapabutan type)	dapa*butan* lopo*butan*

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Stem	*Definition*	*Examples*
-butazone	anti-inflammatory analgesics (phenylbutazone type)	mofe*butazone*
-caine	local anesthetics	dibu*caine*
calci- or -calci-	vitamin D analogues	*calci*potriene ta*calci*tol
-camra	antivirals (intracellular adhesion molecules, icam-1 derivatives)	trema*camra*
-camsule	camphorsulfonic acid derivatives used as UVA sunscreens	e*camsule*
-capoc	agonists of the Gardos channel, or the calcium activated potassium channel of intermediate conductance	seni*capoc*
-carbef	antibiotics (carbacephem derivatives)	lora*carbef*
-casan	caspase (interleukin –1b) converting enzyme inhibitors	pralna*casan*
-caserin	serotonin receptor agonists, primarily 5-HT_2	lor*caserin*
		vabi*caserin*
-castat	(see -stat)	
-catib	cathespin inhibitors	bali*catib*
-cavir	(see -vir)	
cef-	cephalosporins	*cef*azolin
-cept	receptor molecules, native or modified (a preceding infix should designate the target)	alvir*cept*
	subgroups:	
-co-	complement receptors	micro*cocept*
-facept	lymphocyte function-associated with antigen 3 (LFA) receptor	ale*facept*
-farcept	interferon receptors	pi*farcept*
-lefacept	lymphocyte function-associated antigen 3	a*lefacept*
-nercept	tumor necrosis factor receptors	le*nercept*
-tacept	cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)	bela*tacept*
-vircept	antiviral receptors	al*vircept*
-cet	receptors (small molecule)	
	subgroup:	
-calcet	calcium	te*calcet*
-cetrapib	cholesterol ester transfer protein inhibitors	tor*cetrapib*
-cic	hepatoprotectives (timonacic type)	limazo*cic*
-ciclib	cyclin dependent kinase inhibitors	seli*ciclib*
-ciclovir	(see -vir)	
-cidib	cyclin dependent kinase inhibitor	alvo*cidib*
-cidin	natural antibiotics (undefined group)	grami*cidin*
-ciguat	guanaline cyclase activator	ata*ciguat*
		atri*ciguat*
-cillin	penicillins	ampi*cillin*
-citabine	nucleoside antiviral or antineoplastic agents, cytarabine or azarabine derivatives	gem*citabine*
		fia*citabine*
		zal*citabine*
-clidine	muscarinic agonists (various indications)	veda*clidine*
		talsa*clidine*
-clone	hypnotics/tranquilizers (zopiclone type)	pago*clone*
-cog	blood coagulation factors subgroups:	
-eptacog	blood coagulation factor VII	*eptacog* alfa (activated)
-nonacog	blood coagulation factor IX	*nonacog* alfa
-octocog	blood coagulation factor VIII	moro*octocog* alfa
		octocog alfa
-cogin	blood coagulation cascade inhibitor	tifa*cogin*
-conazole	systemic antifungals (miconazole type)	flu*conazole*
		oxi*conazole*
-cort-	cortisone derivatives	hydro*cort*isone
-coxib	cyclooxygenase-2 inhibitors	cele*coxib*
		pare*coxib*
		valde*coxib*
-cridar	(see -dar)	
-crinat	diuretics (ethacrynic acid derivatives)	bro*crinat*
-crine	acridine derivatives	amsa*crine*
		quina*crine*
-cromil	antiallergics (cromoglicic acid derivatives)	nedo*cromil*
-curium	neuromuscular blocking agents (quaternary) (also ammonium compounds)	atra*curium*
-curonium		al*curonium*
		pipe*curonium*
-cycline	antibiotics (tetracycline derivatives)	mino*cycline*
-dan	positive inotropic agents (pimobendan type)	prinoxo*dan*
		indoli*dan*
-dapsone	antimycobacterials (diaminodiphenylsulfone derivatives)	ace*dapsone*
-dar	multidrug resistance inhibitors	
	subgroups:	
-cridar	acridine carboxamide derivatives	ela*cridar*
-icodar	pipecolic acid derivatives	bri*icodar*
-quidar	qunioline derivatives	lami*quidar*
		zozu*quidar*
-spodar	ciclosporin D derivatives	val*spodar*
-denoson	adenosine A receptor agonists	teca*denoson*
		bino*denoson*
-depsin	depsipeptide derivatives	romi*depsin*
-dermin	(see -ermin)	
dil-, -dil- or -dil	vasodilators (undefined group)	foste*dil*
-dipine	phenylpyridine vasodilators (nifedipine type)	daro*dipine*
		felo*dipine*
-dismase	(see -ase)	
-distim	(see -stim)	
-ditan	antimigraine (5-HT_1 receptor agonists)	alni*ditan*
-dopa	dopamine receptor agonists	levo*dopa*
-dore	dopamine D_2D_3	aplin*dore* fumarate
-dotin	synthetic analogs of the dolastatin series	tasi*dotin* HCl

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Stem	*Definition*	*Examples*
-dralazine	antihypertensives (hydrazine-phthalazines)	hy*dralazine* en*dralazine*
-dronate	calcium metabolism regulators	eti*dronate* tilu*dronate*
-dutant	(see -tant)	
-ectedin	ecteinascodin derivatives	mon*ectedin*
-ectin	antiparasitics (ivermectin type)	doram*ectin* moxid*ectin*
-elestat	(see -stat)	
-elvakin	(see -kin)	
-emcinal	erythromycin derivatives lacking antibiotic activity	mit*emcinal*
-entan	endothelin receptor antagonists	bos*entan*
-eptacog	(see -cog)	
-eptakin	(see -kin)	
-erg-	ergot alkaloid derivatives	p*erg*olide
-eridine	analgesics (meperidine type)	anil*eridine*
-ermin	growth factors subgroups:	
-bermin	vascular endothelial growth factors	tel*bermin*
-dermin	epidermal growth factors	muro*dermin*
-fermin	fibroblast growth factors	erso*fermin*
-nermin	tumor necrosis factors	so*nermin* taso*nermin*
-plermin	platelet derived growth factors	beca*plermin*
-sermin	insulin-like growth factors	meca*sermin*
-termin	transforming growth factors	ce*termin*
-otermin	bone morphogenetic proteins	dibo*termin* alfa
estr- or -estr-	estrogens	*estr*one fen*estr*el
-estrant	estrogen antagonists	fulv*estrant*
-etanide	diuretics (piretanide type)	bum*etanide*
-exakin	(see -kin)	
-ezolid	oxazolidinone antibacterials	eper*ezolid* lin*ezolid*
-farnib	farnesyl transferase inhibitor	tipi*farnib*
-fenamate	"fenamic acid" ester or salt derivatives	eto*fenamate*
-fenamic acid	anti-inflammatory agents (anthranilic acid derivatives)	flu*fenamic acid*
-fenin	diagnostic aids [(phenylcarbamoyl)methyl iminodiacetic acid derivatives]	arclo*fenin*
-fenine	analgesics (fenamic acid subgroup)	flocta*fenine*
-fentanil	narcotic analgesics (fentanyl derivatives)	al*fentanil* mir*fentanil* bri*fentanil*
-fentrine	phosphodiesterase inhibitor	puma*fentrine*
-fermin	(see -ermin)	
-fetamin(e)	amfetamine derivatives	levmetam*feta*mine
-fiban	fibrinogen receptor antagonists (glycoprotein II_b/III_a receptor antagonist)	lami*fiban* tiro*fiban*
-fibatide	(see -tide)	
-fibrate	antihyperlipidemics (clofibrate type)	beza*fibrate*
-filcon	hydrophilic contact lens materials	alpha*filcon* A xylo*filcon* A mipa*filcon* A
-fingol	sphingosine derivatives	cede*fingol* sa*fingol*
-flapon	5-lipoxygenase-activating protein (FLAP) inhibitors	qui*flapon*
-flurane	general inhalation anesthetics (halogenated alkane derivatives)	en*flurane*
-fo-	phosphoro-derivatives	ade*fo*vir
-focon	hydrophobic contact lens materials	tri*focon* A pasi*focon* B sata*focon* A
-formin	hypoglycemics (phenformin type)	bu*formin*
-fradil	calcium channel blockers acting as vasodilators	mibe*fradil*
-fulven	antineoplastic, acylfulven derivatives	virido*fulven*
-fungin	antifungal antibiotics (undefined group)	kala*fungin*
-fylline	theophylline derivatives	enpro*fylline* bami*fylline* cipam*fylline*
-gab-	gabamimetics	fen*gab*ine
gado-	gadolinium derivatives (principally for diagnostic use)	*gado*diamide *gado*teridol *gado*benate
-gapil	neuronal apoptosis inhibitors; GAPDH	omi*gapil*
-ganan	antimicrobial, bactericidal permeability increasing polypeptide	ise*ganan* pexi*ganan*
-gatran	thrombin inhibitors (argatroban type)	efe*gatran*
-gest-	progestins	me*gest*rol
-giline	MAO inhibitors, type B	sele*giline*
-gillin	antibiotics (*Aspergillus* strains)	mito*gillin*
gli-	antihypoglycemics	*gli*flumide
-gliflozin	phlorozin derivatives, phenolic glycosides	ser*gliflozin*
-glinide	antidiabetic, SGLT2 inhibitors, not phlorozin derivatives	repa*glinide* mitig*linide*
-gliptin	dipeptidyl aminopeptidase-IV inhibitors	vilda*gliptin*
-glitazar	PPAR agonists (not thiazolidene derivatives)	far*glitazar*
-glitazone	PPST agonists (thiazolidene derivatives)	cig*litazone* rosig*litazone*
-glumide	CCK antagonists, antiulcer, anxiolytic agent	amig*lumide* itrig*lumide*
-golix	GnRH receptor antagonists (nonpeptide)	rupu*golix*ô
-gosivir	(see -vir)	
-gramostim	(see -stim)	
-grastim	(see -stim)	
-grel- or -grel	platelet aggregation inhibitors (undefined group)	itazig*rel* dimeta*grel* fure*grel*ate

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Stem	*Definition*	*Examples*
guan-	antihypertensives (guanidine derivatives)	*guan*octine
-ibat	ileal bile acid transport inhibitor	barix*ibat*
-icam	anti-inflammatory agents (isoxicam type)	enol*icam* tenox*icam*
-icodar	(see -dar)	
-ifen(e)	antiestrogens of the clomifene and tamoxifen groups	nitrom*ifene* ralox*ifene* drolox*ifene*
-ilide	class III antiarrhythmic agents	ibut*ilide* risot*ilide* dofet*ilide*
-imepodib	inosine monophosphate dehydrogenase inhibitors	mer*imepodib*
-imex	immunostimulants	forfen*imex* roquin*imex* uben*imex*
-imibe-	antihyperlipidaemics, acyl CoA: cholesterol acyltransferase (ACAT) inhibitors	eldac*imibe* avas*imibe* pact*imibe*
-imod	immunomodulators	ivar*imod* pidot*imod*
	subgroup:	
-mapimod	mitogen-activated protein (MAP) kinase inhibitors	dor*mapimod*
-imus	immunosuppressives	tacrol*imus* napir*imus* gusper*imus*
	subgroup:	
-rolimus	immunosuppressant, rapamycin derivatives	sirol*imus*
io-	iodine-containing contrast media	*io*damide
-irudin	anticoagulants (hirudin type)	des*irudin*
-isant	histamine H3 receptor antagonists	cipral*isant*
-isomide	antiarrhythmics (disopyramide derivatives)	bid*isomide*
-ium (also -onium)	quaternary ammonium derivatives	clidin*ium* disiquo*nium* polixeto*nium*
-ixafor	CXCR4 antagonists	pler*ixafor*
-kacin	antibiotics obtained from *Streptomyces kanamyceticus* (related to kanamycin)	ami*kacin*
-kalant	potassium channel antagonists	almo*kalant* teri*kalant*
-kalim	potassium channel agonists	croma*kalim* apri*kalim*
-kalner	opener of large conductance calcium-activated (maxi-k) K+ channels	flindo*kalner*
-kef-	enkephalin agonists (various indications)	met*keph*amide caso*kef*amide
-kin	interleukin type substances	
	subgroups:	
-decakin	interleukin-10 analogues and derivatives	ilo*decakin*
-dodekin	interleukin-12 analogues and derivatives	e*dodekin* alfa
-elvekin	interleukin-11 analogues and derivatives	opr*elvekin*
-eptakin	interleukin-7 analogues and derivatives	
-exakin	interleukin-6 analogues and derivatives	at*exakin* alfa
-leukin	interleukin-2 analogues and derivatives	tece*leukin* aldes*leukin*
-nakin	interleukin-1 analogues and derivatives	
	subgroups:	
-onakin	interleukin 1-$_{\alpha}$ analogues and derivatives	pit*onakin*
-benakin	interleukin 1-$_{\beta}$ analogues and derivatives	mo*benakin*
-nonakin	interleukin-9 analogues and derivatives	
-octakin	interleukin-8 analogues and derivatives	em*octakin*
-penkin	interleukin-5 analogues and derivatives	
-trakin	interleukin-4 analogues and derivatives	bine*trakin*
-kinra	interleukin receptor antagonists	
	subgroups:	
-nakinra	interleukin 1 (IL-1) receptor antagonists	a*nakinra*
-kiren	renin inhibitors	dite*kiren* terla*kiren* zan*kiren*
-lazad	lipid peroxidation inhibitors	tiri*lazad*
-leptin	leptin derivatives	metre*leptin*
-leukin	(see -kin)	
-lipim	lipoprotein lipase activators	ibro*lipim*
-locib	antineoplastics that inhibit the formation of 5-LO, LTB_4, LTC_4, and thromboxane B_2 (TxB_2); and Activate PPARγ nuclear receptors	eta*locib*
-lubant	leukotriene receptor antagonists (treatment of inflammatory skin disorders)	tico*lubant*
-lukast	(see -ast)	
-lutamide	antiandrogens	bica*lutamide* *flutamide*
-lutril	neutral endopeptidase inhibitors possessing additional endothelin converting enzyme inhibitory activity	dag*lutril*
-mab	monoclonal antibodies	imciro*mab* abcixi*mab* capro*mab* daclixi*mab* detumo*mab* enlimo*mab*
	subgroup:	
-axo-	rat-murine hybrid antibodies	
-les-	infix for inflammatory/infectious lesions	
-neu(r)-	nervous system	bapi*neuzumab*
-os-	bone	den*osumab*
-toxa-	toxin as a target	ur*toxazumab*
-mantadine or -mantine	antivirals/antiparkinsonians (adamantane derivatives)	ri*mantadine* dopa*mantine*

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Stem	*Definition*	*Examples*
-mastat	(see -stat)	
-meline	cholinergic agonists (arecoline derivatives used in treatment of Alzheimer's disease)	xano*meline*
-melteon	selective melatonin receptor agonist	ra*melteon*
-mer	polymers	cadexo*mer* carbeti*mer*
-mesine	sigma receptor ligands	ig*mesine* pana*mesine*
-mestane	antineoplastics (aromatase inhibitors)	plo*mestane*
-metacin	anti-inflammatory agents (indomethacin type)	zido*metacin*
-micin	antibiotics (*Micromonospora* strains)	madura*micin* genta*micin*
-monam	monobactam antibiotics	glox*imonam* ox*imonam* tige*monam*
-morelin	(see -relin)	
-moren	non-peptidic growth hormone secretagogues	ibuta*moren*
-mostim	(see -stim)	
-motine	antivirals (quinoline derivatives)	fa*motine*
-moxin	monoamine oxidase inhibitors (hydrazine derivatives)	ben*moxin* do*moxin*
-mulin	antibacterials, pleuromulin derivatives	retapa*mulin*
-multin	mucosal tolerance inductors	ismo*multin*
-mustine	antineoplastics (chloroethylamine derivatives)	car*mustine*
-mycin	antibiotics (*Streptomyces* strains)	linco*mycin*
nab- or -nab-	cannabinol derivatives	*nab*azenil dro*nab*inol
-nakalant	mixed sodium/potassium channel blockers	ver*nakalant*
-nakin	(see -kin)	
nal-	narcotic agonists/antagonists (normorphine type)	*nal*mefene
-navir	(see vir-)	
-nercept	(see -cept)	
-nermin	(see -ermin)	
-nertant	neurotensin receptor antagonists	remi*nertant*
-nesib	kinesin inhibitors	ispi*nesib*
-netant	(see -tant)	
-neurin	neurotensin receptor antagonists; neurotropins	abri*neurin*
-nicline	nicotinic acetylcholine receptor partial agonists/agonists	alti*nicline*
-nidap	nonsteroidal anti-inflammatory agents (tenidap type)	ilo*nidap* te*nidap*
-nidazole	antiprotozoal substances (metronidazole type)	ti*nidazole*
nifur-	5-nitrofuran derivatives	*nifur*atel *nifur*atrone
-nil	benzodiazepine receptor antagonists/agonists	
-punil	subgroup: mitochondrial benzodiazepine receptor (MBR) selective, partial, or inverse agonists (purine derivatives)	ema*punil*
-quinil	benzodiazepine receptor agonists, also partial or inverse (quinoline derivatives)	lire*quinil*
-nixin	anti-inflammatory agents (anilinonicotinic acid derivatives)	clo*nixin*
-nonacog	(see -cog)	
-nonakin	(see -kin)	
-octacog	(see -cog)	
-octakin	(see -kin)	
-olol	beta-blockers (propranolol type)	tim*olol* aten*olol*
-olone	steroids (*not* prednisolone derivatives)	minax*olone*
-onide	topical steroids (acetal derivatives)	amcin*onide*
-opilone	epothilone	fil*opilone*
-orex	anorexiants	flud*orex*
-orphan	narcotic antagonists/agonists (morphinan derivatives)	dextrometh*orphan* dextr*orphan*
-osuran	urotensin receptor antagonists	pal*osuran*
-otilate	hepatoprotectants, di-isopropyl-1,3-dithiol-malonate derivatives	miv*otilate*
-oxacin	antibacterials (quinolone derivatives)	difl*oxacin* ciprofl*oxacin*
-oxan	alpha-adrenoceptor antagonists (benzodioxane derivatives)	imil*oxan*
-oxanide	antiparasitics (salicylanilide derivatives)	brom*oxanide*
-oxef	antibiotics (oxacefalosporanic acid derivatives)	flom*oxef*
-oxetine	antidepressants (fluoxetine type)	dap*oxetine* sepr*oxetine*
-pafant	platelet-activating factor antagonists	*apafant* daco*pafant* tulo*pafant* lexi*pafant*
-pamide	diuretics (sulfamoylbenzoic acid derivatives)	ali*pamide*
-pamil	coronary vasodilators (verapamil type)	tia*pamil*
-pamine	dopaminergics (butopamine type)	foso*pamine* ibo*pamine*
-panel	AMPA receptor antagonists	fana*panel* irum*panel* talam*panel*
-parcil	antithrombotics	beci*parcil* ili*parcil*
-parcin	glycopeptide antibiotics	avo*parcin*
-parib	poly-ADP-ribose polymerase inhibitors	ola*parib*
-parin	heparin derivatives and low molecular weight (or depolymerized) heparins	he*parin* tinza*parin* dalte*parin*
-parinux	antithrombotic indirect selective synthetic factor Xa inhibitors	fonda*parinux*

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Stem	*Definition*	*Examples*
-paroid	antithrombotics (heparinoid type)	dana*paroid* sul*paroid*
-peg	PEGylated compounds	*peg*caristim *peg*nartograstim *peg*visomant
-penem	antibacterial antibiotics (carbapenem derivatives)	imi*penem*
-penkin	(see -kin)	
perflu-	blood substitutes and/or diagnostics (perfluorochemicals)	*perflu*bron *perflu*nafene
-peridol	antipsychotics (haloperidol type)	halo*peridol*
-peridone	antipsychotics (risperidone type)	ris*peridone* ilo*peridone* oca*peridone*
-perone	antianxiety agents/neuroleptics (4′-fluoro-4-piperidinobutyrophenone derivatives)	duo*perone*
-pezil	acetylcholinesterase inhibitors used in the treatment of Alzheimer's disease	ico*pezil* done*pezil*
-pidem	hypnotics/sedatives (zolpidem type)	zol*pidem* al*pidem*
-pirdine	cognition enhancers	lino*pirdine* besi*pirdine* sibo*pirdine*
-pirox	antimycotics (pyridone derivatives)	ciclo*pirox*
-pitant	(see -tant)	
-plact	platelet factor 4 analogs and derivatives	iro*plact*
-pladib	phospholipase A2 inhibitors	eco*pladib*
-planin	antibacterials (*Actinoplanes* strains)	mide*planin* ramo*planin* teico*planin*
-platin	antineoplastics (platinum derivatives)	cis*platin*
-plasinin	inhibitors of plasminogen activator inhibitors—type 1	ti*plasinin*
-plermin	(see -ermin)	
-plestim	(see -stim)	
-plon	non-benzodiazepine anxiolytics, sedatives, hypnotics	ocina*plon* zale*plon*
-poetin	erythropoietins	e*poetin* alfa *epoetin* beta
-porfin	benzoporphyrin derivatives	verte*porfin* temo*porfin*
-pramine	antidepressants (imipramine type)	lofe*pramine*
-prazan	acid pump inhibitors, not dependent on acid activation	omida*prazan*
-prazole	antiulcer agents (benzimidazole derivatives) subgroup:	ome*prazole* disu*prazole*
-maprazole	acid pump inhibitors	pu*maprazole*
pred-, -pred- or -pred	prednisone and prednisolone derivatives	*pred*nicarbate clo*pred*nol oxiso*pred*
-pressin	vasoconstrictors (vasopressin derivatives)	desmo*pressin*
-pride	sulpiride derivatives	remoxi*pride* zaco*pride*
-pril	antihypertensives (ACE inhibitors)	enala*pril* temoca*pril* spira*pril*
-prilat	antihypertensives (ACE inhibitors) (diacid analogs of the -pril entity)	enala*prilat* spira*prilat*
-prim	antibacterials (trimethoprim type)	ormeto*prim*
-prinim	nootropic agents, purine derivatives	lete*prinim*
-prisnil	selective progesterone receptor modulators (SPRM)	aso*prisnil*
-pristin	antibacterials, pristinamycin derivatives	quinu*pristin* efe*pristin*
-pristone	progesterone receptor antagonists	mife*pristone*
-profen	anti-inflammatory/analgesic agents (ibuprofen type)	flurbi*profen*
-proget	nonsteroidal ligand for the progesterone receptor	tana*proget*
-prost- or -prost	prostaglandin derivatives	rio*prost*il dino*prost*
-protafib	protein tyrosine phosphatase 1B inhibitors	erti*protafib*
-pultide	(see -tide)	
-queside	cholesterol sequestrants (glycosides)	pama*queside*
-racetam	nootropes (piracetam type)	pi*racetam*
-racil	uracil type antineoplastics	enilu*racil* geme*racil* ote*racil*
-rafenib	Raf kinase inhibitors	so*rafenib*
-relin	prehormones or hormone-release stimulating peptides subgroups:	nafa*relin*
-morelin	growth hormone-release stimulating peptides	du*morelin*
-tirelin	thyrotropin releasing hormone analogues	pro*tirelin*
-relix	hormone-release inhibiting peptides	deti*relix*
-renone	aldosterone antagonists (spironolactone type)	can*renone*
-restat	(see -stat)	
-retin- or -retin	retinol derivatives	et*retin*ate pel*retin*
-rev -tucirev	therapeutic virus tumoricidal	lon*tucirev*
-ribine	ribofuranil derivatives (pyrazofurin type)	loxo*ribine*
rifa-	antibiotics (rifamycin derivatives)	*rifa*pentine *rifa*mpin
-rinone	cardiotonics (amrinone type)	mil*rinone*
-rozole	aromatase inhibitors (imidazole/triazole derivatives)	let*rozole* fad*rozole* vo*rozole*
-rsen	antisense oligonucleotides	alicafo*rsen*
-rubicin	antineoplastic antibiotics (daunorubicin type)	eso*rubicin* ida*rubicin*
sal-, -sal- or -sal	anti-inflammatory agents (salicylic acid derivatives)	mes*al*amine diflun*isal* bal*sal*azide

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Stem	*Definition*	*Examples*
-sartan	angiotensin II receptor antagonists	lo*sartan* epro*sartan*
-semide	diuretics (furosemide type)	azo*semide*
-sermin	(see -ermin)	
-serod	serotonin receptor antagonists and partial agonists	pibo*serod*
-serpine	*Rauwolfia* alkaloid derivatives	re*serpine*
-setron	serotonin 5-HT_3 antagonists	ondan*setron* grani*setron* luro*setron*
-siban	oxytocin antagonists	baru*siban*
-sidomine	antianginals (sydnone derivatives)	pir*sidomine* mol*sidomine* lin*sidomine*
som-	growth hormone derivatives	*som*atrem *som*atropin
som- -bove	bovine somatotropin derivatives	*som*etri*bove*
som- -por	porcine somatotropin derivatives	*som*etri*por* *som*agre*por*
-sonan	5-HT_{1B} receptor antagonists	elza*sonan*
-spirone	anxiolytics (buspirone type)	zalo*spirone* tio*spirone*
-spodar	(see -dar)	
-sporin	immunosuppressants (cyclosporine type)	gecle*sporin* oxeclo*sporin*
-stat or -stat-	enzyme inhibitors	
	subgroups:	
-castat	dopamine β-hydrolase (DBH) inhibitors	nepi*castat*
-elestat	elastase inhibitors	siv*elestat*
-inostat	inhibitors of histone deacetylase	dac*inostat*
-mastat	antineoplastics (matrix metalloproteinase inhibitors)	bati*mastat*
-(a)mostat	proteolytic enzyme inhibitors	naf*amostat*
-restat- or -restat	aldose-reductase inhibitors	ponal*restat* tol*restat*
-vastatin	antihyperlipidemics (HMG-CoA inhibitors)	lo*vastatin* pra*vastatin*
	(other series members)	
	urease inhibitor	ben*urestat*
	renal dehydropeptidase inhibitor	cila*stat*in
	pepsin inhibitor	pep*stat*in
-ster-	steroids (androgens, anabolics)	testo*ster*one
-steride	testosterone reductase inhibitors	epri*steride* fena*steride*
-stigmine	cholinesterase inhibitors (physostigmine type)	quilo*stigmine* teser*stigmine*
-stim	colony-stimulating factors	
	subgroups:	
-distim	conjugates of two different types of colony-stimulating factors	milo*distim*
-gramostim	granulocyte macrophage colony-stimulating factors (GM-CSF)	mol*gramostim* re*gramostim* sar*gramostim* eco*gramostim*
-grastim	granulocyte colony-stimulating factors (G-CSF)	fil*grastim* leno*grastim*
-mostim	macrophage colony-stimulating factors (M-CSF)	miri*mostim*
-plestim	interleukin-3 derivatives; pleiotropic colony-stimulating factors	dani*plestim*
-stinel	(*N*-methyl-D-asparate) NMDA receptor antagonists (glycine recognition site)	lico*stinel*
-sulam	antineoplastics, apoptosis inducing sulfonamide	indi*sulam*
sulfa-	antimicrobials (sulfonamides derivatives)	*sulfa*salazine
-sulfan	antineoplastics, alkylating agents (methanesulfonate derivatives)	bu*sulfan*
	subgroups:	
-lind	pro-apoptotic cGMP phosphodiesterase inhibitors	ractal*ind*
-sulind	sulfone metabolite	exi*sulind* dractal*ind*
-tant	tachykinin (neurokinin) receptor antagonists	
	subgroups:	
-dutant	NK_2 receptor antagonists	sare*dutant*
-netant	NK_2 receptor antagonists	osa*netant*
-pitant	NK_1 receptor antagonists	da*pitant* zina*pitant* lane*pitant*
-tapide	microsomal triglyceride transfer protein (MTP) inhibitors	implit*apide*
-taxel	antineoplastics, taxane derivatives	paclit*axel*
-tecan	antineoplastics (camptothecine derivatives)	topo*tecan* irino*tecan*
-tecarin	antineoplastics (rebeccamycin derivatives)	beca*tecarin*
-tepa	antineoplastics (thiotepa derivatives)	aze*tepa*
-teplase	(see -ase)	
-termin	(see -ermin)	
-terol	bronchodilators (phenethylamine derivatives)	albu*terol*
-tesind	thymidilate synthetase inhibitors (benzindole derivatives)	me*tesind*
-texafin	texaphryn derivatives	mo*texafin*
-thiazide	diuretics (thiazide derivatives)	chloro*thiazide*
-tiapine	antipsychotics (dibenzothiazepine derivatives)	qui*tiapine*
-tiazem	calcium channel blockers (diltiazem type)	dil*tiazem* clen*tiazem* ipro*tiazem*
-tibant	antiasthmatics (bradykimin antagonists)	ica*tibant*
-tide	peptides and glycopeptides	octreo*tide*
	subgroups:	
-fibatide	platelet aggregation inhibitors (glycoprotein IIb/IIIa receptor antagonists)	epti*fibatide*

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Stem	*Definition*	*Examples*
-murtide	peptides with muranic acid present	mifa*murtide*
-pultide	peptides used as pulmonary surfactants	sina*pultide*
-tidine	H_2-receptor antagonists (cimetidine type)	lupi*tidine* done*tidine* rani*tidine*
-tinib	tyrosine kinase inhibitors	caner*tinib* ima*tinib* mubri*tinib*
-tirelin	(see -relin)	
-tirome	antihyperlidaemic, thyromimetic derivatives	anti*tirome* axi*tirome*
-tocin	oxytocin derivatives	oxy*tocin*
-toclax	antineoplastic, BLC-2 inhibitor	oba*toclax*
-toin	antiepileptics (hydantoin derivatives)	albu*toin*
-toran	TLR4 receptor antagonists	eri*toran*
-tox(a)-	toxins	ur*toxa*zumab
-traposin	aP2 inhibitors	sel*traposin*
-trexate	antimetabolites (folic acid derivatives)	metho*trexate*
-trexed	antineoplastic thymidylate synthetase inhibitors	peme*trexed* rali*trexed* nola*trexed*
-tricin	antibiotics (polyene derivatives)	mepar*tricin*
-tril or -trilat	endopeptidase inhibitors	candoxa*tril* candoxa*trilat*
-triptan	antimigraine agents (5-HT_1 receptor agonists)	nara*triptan* oxi*triptan* suma*triptan*
-triptyline	antidepressants (dibenzo[*a*,*d*]cycloheptane derivatives)	ami*triptyline*
-troban	antithrombotics (thromboxane A_2 receptor antagonists)	dal*troban* sulo*troban*
-trodast	(see -ast)	
-troline	antipsychotics (dopamine D_2 antagonists)	carvo*troline* gevo*troline*
-trombopag	thrombopoetin agonists	el*trombopag*
trop- or -trop-	atropine derivatives	benz*trop*ine
-uclin	mucosal tolerance inhibitors	
-uplase	(see -ase)	
-uracil	uracil derivatives used as thyroid antagonists and as antineoplastics	fluoro*uracil*
-(ur)amidine	pentamidine derivatives/analogues	pafu*ramidine*
-uridine	antivirals; antineoplastics (uridine derivatives)	idox*uridine*
-vaptan	vasopressin receptor antagonists	coni*vaptan* relco*vaptan*
-vastatin	(see -stat)	
-verine	spasmolytic agents (papaverine type)	mebe*verine*

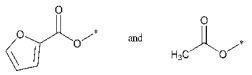
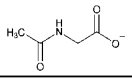
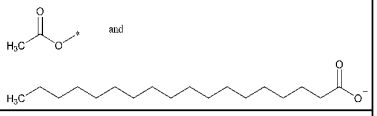
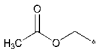
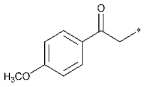
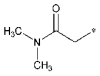
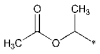
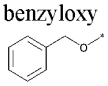
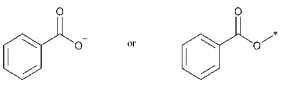
Stem	*Definition*	*Examples*
vin- or -vin-	vinca alkaloids	*vin*epidine apo*vin*camine
vir-, -vir- or -vir	antiviral substances (undefined group)	ganciclo*vir* en*vir*adine *vir*oxime al*vir*cept dela*vir*dine
	subgroups:	
-amivir	neuraminidase inhibitors	zana*mivir*
-cavir	carbocyclic nucleosides	lobu*cavir*
-ciclovir or -cyclovir	antivirals (acyclovir type)	des*ciclovir* fam*ciclovir* pen*ciclovir*
-gosivir	glucosidase inhibitor	celg*osivir*
-navir	HIV protease inhibitors (saquinavir type)	droxi*navir* indi*navir* rito*navir*
-virdine	antivirals (non-nucleoside reverse transcriptase inhibitors; pyridine derivatives)	ate*virdine* dela*virdine*
-virenz	antivirals (non-nucleoside reverse transcriptase inhibitors; benzoxazinone derivatives)	efa*virenz*
-virsen	antivirals (antisense)	afo*virsen* fomi*virsen* treco*virsen*
-vircept	(see -cept)	
-virdine	(see vir)	
-virenz	(see vir)	
-virimat	antiviral, disrupts viral maturation	be*virimat*
-viroc	CCR5 antagonists	mara*viroc*
-criviroc	CCR5 antagonists, immunomodulators	an*criviroc*
-vudine	antineoplastics; antivirals (zidovudine group) (exception: edoxudine)	sta*vudine* lami*vudine* alo*vudine*
-xaban	antithrombotic: blood coagulation factor X^A inhibitors	tami*xaban*
-xanox	antiallergic respiratory tract drugs (xanoxic acid derivatives)	ti*xanox*
-(x)antrone	antineoplastics, mitoxantrone derivatives aza-anthracenedione class of antitumor agents	pi*xantrone*
-zolamide	carbonic anhydrase inhibitors	brin*zolamide* dor*zolamide* se*zolamide*
-zolast	(see -ast)	
-zomib	proteozome inhibitors	borte*zomib*
-zotan	5-HT_{1A} receptor agonists/antagonists acting primarily as neuroprotectors	robal*zotan* sari*zotan* ibal*zotan* leco*zotan*

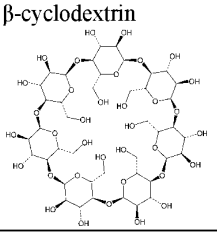
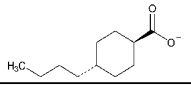
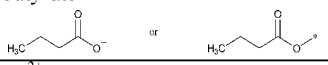
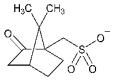
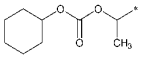
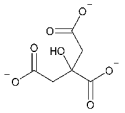
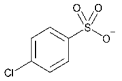
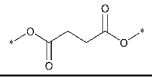
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Organic Moieties, Counterions, and Solvent Molecules Used in Coining Two-Word Names

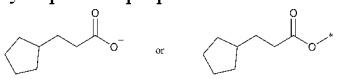
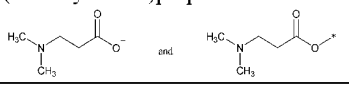
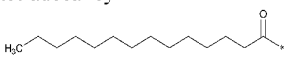
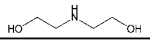
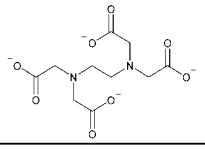
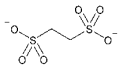
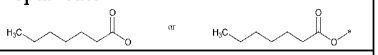
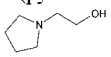
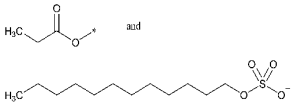
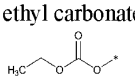
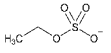
Note: names for carboxylic acid or sulfonate anions would also be applied to the parent acids or their esters.

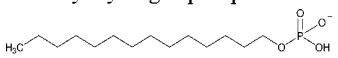
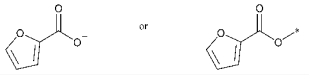
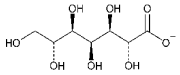
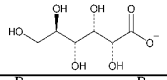
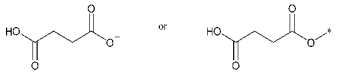
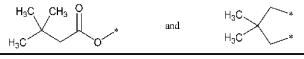
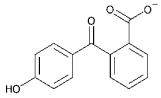
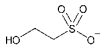
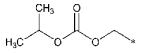
Name Used	Chemical Name and/or Formula
acefurate	acetate ester and furan-2-carboxylate ester 
acetate	acetate 
acetonide	isopropylidenedioxy, or acetonide 
aceturate	*N*-acetylglycinate 
acistrate	acetate ester and stearate salt 
acoxil	(acetyloxy)methyl 
anisatil	2-(4-methoxyphenyl)-2-oxoethyl 
arbamel	2-(dimethylamino)-2-oxoethyl 
argine	30^{B}α-L-arginine-30^{B}β-L-arginine —Arg—Arg
aspart	38^{B}-L-aspartic acid —Asp—
axetil	(*RS*)-1-(acetyloxy)ethyl 
beloxil	benzyloxy 
benzoate	benzoate 
besylate INN: besilate	benzenesulfonate 

Name Used	Chemical Name and/or Formula
betadex	β-cyclodextrin 
bromide	Br^-
buciclate	*trans*-4-butylcyclohexanecarboxylate 
butyrate INN: butirate	butyrate 
calcium	Ca^{2+}
camsylate INN: camsilate	(1*S*)-(+)-(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate or (1*S*)-(+)-10-camphorsulfonate 
caproate	hexanoate 
chloride	Cl^-
cilexetil	(*RS*)-1-[[(cyclohexyloxy)carbonyl]-oxy]ethyl 
citrate	2-hydroxypropane-1,2,3-tricarboxylate 
closylate INN: closilate	4-chlorobenzene-1-sulfonate 
crosfumaril	(2*E*)-but-2-enedioyl 
cyclotate INN: ciclotate	4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylate 

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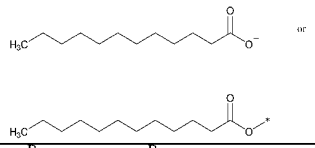
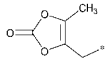
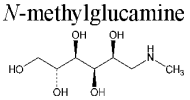
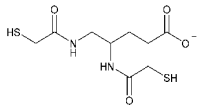
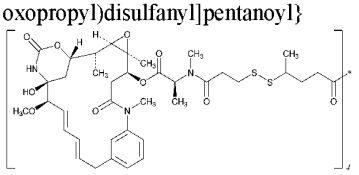
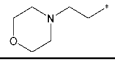
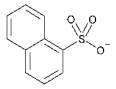
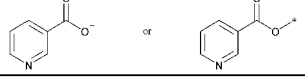
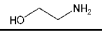
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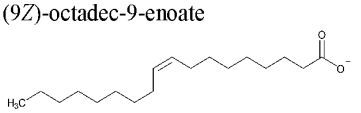
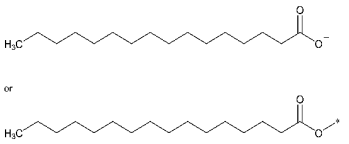
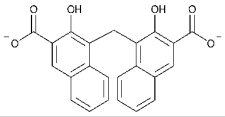
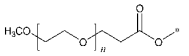
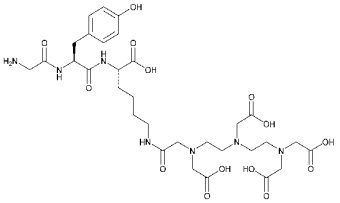
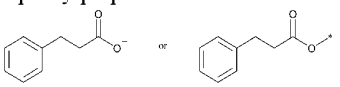
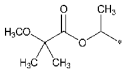
Name Used	Chemical Name and/or Formula
cypionate INN: cipionate	cyclopentane propionate 
dapropate INN: daropate	*N,N*-dimethyl-β-alaninate or 3-(dimethylamino)propanoate 
detemir	tetradecanoyl 
diftitox	*N*-L-methionyl-387-L-histidine-388-L-alanine-1-388-toxin (*Corynebacterium diptheriae* strain C7) (388→2')-protein
diolamine	2,2'-azanediyldiethanol or diethanolamine 
edamine	ethane-1,2-diamine or ethylenediamine 
edetate (formerly edathamil)	ethylenediaminetetraacetate, and all anions derived from edetic acid (EDTA) 
edisylate	1,2-ethanedisulfonate 
enanthate INN: enantate	heptanoate 
epolamine	2-(pyrrolidin-1-yl)ethanol 
erbumine	*tert*-butylamine 
estolate	propionate ester and dodecyl sulfate salt 
esylate INN: esilate	ethanesulfonate 
etabonate	ethyl carbonate 
ethylsulfate INN: etilsulfate	ethyl sulfate 

Name Used	Chemical Name and/or Formula
fostedate	tetradecyl hydrogen phosphate 
furoate	furan-2-carboxylate 
glargine	21[A]-glycine-30[B]α-L-arginine-30[B]β-L-arginine —Gly— and —Arg—Arg
gluceptate	D-*glycero*-D-*gulo*-heptanoate 
gluconate	(2*R*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoate 
glulisine	3[B]-L-lysine,29[B]-L-glutamic acid —Lys— and —Glu—
hemisuccinate	3-carboxypropanoate 
hexacetonide	3,3-dimethylbutyrate ester and acetonide 
hybenzate INN: hibenzate	2-(4-hydroxylbenzoyl)benzoate 
hyclate	monohydrochloride, hemiethanolate, and hemihydrate $HCl \cdot \frac{1}{2} C_2H_5OH \cdot \frac{1}{2} H_2O$
hydrochloride	hydrochloric acid HCl
hydroxide	OH^-
iodide	I^-
isethionate INN: isetionate	2-hydroxyethane-1-sulfonate 
isoproxil	isopropoxycarbonyloxymethyl 
lactate	2-hydroxypropanoate 

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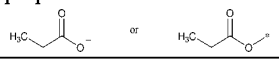
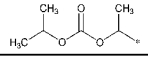
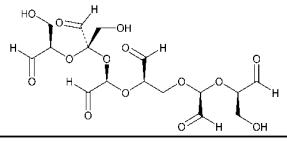
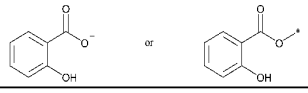
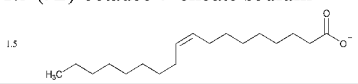
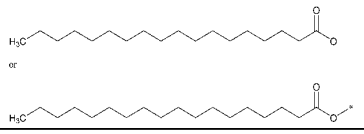
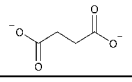
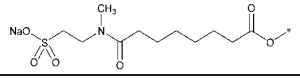
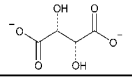
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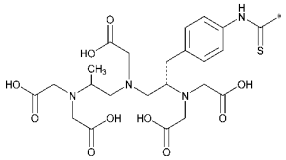
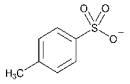
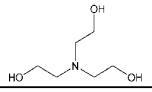
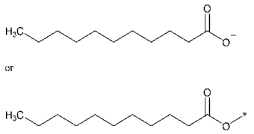
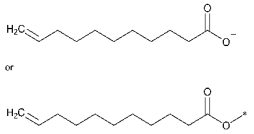
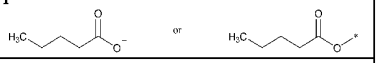
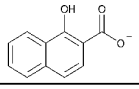
Name Used	Chemical Name and/or Formula
laurate	dodecanoate 
lispro	28^{B}-L-lysine-29^{B}-L-proline —Lys—Pro
medoxomil	(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 
meglumine	*N*-methylglucamine 
merpentan	4,5-bis(2-mercaptoacetamido)valeric acid and anions derived from this acid 
mertansine	tetrakis{(4*RS*)-4[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.110,14.03,5]-hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}1-methyl-2-oxoethyl]methylamino}-3-oxopropyl)disulfanyl]pentanoyl} 
mesylate INN: mesilate	methanesulfonate 
mofetil	2-(4-morpholin-4-yl)ethyl 
napsylate INN: napsilate	2-naphthalenesulfonate 
nicotinate	pyridine-3-carboxylate 
nitrate	nitric acid or nitrate salt HNO_3 or NO_3^-
olamine	ethanolamine or 2-aminoethanol 

Name Used	Chemical Name and/or Formula
oleate	(9*Z*)-octadec-9-enoate 
palmitate	hexadecanoate 
pamoate INN: embonate	4,4'-methylenebis[3-hydroxy-2-naphthoate] 
pegol	α-(2-carboxyethyl)-ω-methoxypoly(oxyethane-1,2-diyl) 
pendetide	N^6-[*N*-[2-[[2-[bis(carboxymethyl)-amino]ethyl] (carboxymethyl)amino]-ethyl]-*N*-(carboxymethyl)glycyl]-N^2-(*N*-glycyl-L-tyrosyl)-L-lysine 
perchlorate	perchloric acid or perchlorate salt $HClO_4$, ClO_4^-
peroxide	H_2O_2
phenpropio-nate	3-phenylpropionate 
phosphate	phosphoric acid and salts derived from phosphoric acid H_3PO_4, $H_2PO_4^-$, HPO_4^{2-} or PO_4^{3-}
pivalate	pivalate or trimethylacetate 
pivoxetil	1-[(2-methoxy-2-methylpropionyl)-oxy]ethyl 
potassium	K^+
probutate INN: buteprate	propionate ester and butyrate ester 

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Name Used	Chemical Name and/or Formula
propionate	propionate 
proxetil	(*RS*)-1-[(isopropoxycarbonyl)oxy]-ethyl 
raffimer	(2*R*,4*S*,6*R*,8*R*,11*S*,13*R*)-1,14-dihydroxy-4-(hydroxymethyl)-3,5,7,10,12-pentaoxatetradecane-2,4,6,8,11,13-hexacarbaldehyde, a cross-linking agent (i.e., hemoglobin raffimer) that polymerizes with reaction at the aldehyde groups, the polymerized form (without aldehydes) is also called by this name 
salicylate	2-hydroxybenzoate 
sesquioleate	1.5 (9*Z*)-octadec-9-enoate sodium 
stearate	octadecanoate 
succinate	succinate 
sulfate	sulfate SO_4^{2-}
suleptanate	sodium 7-methyl[(2-sulfoethyl)carbamoyl]heptanoyl 
tartrate	(2*R*,3*R*)-2,3-dihydroxysuccinate 
tebutate	*tert*-butylacetate 

Name Used	Chemical Name and/or Formula
tiuxetan	*N*-(4-{(2*S*)-2-[bis(carboxymethyl)amino]-3-[(2*RS*)-{2-[bis(carboxymethyl)amino]propyl}-(carboxymethyl)amino]propyl}phenyl) thiocarbamoyl 
tosylate INN: tosilate	*p*-toluenesulfonate or 4-methylbenzene-1-sulfonate 
triflutate	trifluoroacetate 
trolamine	triethanolamine or 2,2',2''-nitrilotriethanol 
undecylate	undecanoate 
undecylenate	undec-10-enoate 
valerate	pentanoate 
xinafoate	1-hydroxy-2-naphthoate 

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Appendix IX
USAN Submission Forms

The application forms on the next pages may be photocopied and submitted as part of a new negotiation. An editable version of the USAN application form is available as a MS-Word document at the USAN Program website, www.ama-assn.org/go/usan.

An official USAN application must be used for the purpose of applying for a USAN, and forwarded to the American Medical Association/United States Adopted Names (USAN) Council at the address below.

American Medical Association
Attn: USAN Program
515 North State Street
Chicago, IL 60610

Send a check payable to the American Medical Association/USAN for the appropriate amount and send to the following address:

American Medical Association
Attn: Remittance
515 North State Street
Chicago, IL 60610

Please make sure to reference that the payment is for a USAN application. Electronic credit card payments cannot be accepted at this time; however, electronic fund transfers are possible. Please call 312-464-4906 for details.

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Samsung Bioepis Exhibit No. 1002
Page 12466

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USAN

UNITED STATES ADOPTED NAMES COUNCIL
AMERICAN MEDICAL ASSOCIATION
515 N. STATE ST.
CHICAGO, IL 60610
312-464-4046

REQUEST FOR A UNITED STATES ADOPTED NAME (USAN)

(for USAN staff use only)

File No:	Acknowledged:
INN Status:	WHO No.:
Invoice No.:	

SUGGESTED NAME(S) IN ORDER OF PREFERENCE:
(Please attach verification of the absence of conflicts with existing chemical names, insecticides, other nonproprietary names or trademarks)

1.
2.
3.

CHEMICAL NAME(S) OR DESCRIPTION:
(Chemical Abstract Service Index Name must be supplied)

STRUCTURAL FORMULA:
(Provide stereochemistry)

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MOLECULAR FORMULA:

MOLECULAR WEIGHT:

CHEMICAL ABSTRACTS SERVICE (CAS) REGISTRY NUMBER:
(CAS Registry number must be supplied)

CODE DESIGNATIONS:

TRADEMARK(S):

TRIVIAL NAME(S):

MANUFACTURER(S):

PRINCIPAL THERAPEUTIC USE(S):*

PHARMACOLOGIC ACTION:*

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1. **The process of selecting a USAN should be initiated during that period of investigation when the compound is undergoing clinical studies.**

   Please indicate the date clinical trials began:

   IND Application Number(s):

2. **The undersigned confirms that the CAS registry number and Index name are correct. Permission is granted to USAN to utilize this information in USAN-generated publications.**

3. **Permission is granted for the USAN Council Secretariat to secure the International Union of Pure and Applied Chemistry (IUPAC) chemical name for the compound herewith submitted.**

4. **Permission is granted for the USAN Council Secretariat to submit the negotiated nonproprietary name to the World Health Organization (WHO) Nomenclature Committee for consideration. A fee of $6,000.00 assessed by the WHO is payable by check to the WHO; payment will be made when the name is forwarded to WHO for consideration. If the name is an International Nonproprietary Name (INN), permission is granted to forward it to WHO as a matter of information.**

5. **This submission is made with the understanding that insofar as is known, none of the suggested names are trademarked or the subject of pending registration. It is further understood that the adopted USAN will remain a free and unrestricted nonproprietary name that will not be trademarked.**

6. **This submission is made with the understanding that all names submitted to the USAN Council for this compound will be posted on the USAN Web site as "Names Under Consideration."**

7. **The appropriate fee-for-service is enclosed. Check one:**

☐	**Name for a single-entity drug (including compounds that have been assigned an International Nonproprietary Name)**	**$10,000.00**
☐	**USAN modified (name for a salt of a drug for which an adopted USAN already exists)**	**$5,000.00**
☐	**USAN revised (revision of support information used to define a USAN or USAN modified, resulting in a revised adoption and/or revised publication)**	**$2,500.00**
☐	**Other (explain):**	

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8. Make check payable to American Medical Association/USAN

Submitted by:

Applicant: (Name of firm, sponsor or legal representative)

Address:

Telephone:

Fax:

Name of Contact Person:

Title:

Email Address:

Signature:

Date:

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USAN
Contact Lens Application

UNITED STATES ADOPTED NAMES COUNCIL
AMERICAN MEDICAL ASSOCIATION
515 N. STATE ST.
CHICAGO, IL 60610
312-464-4046

REQUEST FOR A UNITED STATES ADOPTED NAME (USAN) FOR CONTACT LENS MATERIAL

(for USAN staff use only)

File No: Acknowledged:
Invoice No.:

SUGGESTED NAME(S) IN ORDER OF PREFERENCE:
(Please attach verification of the absence of conflicts with existing chemical names, insecticides, other nonproprietary names or trademarks)

1.
2.
3.

CHEMICAL NAME(S) OR DESCRIPTION:
(List all repeating monomers including crosslinking agents)
(Chemical Abstract Service Index Name must be supplied)

STRUCTURAL FORMULA:
(Provide stereochemistry)

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MOLECULAR FORMULA:
(List formula for each monomer)

CHEMICAL ABSTRACTS SERVICE (CAS) REGISTRY NUMBER:
(CAS Registry number must be supplied)

PURITY OF 2-hydroxyethyl methacrylate (if applicable):

WATER CONTENT at ambient temperature (23 ± 2°C):

[mean value ± standard deviation _____; number of measurements_____]

OXYGEN PERMEABILITY AT 35° C:

[mean value ± standard deviation _____; number of measurements_____]

TRADEMARK(S):

MANUFACTURER(S):

1. **The process of selecting a USAN should be initiated during that period of investigation when the compound is undergoing clinical studies.**

   Please indicate the date clinical trials began:

   IND Application Number(s):

2. **The undersigned confirms that the CAS registry number and Index name are correct. Permission is granted to USAN to utilize this information in USAN-generated publications.**

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3. Permission is granted for the USAN Council Secretariat to secure the International Union of Pure and Applied Chemistry (IUPAC) chemical name for the compound herewith submitted.

4. This submission is made with the understanding that insofar as is known, none of the suggested names are trademarked or the subject of pending registration. It is further understood that the adopted USAN will remain a free and unrestricted nonproprietary name that will not be trademarked.

5. The appropriate fee-for-service is enclosed. Check one:

☐	Name for a new contact lens material	$10,000.00
☐	USAN modified (name for a contact lens material for which an adopted USAN already exists)	$5,000.00
☐	USAN revised (revision of support information used to define a USAN or USAN modified, resulting in a revised adoption and/or revised publication)	$2,500.00
☐	Other (explain):	

6. This submission is made with the understanding that all names submitted to the USAN Council for this compound will be posted on the USAN Web site as "Names Under Consideration."

7. Make check payable to American Medical Association/USAN

Submitted by:

Applicant: (Name of firm, sponsor or legal representative)

Address:

Telephone:

Fax:

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Name of Contact Person:

Title:

Email Address:

Signature:

Date:

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HISTORICAL NOTE

The organization responsible for the periodic revision and publication of the United States Pharmacopeia came into existence in January 1820, and was incorporated in 1900 under the name, The United States Pharmacopeial Convention. In keeping with the growth of the medical and pharmaceutical professions and over a century and a half of medical progress, the Convention has continued to draw upon the organizations that are broadly representative of the teaching and practice of these and allied professions in providing a base of authority for the Pharmacopeia.

From the outset and over the years since 1820, those physicians and pharmacists who have devoted countless hours to creating and maintaining the Pharmacopeia have been deeply concerned with the names by which drugs are commonly known. Indeed, encouraging the use of standard names for drugs has been almost as important a function of the Pharmacopeia as that of providing high standards of quality for them.

The acquisition by the USP Convention of the National Formulary, on January 2, 1975, consolidated the responsibility for the names in the USP and NF, the legally recognized compendia of standards for drugs. The standards-setting process, however, is such that the USP Council of Experts ordinarily has not entered the picture until after the drug names, both those for nonproprietary use and those protected by trademarks, have been selected and put into use.

The foundations of the United States Adopted Names (USAN) Council were established in June 1961, when the American Medical Association and the United States Pharmacopeial Convention formed the AMA-USP Nomenclature Committee. The American Pharmaceutical Association became the third sponsor in 1964. At that time, the name of the committee was changed to the United States Adopted Names Council, and "United States Adopted Name" or "USAN" was designated as the term to describe any nonproprietary name formally adopted by the council. In 1967, the U.S. Food and Drug Administration began its participation in the USAN Council through appointment of a liaison representative to the council. The FDA later strengthened this relationship by publishing in the Federal Register regulations which state in part that "Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN. . . ."

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Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

FOR ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(D) OF THE SECURITIES AND EXCHANGE ACT OF 1934

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2008

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)

203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒
Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐
Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐
Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒
Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. Please see definition of "accelerated and large accelerated filer" in Rule 12b-2 of the Exchange Act. Check One:
Large Accelerated Filer: ☒ Accelerated Filer: ☐ Non-Accelerated Filer: ☐
The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2008, was approximately $2,795,465,875.
The number of shares of Common Stock outstanding as of February 17, 2009 was 81,695,309.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 13, 2009, are incorporated by reference into Part III of this report.

PART I

Unless the context requires otherwise, references in this report to "we," "our," "us," "Company" and "Alexion" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries. Amounts, except per share amounts, are denominated in thousands.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab), for its approved indications and any future indications, timing and effect of sales of Soliris in various markets worldwide, level of future Soliris sales and collections, costs, expenses and capital requirements, cash outflows, cash from operations, status of reimbursement, price approval and funding processes in various countries worldwide, progress in developing commercial infrastructure and interest about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies in other countries, prospects for regulatory approval in other countries, the need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, potential costs resulting from product liability or other third party claims, the sufficiency of our existing capital resources and projected cash needs, assessment of impact of recent accounting pronouncements, and the effect of shifting currency exchange rates. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors." Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. *BUSINESS.*

Overview

Alexion Pharmaceuticals, Inc., Alexion or the Company, is a biopharmaceutical company engaged in the discovery, development and delivery of biologic therapeutic products aimed at treating patients with severe and life-threatening disease states, including hematologic and neurologic diseases, transplant rejection, cancer and autoimmune disorders. Our marketed product Soliris® (eculizumab) is the first therapy approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria, or PNH.

Customers

In the United States, our customers are primarily specialty distributors and specialty pharmacies who supply physician office clinics, hospital outpatient clinics, infusion clinics or home health care providers. In some cases, we also sell Soliris to government agencies. Outside the United States, our customers are primarily hospitals, hospital buying groups, pharmacies, other health care providers and distributors.

During 2008, sales to our single largest customer, AmerisourceBergen, accounted for 21% of our Soliris net product sales, and no other customer individually accounted for more than 10% of total net product sales.

During 2007, sales to our three largest customers accounted for the following portions of our Soliris net product sales, and no other customer individually accounted for more than 10% of net sales:

Customer	December 31, 2007
Amerisource Bergen Corporation	40.4%
IDIS Limited	24.7%
McKesson Corporation	11.1%
	76.2%

We generally do not focus our promotional activities on distributors, and they do not set or determine demand for Soliris. Because of the pricing of Soliris, the limited number of patients, the short period from sale of product to patient infusion and the lack of contractual return rights, Soliris customers generally carry limited inventory.

Please also see Management's Discussion and Analysis – Revenues, and Note 17 on Page F-41, for financial information about geographic areas.

Patents and Proprietary Rights

Patents and other proprietary rights are important to our business. Our policy is to file patent applications to protect technology, inventions and improvements to our technologies that are considered important to the development of our business. We also rely upon our trade secrets, know-how, and continuing technological innovations, as well as patents that we have licensed or may license from other parties, to develop and maintain our competitive position.

We have filed several U.S. patent applications and international counterparts of certain of these applications. In addition, we have in-licensed several additional U.S. and international patents and patent applications. As of December 31, 2008, we own or in-license over 78 U.S. patents and 42 U.S. patent applications. These patents and patent applications relate to technologies or products in the C5 Inhibitor program, high throughput screening, vectors, cancer, recombinant antibodies, and other technologies. We own or in-license 61 foreign patents and 140 pending foreign patent applications. We owe royalties to a third party and other fees to owners of one or more patents in connection with the manufacture and sale of Soliris for PNH, and we may owe royalties and fees to other third parties with respect to any future commercial manufacture and sale of Soliris and our product candidates.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2009

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)

203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:	**Common Stock, par value $0.0001** **Rights to Purchase Junior Participating** **Cumulative Preferred Stock, par value $0.0001**
Name of each exchange on which registered:	**The Nasdaq Stock Market LLC**
Securities registered pursuant to Section 12(g) of the Act:	**None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☐ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)

Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2009, was approximately $3,615,450,070.

The number of shares of Common Stock outstanding as of February 16, 2010 was 89,137,398.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 12, 2010, are incorporated by reference into Part III of this report.

PART I

Unless the context requires otherwise, references in this report to "we," "our," "us," "Company" and "Alexion" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab) for its approved indications and any future indications, timing and effect of sales of Soliris in various markets worldwide, level of future Soliris sales and collections, costs, expenses and capital requirements, cash outflows, cash from operations, status of reimbursement, price approval and funding processes in various countries worldwide, progress in developing commercial infrastructure and interest about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies in other countries, prospects for regulatory approval in other countries, the need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, the timing for regulatory approval of our manufacturing facility in Rhode Island, potential costs resulting from product liability or other third party claims, the sufficiency of our existing capital resources and projected cash needs, assessment of impact of recent accounting pronouncements, and the effect of shifting currency exchange rates. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors." Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. *BUSINESS.*

Overview

Alexion Pharmaceuticals, Inc. was incorporated in Delaware in 1992. We are a biopharmaceutical company engaged in the discovery, development and commercialization of biologic therapeutic products aimed at treating patients with severe and life-threatening disease states, including hematologic, kidney and neurologic diseases, transplant rejection, cancer and autoimmune disorders. Our marketed product Soliris® (eculizumab) is the first and only therapy approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria, or PNH.

Samsung Bioepis Exhibit No. 1002
Page 12481

We estimate that we will pay employer contributions of approximately $645 in 2010. The expected future cash flows to be paid in respect of the pension plans as of December 31 were as follows:

Estimated future benefit payments	
2010	$ 233
2011	236
2012	228
2013	226
2014	251
2015 to 2019	1,179

16. Revenue and assets by geography

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	2009	2008	2007
United States	$ 159,829	$ 113,299	$ 51,856
Europe	215,763	143,645	20,185
Other	11,208	2,155	—
	$ 386,800	$ 259,099	$ 72,041

	December 31,		
Long-lived assets (1):	2009	2008	2007
United States	$ 158,621	$ 138,200	$ 103,735
Europe	5,637	1,478	545
Other	433	207	—
	$ 164,691	$ 139,885	$ 104,280

(1) Long-lived assets consist of property, plant and equipment.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

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For the fiscal year ended December 31, 2011

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2011, was $8,659,265,185.

The number of shares of Common Stock outstanding as of February 11, 2012 was 185,993,409.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 07, 2012, are incorporated by reference into Part III of this report.

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Samsung Bioepis Exhibit No. 1002
Page 12483

PART I

Unless the context requires otherwise, references in this report to "Alexion", the "Company", "we", "our" or "us" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs, and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab) for its approved indications and any expanded uses, timing and effect of sales of Soliris in various markets worldwide, level of coverage and reimbursement for Soliris, pricing, level of future Soliris sales and collections, plans for acquired companies and programs, timing regarding development and regulatory approvals for additional indications or in additional territories for Soliris, including for the treatment of aHUS and other product candidates, the medical and commercial potential of additional indications for Soliris and other product candidates, costs, expenses and capital requirements, cash outflows, cash from operations, status of reimbursement, price approval and funding processes in various countries worldwide, progress in developing commercial infrastructure and interest about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies, prospects for regulatory approval, need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, the outcome of challenges and opposition proceedings to our intellectual property, and assertion or potential assertion by third parties that the manufacture, use or sale of Soliris infringes their intellectual property, estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, potential costs resulting from product liability or other third party claims, the sufficiency of our existing capital resources and projected cash needs, assessment of impact of recent accounting pronouncements, declines in sovereign credit ratings or sovereign defaults in countries where we sell Soliris, delay of collection or reduction in reimbursement due to adverse economic conditions or changes in government and private insurer regulations and approaches to reimbursement, the short and long term effects of other government healthcare measures, and the effect of shifting foreign exchange rates. Words such as "anticipates", "expects", "intends", "plans", "believes", "seeks", "estimates", variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors". Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. *BUSINESS.*

Overview

Alexion is a biopharmaceutical company focused on serving patients with severe and ultra-rare disorders through the innovation, development and commercialization of life-transforming therapeutic products. Our marketed product Soliris® (eculizumab) is the first and only therapeutic approved for patients with two ultra-rare and severe disorders resulting from chronic uncontrolled activation of the complement component of the immune system: paroxysmal nocturnal hemoglobinuria (PNH), an ultra-rare and life-threatening blood disorder, and atypical hemolytic uremic syndrome (aHUS), an ultra-rare and life-threatening genetic disease. We are also evaluating other potential indications for Soliris in other diseases in which chronic uncontrolled complement activation is the underlying mechanism, and we are progressing with other biotechnology product candidates in ultra-rare and severe disorders which are now in various stages of development. We were incorporated in 1992 and began commercial sale of Soliris in 2007.

Soliris is designed to inhibit a specific aspect of the complement component of the immune system and thereby treat inflammation associated with chronic disorders in the therapeutic areas of hematology, nephrology, transplant rejection, neurology and ophthalmology. Soliris is a humanized monoclonal antibody that blocks terminal complement activity at the doses currently prescribed. The initial indication for which we received approval for Soliris is PNH. PNH is an ultra-rare, debilitating and life-threatening, deficiency blood disorder defined by chronic uncontrolled complement activation leading to

Samsung Bioepis Exhibit No. 1002
Page 12484

17. Segment Information

We operate as one business segment, which is the business of focusing on serving patients with severe and ultra-rare disorders though the innovation, development and commercialization of life-transforming therapeutic products and therefore, our chief operating decision-maker manages the operations of our Company as a single operating segment.

Revenues and tangible long-lived assets by significant geographic region are as follows:

	December 31,		
Revenues:	**2011**	**2010**	**2009**
United States	$ 263,387	$ 205,792	$ 159,829
Europe	340,812	275,608	215,763
Asia Pacific (primarily Japan)	115,377	22,188	—
Other	63,855	37,369	11,208
	$ 783,431	$ 540,957	$ 386,800

	December 31,	
Long-lived assets (1):	**2011**	**2010**
United States	$ 157,473	$ 154,227
Europe	6,288	6,557
Other	2,091	1,456
	$ 165,852	$ 162,240

(1) Long-lived assets consist of property, plant and equipment.

18. Subsequent Events

On February 7, 2012, we acquired Enobia Pharma Corp. (Enobia), a privately held clinical-stage biotechnology company based in Montreal, Canada and Cambridge, Massachusetts, in a transaction expected to be accounted for as a business combination. The acquisition was intended to broaden our objective to develop and deliver therapies for patients with ultra-rare, severe, and life-threatening disorders. Enobia's lead product candidate ENB-0040 (asfotase alfa), is a human recombinant targeted alkaline phosphatase enzyme-replacement therapy for patients suffering with hypophosphatasia (HPP), an ultra-rare, life-threatening, genetic metabolic disease for which there are no approved treatments. We made an upfront cash payment of $610,000, subject to purchase price adjustments, for 100% of Enobia's capital stock. Additional contingent payments would be earned upon reaching various regulatory and sales milestones. If all such regulatory and sales milestones were achieved, the total additional payments would be $470,000. We financed the acquisition through available cash and proceeds from our new credit facility as noted below. As of December 31, 2011, we incurred $2,039 of acquisition-related costs comprised primarily of professional fees.

In conjunction with our acquisition of Enobia, we entered into a five-year, $440,000 credit facility with a syndication of banks. The credit facility consists of a $240,000 term loan payable in equal quarterly installments of $12,000 starting June 30, 2012 and a $200,000 revolving line of credit. The credit facility bears interest at a per annum rate of LIBOR plus 1.25% to 2.00% depending on certain leverage ratios (as calculated in accordance with the agreement). We borrowed $80,000 on the revolving line of credit in connection with the Enobia acquisition.

Samsung Bioepis Exhibit No. 1002
Page 12485

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

FOR ANNUAL AND TRANSITION REPORTS PURSUANT TO SECTIONS 13 OR 15(D)
OF
THE SECURITIES AND EXCHANGE ACT OF 1934

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2007

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

352 Knotter Drive, Cheshire Connecticut 06410
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203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. Please see definition of "accelerated and large accelerated filer" in Rule 12b-2 of the Exchange Act. Check One:

Large Accelerated Filer: ☒ Accelerated Filer: ☐ Non-Accelerated Filer: ☐

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2007, was approximately $1,658,668,873.68.

The number of shares of Common Stock outstanding as of February 25, 2008 was 38,106,662.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 9, 2008, are incorporated by reference into Part III of this report.

PART I

Unless the context requires otherwise, references in this report to "we," "our," "us," "Company" and "Alexion" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab), timing and effect of sales of Soliris in various European markets, status of reimbursement, price approval and funding processes in Europe, progress in developing commercial infrastructure and interest and sense of urgency about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies in other countries, prospects for regulatory approval in other countries, the need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, potential costs resulting from product liability or other third party claims, including pending litigation, the sufficiency of our existing capital resources and projected cash needs, results of pending litigation, assessment of impact of recent accounting pronouncements as well as assumptions relating to the foregoing. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors." Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. *BUSINESS.*

Overview

We are a biopharmaceutical company engaged in the discovery, development and delivery of biologic therapeutic products aimed at treating patients with severe and life-threatening disease states, including hematologic and neurologic diseases, cancer and autoimmune disorders. We have one marketed product, Soliris® (eculizumab), which is the first therapy approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria, or PNH.

Since our incorporation in January 1992 until April 2007, we have devoted most of our resources to drug discovery, research, and product and clinical development. In March 2007, the Food and Drug Administration, or

Samsung Bioepis Exhibit No. 1002
Page 12487

Alexion Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements—(Continued)
For the Years Ended December 31, 2007 and 2006, Five Month Period Ended December 31, 2005, and Year Ended July 31, 2005
(amounts in thousands, except share and per share amounts)

In the event that we are acquired in a merger, other business combination transaction, or 50 percent or more of our assets, cash flow, or earning power are sold, proper provision shall be made so that each holder of a right shall have the right to receive, upon exercise thereof at the then current exercise price, that number of shares of Common Stock of the surviving company which at the time of such transaction would have a market value of two times the exercise price of the right.

13. 401(k) Plan

We have a qualified 401(k) plan covering all eligible employees. Under the plan, employees may contribute up to the statutory allowable amount for any calendar year. We make matching contributions at a rate of $1.00 for each dollar contributed up to the first 3 percent and $0.50 for each dollar contributed of the next 2 percent of compensation. For the years ended December 31, 2007 and 2006, five month period ended December 31, 2005 and the year ended July 31, 2005, we made matching contributions of approximately $1,535, $406, $202 and $390, respectively.

14. Segment Information

In accordance with SFAS 131, "Disclosures about Segments of an Enterprise and Related Information," we present segment information in a manner consistent with the method we use to report this information to our management. We have determined we operate in a single segment.

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		Five Month Period Ended December 31,	Year Ended July 31,
Revenues:	2007	2006	2005	2005
United States	$ 51,856	$ 1,558	$ 664	$ 1,064
Europe	20,185	—	—	—
	$ 72,041	$ 1,558	$ 664	$ 1,064

	December 31, 2007	
Long-lived assets:	2007	2006
United States	$ 126,457	$ 62,534
Europe	545	—
	$ 127,002	$ 62,534

Table of Contents

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
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FORM 10-K

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or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
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Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)

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(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2010, was approximately $4,611,459,750.

The number of shares of Common Stock outstanding as of February 11, 2011 was 91,308,703.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 10, 2011, are incorporated by reference into Part III of this report.

PART I

Unless the context requires otherwise, references in this report to "we," "our," "us," "Company" and "Alexion" refer to Alexion Pharmaceuticals, Inc. and its subsidiaries.

Note Regarding Forward-Looking Statements

This annual report on Form 10-K contains forward-looking statements that have been made pursuant to the provisions of the Private Securities Litigation Reform Act of 1995. Such forward-looking statements are based on current expectations, estimates and projections about our industry, management's beliefs, and certain assumptions made by our management, and may include, but are not limited to, statements regarding the potential benefits and commercial potential of Soliris® (eculizumab) for its approved indication and any expanded uses, timing and effect of sales of Soliris in various markets worldwide, level of coverage and reimbursement for Soliris, pricing, level of future Soliris sales and collections, plans for acquired companies and programs, timing regarding development and regulatory approvals for additional product candidates and the medical and commercial potential of those product candidates, costs, expenses and capital requirements, cash outflows, cash from operations, status of reimbursement, price approval and funding processes in various countries worldwide, progress in developing commercial infrastructure and interest about Soliris in the patient, physician and payor communities, the safety and efficacy of Soliris and our product candidates, estimates of the potential markets and estimated commercialization dates for Soliris around the world, sales and marketing plans, any changes in the current or anticipated market demand or medical need for Soliris, status of our ongoing clinical trials, commencement dates for new clinical trials, clinical trial results, evaluation of our clinical trial results by regulatory agencies, prospects for regulatory approval, need for additional research and testing, the uncertainties involved in the drug development process and manufacturing, our future research and development activities, assessment of competitors and potential competitors, the outcome of challenges and opposition proceedings to our intellectual property, and assertion or potential assertion by third parties that the manufacture, use or sale of Soliris infringes their intellectual property estimates of the capacity of manufacturing and other facilities to support Soliris and our product candidates, potential costs resulting from product liability or other third party claims, the sufficiency of our existing capital resources and projected cash needs, assessment of impact of recent accounting pronouncements, declines in sovereign credit ratings or sovereign defaults in countries where we commercialize our products, delay of collection or reduction in reimbursement due to adverse economic conditions, the short and long term effects of government healthcare measures, and the effect of shifting foreign exchange rates. Words such as "anticipates," "expects," "intends," "plans," "believes," "seeks," "estimates," variations of such words and similar expressions are intended to identify such forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are not guarantees of future performance and are subject to certain risks, uncertainties, and assumptions that are difficult to predict; therefore, actual results may differ materially from those expressed or forecasted in any such forward-looking statements. Such risks and uncertainties include, but are not limited to, those discussed later in this report under the section entitled "Risk Factors". Unless required by law, we undertake no obligation to update publicly any forward-looking statements, whether because of new information, future events or otherwise. However, readers should carefully review the risk factors set forth in other reports or documents we file from time to time with the Securities and Exchange Commission.

Item 1. *BUSINESS.*

Overview

Alexion Pharmaceuticals, Inc. is a biopharmaceutical company engaged in the discovery, development and commercialization of innovative therapeutic products aimed at treating patients with severe and life-threatening disease states, including those in the therapeutic areas of hematology, nephrology including transplant rejection, neurology, ophthalmology and cancer. Our marketed product Soliris® (eculizumab) is the first and only therapy approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), an ultra-rare and life-threatening blood disorder. We were incorporated in 1992 and began commercial sale of Soliris in 2007.

Samsung Bioepis Exhibit No. 1002
Page 12490

Alexion Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements
For the Years Ended December 31, 2010, 2009 and 2008
(amounts in thousands, except per share amounts)

16. Revenue and assets by geography

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	**2010**	**2009**	**2008**
United States	$205,792	$159,829	$113,299
Europe	274,919	215,763	143,645
Other	60,246	11,208	2,155
	$540,957	$386,800	$259,099

	December 31,	
Long-lived assets (1):	**2010**	**2009**
United States	$154,227	$158,621
Europe	6,557	5,637
Other	1,456	433
	$162,240	$164,691

(1) Long-lived assets consist of property, plant and equipment.

17. Subsequent Events

On January 28, 2011, Alexion acquired Taligen Therapeutics, Inc. (Taligen), a privately held development-stage biotechnology company based in Cambridge, Massachusetts, in a transaction accounted for as a business combination. The acquisition was intended to broaden Alexion's portfolio of pre-clinical compounds and to expand Alexion's capabilities in translational medicine. Taligen's pre-clinical compounds include product candidates for the potential treatment of patients with ophthalmic diseases such as age-related macular degeneration (AMD), as well as other novel antibody and protein regulators of the complement inflammatory pathways. Alexion made an upfront cash payment of $111,000 for 100 percent of Taligen's equity interests. Additional contingent payments would be earned upon reaching various clinical efficacy and product approval milestones in both the U.S. and European Union for up to six product candidates. If all such clinical efficacy and product approval milestones were achieved in both the U.S. and European Union for six product candidates, the total payments would be $367,000.

On February 10, 2011, Alexion acquired patents and assets from Germany-based Orphatec Pharmaceuticals GmbH (Orphatec) related to an investigational therapy for patients with Type A molybdenum cofactor deficiency (MoCD), an ultra-rare disorder characterized by severe brain damage and rapid death in newborn infants. The acquisition will be accounted for as a business combination. Orphatec is a privately held development-stage biotechnology company with headquarters in Cologne, Germany. Alexion made an upfront cash payment of approximately $3,000. Additional contingent payments of up to $42,000 would be earned upon reaching various development, regulatory and commercial milestones. Alexion also established a research collaboration with key MoCD researchers from Orphatec to accelerate development of the investigational therapy.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2016

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

100 College Street, New Haven, Connecticut 06510
(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**

Name of each exchange on which registered: **The NASDAQ Stock Market LLC**
Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The NASDAQ Stock Market LLC on June 30, 2016, was $25,314,108,813.(1)

The number of shares of Common Stock outstanding as of February 13, 2017 was 224,613,750.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 10, 2017, are incorporated by reference into Part III of this report.

(1) Excludes 7,417,897 shares of common stock held by directors and executive officers at June 30, 2016. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

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Alexion Pharmaceuticals, Inc.

Table of Contents

PART I		Page
Item 1.	Business	3
Item 1A.	Risk Factors	25
Item 1B.	Unresolved Staff Comments	43
Item 2.	Properties	43
Item 3.	Legal Proceedings	44
Item 4.	Mine Safety Disclosures	44
PART II		
Item 5.	Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	45
Item 6.	Selected Financial Data	48
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	49
Item 7.A	Quantitative and Qualitative Disclosures About Market Risk	73
Item 8.	Financial Statements and Supplementary Data	74
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	74
Item 9A.	Controls and Procedures	74
Item 9A(T).	Controls and Procedures	75
Item 9B.	Other Information	76
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	77
Item 11.	Executive Compensation	77
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	77
Item 13.	Certain Relationships and Related Transactions, and Director Independence	77
Item 14.	Principle Accounting Fees and Services	77
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	78
Item 16.	Form 10-K Summary	80
SIGNATURES		81

Samsung Bioepis Exhibit No. 1002
Page 12493

Comparison of the Year Ended December 31, 2016 to the Year Ended December 31, 2015

Net Product Sales

Net product sales by significant geographic region are as follows:

	Year Ended December 31,		
	2016	2015	% Change
Net product sales:			
United States	$ 1,257	$ 951	32%
Europe	961	841	14%
Asia Pacific	318	276	15%
Rest of World	546	535	2%
	$ 3,082	$ 2,603	18%

Net product sales by product are as follows:

	Year Ended December 31,		
	2016	2015	% Change
Net product sales:			
Soliris	2,843	2,591	10%
Strensiq	210	12	-
Kanuma	29	—	-
	$ 3,082	$ 2,603	18%

The components of the increase in net product sales for the year ended December 31, 2016 are as follows:

	Year Ended December 31,
	2016
Components of change:	
Price	(1)%
Volume	22 %
Foreign exchange	(3)%
Total change in net product sales	**18 %**

The increase in net product sales for fiscal year 2016 as compared to the same period in 2015 was primarily due to an increase in unit volumes of 22% due to increased demand globally for Soliris therapy for patients with PNH or aHUS and sales of Strensiq and Kanuma during 2016.

The positive impact of volume on net product sales was partially offset by the negative impact on foreign exchange of 3%, for the year ended December 31, 2016, as compared to the same period in 2015. The negative impact on foreign exchange of $(74), or 3%, was due to changes in foreign currency exchange rates (inclusive of hedging activity) versus the U.S. dollar for the year ended December 31, 2015. The negative impact was primarily due to the weakening of the Euro, Japanese Yen, Russian Ruble, and the British Pound. We recorded a gain in revenue of $73 and $118 related to our foreign currency cash flow hedging program, for the years ended December 31, 2016 and 2015, respectively. We expect the strong dollar compared to other currencies to continue to have a negative impact on revenue into 2017.

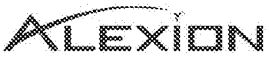
Samsung Bioepis Exhibit No. 1002
Page 12494

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934
For the fiscal year ended December 31, 2017
or

☐ Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934
For the transition period from to
Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

100 College Street, New Haven, Connecticut 06510
(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐ Emerging growth company ☐
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2017, was $26,128,956,666.(1)

The number of shares of Common Stock outstanding as of February 5, 2018 was 221,681,437.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 8, 2018, are incorporated by reference into Part III of this report.

(1) Excludes 8,789,185 shares of common stock held by directors and executive officers at June 30, 2017. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Alexion Pharmaceuticals, Inc.

Table of Contents

		Page
PART I		
Item 1.	Business	4
Item 1A.	Risk Factors	27
Item 1B.	Unresolved Staff Comments	47
Item 2.	Properties	48
Item 3.	Legal Proceedings	49
Item 4.	Mine Safety Disclosures	50
PART II		
Item 5.	Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	51
Item 6.	Selected Financial Data	54
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	56
Item 7.A	Quantitative and Qualitative Disclosures About Market Risk	81
Item 8.	Financial Statements and Supplementary Data	82
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	82
Item 9A.	Controls and Procedures	82
Item 9A(T).	Controls and Procedures	83
Item 9B.	Other Information	83
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	84
Item 11.	Executive Compensation	84
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	84
Item 13.	Certain Relationships and Related Transactions, and Director Independence	84
Item 14.	Principle Accounting Fees and Services	84
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	85
Item 16.	Form 10-K Summary	88
SIGNATURES		89

Samsung Bioepis Exhibit No. 1002
Page 12496

Net Product Sales

Net product sales by product and significant geographic region are as follows:

	Year Ended December 31,			% Change:	
	2017	2016	2015	2017 compared to 2016	2016 compared to 2015
Soliris					
United States	$ 1,235.0	$ 1,058.5	$ 943.6	16.7%	12.2%
Europe	985.2	939.7	838.3	4.8%	12.1%
Asia Pacific	328.1	303.8	274.0	8.0%	10.9%
Rest of World	595.8	541.2	534.3	10.1%	1.3%
	$ 3,144.1	2,843.2	2,590.2	10.6%	9.8%
Strensiq					
United States	$ 280.1	$ 177.5	$ 7.7	57.8%	**
Europe	35.6	15.3	1.7	132.7%	**
Asia Pacific	18.6	13.0	2.4	43.1%	**
Rest of World	5.5	3.6	0.1	52.8%	**
	339.8	209.4	11.9	62.3%	**
Kanuma					
United States	$ 42.4	$ 20.4	$ —	107.8%	N/A
Europe	14.6	6.3	0.4	131.7%	**
Asia Pacific	2.7	1.3	—	107.7%	N/A
Rest of World	5.6	1.1	—	**	N/A
	$ 65.3	29.1	0.4	125.4%	**
Total Net Product Sales	3,549.2	3,081.7	2,602.5	15.2%	18.4%

** Percentages not meaningful

Long-Lived Assets

Long-lived assets consist of property, plant and equipment.

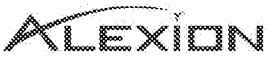
	December 31,	
	2017	2016
United States	$ 466.9	$ 489.7
Europe	854.6	538.4
Other	4.9	7.5
	$ 1,326.4	$ 1,035.6

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934
For the fiscal year ended December 31, 2018
or

☐ Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934
For the transition period from to
Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210

(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company ☐ Emerging growth company ☐
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 29, 2018, was $26,514,235,288.(1)

The number of shares of Common Stock outstanding as of January 31, 2019 was 223,469,381.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its 2019 Annual Meeting of Stockholders currently anticipated to be held on May 14, 2019, are incorporated by reference into Part III of this report.

(1) Excludes 9,186,789 shares of common stock held by directors, executive officers and their respective affiliates at June 29, 2018. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Alexion Pharmaceuticals, Inc.

Table of Contents

		Page
PART I		
Item 1.	Business	5
Item 1A.	Risk Factors	29
Item 1B.	Unresolved Staff Comments	56
Item 2.	Properties	56
Item 3.	Legal Proceedings	56
Item 4.	Mine Safety Disclosures	56
PART II		
Item 5.	Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	57
Item 6.	Selected Financial Data	59
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	61
Item 7.A	Quantitative and Qualitative Disclosures About Market Risk	85
Item 8.	Financial Statements and Supplementary Data	86
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	86
Item 9A.	Controls and Procedures	86
Item 9A(T).	Controls and Procedures	87
Item 9B.	Other Information	87
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	88
Item 11.	Executive Compensation	89
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	88
Item 13.	Certain Relationships and Related Transactions, and Director Independence	88
Item 14.	Principle Accounting Fees and Services	89
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	89
Item 16.	Form 10-K Summary	91
SIGNATURES		92

Samsung Bioepis Exhibit No. 1002
Page 12499

19. Segment Information

We operate in a single segment, focusing on serving patients affected by rare diseases through the innovation, development and commercialization of life-changing therapies. Consistent with our operational structure, our chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, results of our operations are reported on a consolidated basis for purposes of segment reporting, consistent with our management reporting. Disclosures about net product sales and long-lived assets by geographic area are presented below.

Net Product Sales

Net product sales by product and geographic region are as follows:

	Year Ended December 31,			% Change	
	2018	2017	2016	2018 compared to 2017	2017 compared to 2016
SOLIRIS					
United States	$ 1,588.4	$ 1,235.0	$ 1,058.5	28.6 %	16.7%
Europe	1,036.7	985.2	939.7	5.2 %	4.8%
Asia Pacific	382.0	328.1	303.8	16.4 %	8.0%
Rest of World	355.9	595.8	541.2	(6.7)%	10.1%
	$ 3,363.0	$ 3,144.1	$ 2,843.2	13.3 %	10.6%
STRENSIQ					
United States	$ 374.3	$ 280.1	$ 177.5	33.6 %	57.8%
Europe	61.7	35.6	15.3	73.3 %	132.7%
Asia Pacific	27.9	18.6	13.0	50.0 %	43.1%
Rest of World	11.2	5.5	3.6	103.6 %	52.8%
	$ 475.1	$ 339.8	$ 209.4	39.8 %	62.3%
KANUMA					
United States	$ 81.3	$ 42.4	$ 20.4	21.0 %	107.8%
Europe	21.6	14.6	6.3	47.9 %	131.7%
Asia Pacific	3.7	2.7	1.3	37.0 %	107.7%
Rest of World	15.4	5.9	1.1	**	**
	$ 92.0	$ 65.6	$ 29.1	40.2 %	125.4%
Total Net Product Sales	4,130.1	$ 3,549.5	$ 3,081.7	16.4 %	15.2%

** Percentages not meaningful

Long-Lived Assets

Long-lived assets consist of property, plant and equipment.

	December 31,	
	2018	2017
United States	$ 468.3	$ 455.9
Europe	1,001.1	864.6
Other	2.1	4.9
	$ 1,471.5	$ 1,325.4

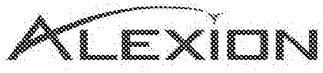
Samsung Bioepis Exhibit No. 1002
Page 12500

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q

☒ Quarterly report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934
For the quarterly period ended March 31, 2019
or

☐ Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934
For the transition period from to
Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210
(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)
N/A
(Former name, former address, and former fiscal year, if changed since last report)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company ☐ Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Common Stock, $0.0001 par value	224,237,214
Class	Outstanding as of April 23, 2019

ALXN2071
IPR2019-00740

Samsung Bioepis Exhibit No. 1002
Page 12501

Alexion Pharmaceuticals, Inc.

Table of Contents

			Page
PART I.		FINANCIAL INFORMATION	
	Item 1.	Condensed Consolidated Financial Statements (Unaudited)	
		Condensed Consolidated Balance Sheets as of March 31, 2019 and December 31, 2018	2
		Condensed Consolidated Statements of Operations for the three months ended March 31, 2019 and 2018	3
		Condensed Consolidated Statements of Comprehensive Income for the three months ended March 31, 2019 and 2018	4
		Condensed Consolidated Statements of Changes in Stockholders' Equity for the three months ended March 31, 2019 and 2018	5
		Condensed Consolidated Statements of Cash Flows for the three months ended March 31, 2019 and 2018	6
		Notes to Condensed Consolidated Financial Statements	7
	Item 2.	Management's Discussion and Analysis of Financial Condition and Results of Operations	32
	Item 3.	Quantitative and Qualitative Disclosures about Market Risk	53
	Item 4.	Controls and Procedures	55
PART II.		OTHER INFORMATION	57
	Item 1.	Legal Proceedings	58
	Item 1A.	Risk Factors	59
	Item 2.	Unregistered Sales of Equity Securities and Use of Proceeds	85
	Item 5.	Other Information	85
	Item 6.	Exhibits	86
SIGNATURES			

14. Revenue Recognition

Disaggregation of Revenue

The Company disaggregates revenue from contracts with customers into product and geographical regions as summarized below.

	Three months ended March 31,	
	2018	2017
SOLIRIS		
United States	$ 463.7	$ 336.0
Europe	264.5	250.8
Asia Pacific	100.9	85.5
Rest of World	132.9	127.8
Total	$ 962.0	$ 800.1
ULTOMIRIS		
United States	$ 24.6	$ —
Europe	—	—
Asia Pacific	—	—
Rest of World	—	—
Total	$ 24.6	$ —
STRENSIQ		
United States	$ 99.5	$ 89.2
Europe	17.5	14.0
Asia Pacific	9.9	5.7
Rest of World	3.2	1.8
Total	$ 130.1	$ 110.7
KANUMA		
United States	$ 13.8	$ 11.9
Europe	6.3	5.9
Asia Pacific	0.8	1.0
Rest of World	2.6	0.8
Total	$ 23.5	$ 19.6
Total Net Product Sales	$ 1,140.2	$ 930.4

Contract Balances and Receivables

Contract liabilities relate to consideration received and/or billed for goods that have not been delivered to the customer and for which the performance obligation has not yet been completed. These amounts are included within other current liabilities in the condensed consolidated balance sheets.

The following table provides information about receivables and contract liabilities from our contracts with customers.

	March 31, 2018	December 31, 2017
Receivables, which are included in "Trade accounts receivable, net"	$ 1,016.3	$ 922.3
Contract liabilities, which are included in "Other current liabilities"	$ 3.0	$ 3.4

Samsung Bioepis Exhibit No. 1002
Page 12503

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q

☒ Quarterly report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934

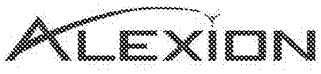
For the quarterly period ended June 30, 2019

or

☐ Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934

For the transition period from to

Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210
(Address of Principal Executive Offices) (Zip Code)

475-230-2596
(Registrant's telephone number, including area code)

N/A
(Former name, former address, and former fiscal year, if changed since last report)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock $0.0001 par value	ALXN	NASDAQ Stock Market LLC

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐

Smaller reporting company ☐ Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Common Stock $0.0001 par value	224,226,878
Class	Outstanding as of July 22, 2019

ALXN2072
IPR2019-00740

Alexion Pharmaceuticals, Inc.

Table of Contents

			Page
PART I.		FINANCIAL INFORMATION	
	Item 1.	Condensed Consolidated Financial Statements (Unaudited)	
		Condensed Consolidated Balance Sheets as of June 30, 2019 and December 31, 2018	2
		Condensed Consolidated Statements of Operations for the three and six months ended June 30, 2019 and 2018	3
		Condensed Consolidated Statements of Comprehensive Income for the three and six months ended June 30, 2019 and 2018	4
		Condensed Consolidated Statements of Changes in Stockholders' Equity for the three and six months ended June 30, 2019 and 2018	5
		Condensed Consolidated Statements of Cash Flows for the six months ended June 30, 2019 and 2018	7
		Notes to Condensed Consolidated Financial Statements	9
	Item 2.	Management's Discussion and Analysis of Financial Condition and Results of Operations	34
	Item 3.	Quantitative and Qualitative Disclosures about Market Risk	54
	Item 4.	Controls and Procedures	56
PART II.		OTHER INFORMATION	57
	Item 1.	Legal Proceedings	57
	Item 1A.	Risk Factors	58
	Item 2.	Unregistered Sales of Equity Securities and Use of Proceeds	86
	Item 5.	Other Information	86
	Item 6.	Exhibits	86
SIGNATURES			

14. Revenue Recognition

Disaggregation of Revenue

The Company disaggregates revenue from contracts with customers into product and geographical regions as summarized below.

	Three months ended June 30,		Six months ended June 30,	
	2019	2018	2019	2018
SOLIRIS				
United States	$ 496.3	$ 395.8	$ 960.0	$ 731.8
Europe	280.2	253.4	544.7	504.2
Asia Pacific	110.3	93.6	211.2	179.1
Rest of World	94.0	155.4	226.9	283.2
Total	$ 980.8	$ 898.2	$ 1,942.8	$ 1,698.3
ULTOMIRIS				
United States	$ 54.2	$ —	$ 78.8	$ —
Europe	—	—	—	—
Asia Pacific	—	—	—	—
Rest of World	—	—	—	—
Total	$ 54.2	$ —	$ 78.8	$ —
STRENSIQ				
United States	$ 108.2	$ 99.9	$ 205.7	$ 189.1
Europe	19.5	16.4	37.0	30.4
Asia Pacific	12.1	6.3	22.8	12.0
Rest of World	3.5	2.5	6.7	4.3
Total	$ 143.3	$ 125.1	$ 272.4	$ 235.8
KANUMA				
United States	$ 15.3	$ 13.0	$ 29.1	$ 24.9
Europe	6.8	5.8	13.1	11.7
Asia Pacific	1.3	1.1	2.1	2.1
Rest of World	2.8	1.5	5.4	2.3
Total	$ 26.2	$ 21.4	$ 49.7	$ 41.0
Total Net Product Sales	$ 1,202.5	$ 1,044.7	$ 2,342.7	$ 1,975.1

Contract Balances and Receivables

Contract liabilities relate to consideration received and/or billed for goods that have not been delivered to the customer and for which the performance obligation has not yet been completed. These amounts are included within other current liabilities in the condensed consolidated balance sheets.

The following table provides information about receivables and contract liabilities from our contracts with customers.

	June 30, 2019	December 31, 2018
Receivables, which are included in "Trade accounts receivable, net"	$ 1,123.6	$ 922.3
Contract liabilities, which are included in "Other current liabilities"	$ 3.1	$ 3.4

Samsung Bioepis Exhibit No. 1002
Page 12506

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-Q

Quarterly report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934

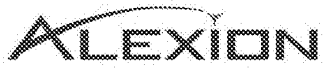
For the quarterly period ended September 30, 2019

or

Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934

For the transition period from to

Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210
(Address of Principal Executive Offices) (Zip Code)

475-230-2596
(Registrant's telephone number, including area code)

N/A
(Former name, former address, and former fiscal year, if changed since last report)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock $0.0001 par value	ALXN	NASDAQ Stock Market LLC

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No ☒

Common Stock $0.0001 par value	221,290,691
Class	Outstanding as of October 21, 2019

ALXN2073
IPR2019-00740

Alexion Pharmaceuticals, Inc.

Table of Contents

			Page
PART I.		FINANCIAL INFORMATION	
	Item 1.	Condensed Consolidated Financial Statements (Unaudited)	
		Condensed Consolidated Balance Sheets as of September 30, 2019 and December 31, 2018	2
		Condensed Consolidated Statements of Operations for the three and nine months ended September 30, 2019 and 2018	3
		Condensed Consolidated Statements of Comprehensive Income for the three and nine months ended September 30, 2019 and 2018	4
		Condensed Consolidated Statements of Changes in Stockholders' Equity for the three and nine months ended September 30, 2019 and 2018	5
		Condensed Consolidated Statements of Cash Flows for the nine months ended September 30, 2019 and 2018	7
		Notes to Condensed Consolidated Financial Statements	9
	Item 2.	Management's Discussion and Analysis of Financial Condition and Results of Operations	35
	Item 3.	Quantitative and Qualitative Disclosures about Market Risk	58
	Item 4.	Controls and Procedures	60
PART II.		OTHER INFORMATION	61
	Item 1.	Legal Proceedings	61
	Item 1A.	Risk Factors	62
	Item 2.	Unregistered Sales of Equity Securities and Use of Proceeds	90
	Item 5.	Other Information	90
	Item 6.	Exhibits	90
SIGNATURES			

Our derivative assets and liabilities include foreign exchange and interest rate derivatives that are measured at fair value using observable market inputs such as forward rates, interest rates, our own credit risk as well as an evaluation of our counterparties' credit risks. Based on these inputs, the derivative assets and liabilities are classified within Level 2 of the valuation hierarchy.

Contingent consideration liabilities related to business acquisitions and derivative liabilities associated with other contingent payments are classified as Level 3 within the valuation hierarchy and are valued based on various estimates, including probability of success, discount rates and amount of time until the conditions of the milestone payments are met.

As of September 30, 2019, there has not been any impact to the fair value of our derivative liabilities due to our own credit risk. Similarly, there has not been any significant adverse impact to our derivative assets based on our evaluation of our counterparties' credit risks.

Acquisition-Related Contingent Consideration

In connection with prior business combinations, we may be required to pay future consideration that is contingent upon the achievement of specified development, regulatory approvals or sales-based milestone events. We determine the fair value of these obligations using various estimates that are not observable in the market and represent a Level 3 measurement within the fair value hierarchy. The resulting probability-weighted cash flows were discounted using a cost of debt of 5.1% for developmental and regulatory milestones and a weighted average cost of capital of 10.0% for sales-based milestones.

Each reporting period, we adjust the contingent consideration to fair value with changes in fair value recognized in operating earnings. Changes in fair values reflect new information about the probability and timing of meeting the conditions of the milestone payments. In the absence of new information, changes in fair value will only reflect the interest component of contingent consideration related to the passage of time.

As of September 30, 2019, estimated future contingent milestone payments related to prior business combinations range from zero if no milestone events are achieved, to a maximum of $602.0 if all development, regulatory and sales-based milestones are reached. In the second quarter 2019, a sales-based milestone associated with our acquisition of Enobia Pharma Corp. was achieved. In connection with such achievement, we made a $100.0 milestone payment in the third quarter 2019.

As of September 30, 2019, the fair value of acquisition-related contingent consideration was $188.0. The following table represents a roll-forward of our acquisition-related contingent consideration:

	Nine months ended September 30, 2019
Balance at beginning of period	$ 280.8
Milestone payments	(100.0)
Changes in fair value	7.2
Balance at end of period	$ 188.0

Other Contingent Payments

In January 2019, we entered into an agreement with Caelum, a biotechnology company that is developing CAEL101 for light chain (AL) amyloidosis. Under the terms of the agreement, we acquired a minority equity interest in preferred stock of Caelum and an exclusive option to acquire the remaining equity in Caelum based on Phase II data, for pre-negotiated economics. We paid $30.0 during the first quarter 2019 and could be required to pay up to an additional $30.0 in contingent milestone-dependent fees. These contingent payments meet the definition of a derivative liability and were initially recorded at fair value of $27.1, based on the probability-weighted cash flows, discounted using a cost of debt ranging from 3.3% to 3.5%.

Each reporting period, we adjust the derivative liability associated with the contingent fees to fair value with changes in fair value recognized in other income and expense. Changes in fair values reflect new information about the probability and timing of meeting the conditions of the milestone payments. In the absence of new information, changes in fair value will only reflect the interest component of the liability related to the passage of time. As of September 30, 2019, the fair value of our contingent fees was $27.6. We recorded $(0.2) and $(0.5) in other income and (expense) during

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2012

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 30, 2012, was $18,920,399,568.(1)

The number of shares of Common Stock outstanding as of February 11, 2013 was 195,209,249.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 06, 2013, are incorporated by reference into Part III of this report.

ALXN2064
IPR2019-00740
Samsung Bioepis Exhibit No. 1002
Page 12510

(1) Excludes 2,231,014 shares of common stock held by directors and executive officers at June 30, 2012. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Samsung Bioepis Exhibit No. 1002
Page 12511

The amount in accumulated other comprehensive income as of December 31, 2012 that is expected to be recognized as a component of the net periodic pension costs in 2013 is $424.

We estimate that we will pay employer contributions of approximately $4,285 in 2013. The expected future cash flows to be paid in respect of the pension plans as of December 31, 2012 were as follows:

Year	
2013	$ 1,378
2014	1,271
2015	1,340
2016	1,279
2017	1,513
2018 to 2022	6,510

15. Segment Information

We operate as one business segment, which is the business of serving patients with severe and ultra-rare disorders though the innovation, development and commercialization of life-transforming therapeutic products and therefore, our chief operating decision-maker manages our operations as a single operating segment.

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	**2012**	**2011**	**2010**
United States	$ 400,483	$ 263,387	$ 205,792
Europe	418,321	340,812	275,608
Asia Pacific (primarily Japan)	161,480	115,377	22,188
Other	153,830	63,855	37,369
	$ 1,134,114	$ 783,431	$ 540,957

	December 31,	
Long-lived assets (1):	**2012**	**2011**
United States	$ 157,019	$ 157,473
Europe	5,988	6,288
Other	2,622	2,091
	$ 165,629	$ 165,852

(1) Long-lived assets consist of property, plant and equipment.

16. Subsequent Events

In January 2013, we entered into a license agreement providing an exclusive research license and an option for an exclusive commercial license for specific targets and products to be developed from a platform technology. Under the terms of the agreement, we made an upfront payment of $3,000 and are also required to pay annual maintenance fees. In addition, for each product we develop, we could be required to pay up to an additional $70,500 in license fees, development and sales milestones as the specific milestones are met over time.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2013

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:	**Common Stock, par value $0.0001**
	Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001
Name of each exchange on which registered:	**The NASDAQ Stock Market LLC**
Securities registered pursuant to Section 12(g) of the Act:	**None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The NASDAQ Stock Market LLC on June 30, 2013, was $17,833,350,643.(1)

The number of shares of Common Stock outstanding as of February 3, 2014 was 197,830,376.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 6, 2014, are incorporated by reference into Part III of this report.

ALXN2065
IPR2019-00740
Samsung Bioepis Exhibit No. 1002
Page 12513

(1) Excludes 1,898,588 shares of common stock held by directors and executive officers at June 30, 2013. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Samsung Bioepis Exhibit No. 1002
Page 12514

We estimate that we will pay employer contributions of approximately $3,886 in 2014. The expected future cash flows to be paid in respect of the pension plans as of December 31, 2013 were as follows:

Year	
2014	$ 2,140
2015	1,960
2016	1,910
2017	2,020
2018	1,851
2019 to 2023	8,306

17. Segment Information

We operate as one business segment, which is the innovation, development and commercialization of life-transforming therapeutic products. Therefore, our chief operating decision-maker manages our operations as a single operating segment.

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	**2013**	**2012**	**2011**
United States	$ 561,405	$ 400,483	$ 263,387
Europe	514,987	418,321	340,812
Asia Pacific (primarily Japan)	203,538	161,480	115,377
Other	271,416	153,830	63,855
	$ 1,551,346	$ 1,134,114	$ 783,431

	December 31,	
Long-lived assets (1):	**2013**	**2012**
United States	$ 190,791	$ 157,019
Europe	5,413	5,988
Other	4,905	2,622
	$ 201,109	$ 165,629

(1) Long-lived assets consist of property, plant and equipment.

18. Subsequent Events

In January 2014, we entered into an agreement with Moderna Therapeutics, Inc. (Moderna) that provides the option to purchase drug products for clinical development and commercialization of Moderna's messenger RNA (mRNA) therapeutics to treat rare diseases. Due to the early stage of these assets, we recorded expense for an upfront payment of $100,000 in 2014. We will also be responsible for funding research activities under the program. In addition, for each drug target, up to a maximum of ten targets, would could be required to make an option exercise payment of $15,000 and to pay up to an additional $120,000 with respect to a rare disease product and $400,000 with respect to a non-rare disease product in development and sales milestones if the specific milestones are met over time as well as royalties on commercial sales. In addition to the option agreement, we purchased $25,000 of preferred equity of Moderna LLC, Moderna's parent company.

In January 2014, we agreed to purchase a vialing facility in Athlone, Ireland. The closing of the acquisition is expected to occur during the first quarter of 2014 upon satisfaction of agreed upon closing conditions. Following closing and refurbishment of the facility, and after successful completion of the appropriate validation processes and regulatory approvals, such facility will become our first company-owned vialing facility for Soliris and other clinical and commercial products.

Samsung Bioepis Exhibit No. 1002
Page 12515

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2014

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

352 Knotter Drive, Cheshire Connecticut 06410
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**
Rights to Purchase Junior Participating Cumulative Preferred Stock, par value $0.0001

Name of each exchange on which registered: The NASDAQ Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The NASDAQ Stock Market LLC on June 30, 2014, was $30,706,252,188.(1)

The number of shares of Common Stock outstanding as of February 3, 2015 was 202,148,509.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 6, 2015, are incorporated by reference into Part III of this report.

ALXN2066
IPR2019-00740
Samsung Bioepis Exhibit No. 1002
Page 12516

(1) Excludes 1,378,571 shares of common stock held by directors and executive officers at June 30, 2014. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Samsung Bioepis Exhibit No. 1002
Page 12517

Revenues and tangible long-lived assets by significant geographic region are as follows:

	Year Ended December 31,		
Revenues:	**2014**	**2013**	**2012**
United States	$ 730,089	$ 561,405	$ 400,483
Europe (1)	836,134	514,987	418,321
Asia Pacific	244,059	203,538	161,480
Other	423,451	271,416	153,830
	$ 2,233,733	$ 1,551,346	$ 1,134,114

(1) As described in Note 19 "Quarterly Financial Information (unaudited)", included within the Europe revenues for 2014 is a reimbursement of $87,830 for shipments made in years prior to January 1, 2014 as a result of an agreement with the French government.

	December 31,	
Long-lived assets (2):	**2014**	**2013**
United States	$ 298,122	$ 190,791
Europe	88,543	5,413
Other	5,583	4,905
	$ 392,248	$ 201,109

(2) Long-lived assets consist of property, plant and equipment.

18. Subsequent Events

In January 2015, we entered into a license agreement with a third party to obtain certain intellectual property rights and technology related to specific therapeutic compounds. The agreement provides an exclusive research, development and commercial license for products to be developed using such compounds. Pursuant to the terms of the agreement, we made an upfront payment of $50,000 during the first quarter 2015. We could be required to pay up to an additional $213,000 in development and regulatory milestones related to a product developed under the agreement for a single disease indication. An additional $437,000 in milestone payments could be due if certain development and regulatory milestones are achieved for additional disease indications. The agreement also provides for royalty payments and potential milestone payments of up to $180,000 on commercial sales of products developed under the agreement.

In January 2015, we entered into a new lease agreement for approximately 44,000 square feet of office space in Zurich, Switzerland to support the relocation of the European headquarters. The lease is estimated to commence in the second quarter of 2015 and will expire 10 years later, with a minimum renewal option of 5 years and a maximum renewal option of 10 years. The lease provides for annual payments of $2,600 over the term of the lease.

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2015

or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to

Commission file number: 0-27756

ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	**13-3648318**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

100 College Street, New Haven, Connecticut 06510
(Address of Principal Executive Offices) (Zip Code)
203-272-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **Common Stock, par value $0.0001**

Name of each exchange on which registered: The NASDAQ Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Website, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐ (Do not check if a smaller reporting company)
Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The NASDAQ Stock Market LLC on June 30, 2015, was $39,491,560,848.(1)

The number of shares of Common Stock outstanding as of February 3, 2016 was 225,291,331.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its Annual Meeting of Stockholders to be held on May 11, 2016, are incorporated by reference into Part III of this report.

ALXN2067
IPR2019-00740
Samsung Bioepis Exhibit No. 1002
Page 12519

(1) Excludes 7,551,963 shares of common stock held by directors and executive officers at June 30, 2015. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Samsung Bioepis Exhibit No. 1002
Page 12520

The following table presents a reconciliation of the restructuring reserve recorded within accrued expenses on the Company's condensed consolidated balance sheet for the year ended December 31, 2015 and December 31, 2014, respectively:

	December 31, 2015				December 31, 2014			
	Employee Separation Costs	Contract Termination Costs	Other Costs	Total	Employee Separation Costs	Contract Termination Costs	Other Costs	Total
Liability, beginning of period	$ 15,365	$ —	$ —	$ 15,365	$ —	$ —	$ —	$ —
Restructuring expenses	21,524	12,419	3,847	37,790	15,365	—	—	15,365
Cash settlements	(34,843)	(11,772)	(3,678)	(50,293)	—	—	—	—
Adjustments to previous estimates	4,344	35	—	4,379	—	—	—	—
Liability, end of period	$ 6,390	$ 682	$ 169	$ 7,241	$ 15,365	$ —	$ —	$ 15,365

18. Segment Information

We operate as one business segment, which is the innovation, development and commercialization of life-transforming therapeutic products. Therefore, results of our operations are reported on a consolidated basis for purposes of segment reporting, consistent with our management reporting. Disclosures about net product sales and long-lived assets by geographic area are presented below.

Net product sales

Net product sales by product are as follows:

	Year Ended December 31,		
	2015	2014	2013
Net product sales:			
Soliris (1)	$ 2,590,197	$ 2,233,733	$ 1,551,346
Strensiq	11,969	—	—
Kanuma	366	—	—
	$ 2,602,532	$ 2,233,733	$ 1,551,346

Geographical information

	Year Ended December 31,		
Net product sales:	2015	2014	2013
United States	$ 951,307	$ 730,089	$ 561,405
Europe (1)	840,465	836,134	514,987
Asia Pacific	276,350	244,059	203,538
Other	534,410	423,451	271,416
	$ 2,602,532	$ 2,233,733	$ 1,551,346

(1) As described in Note 19, "Quarterly Financial Information (unaudited)", included within the Soliris and Europe revenues for 2014 is a reimbursement of $87,830 for shipments made in years prior to January 1, 2014 as a result of an agreement with the French government.

	December 31,	
Long-lived assets (2):	2015	2014
United States	$ 444,282	$ 298,122
Europe	247,474	88,543
Other	5,269	5,583
	$ 697,025	$ 392,248

(2) Long-lived assets consist of property, plant and equipment.

Samsung Bioepis Exhibit No. 1002
Page 12521

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **Annual report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the fiscal year ended December 31, 2018
or

☐ **Transition report pursuant to Section 13 or 15 (d) of the Securities Exchange Act of 1934**
For the transition period from to
Commission file number: 0-27756



ALEXION PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Its Charter)

Delaware	13-3648318
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)

121 Seaport Boulevard, Boston Massachusetts 02210

(Address of Principal Executive Offices) (Zip Code)
475-230-2596
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.0001

Name of each exchange on which registered: The Nasdaq Stock Market LLC
Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. Check One:

Large accelerated filer ☒ Accelerated filer ☐ Non-accelerated filer ☐
Smaller reporting company ☐ Emerging growth company ☐
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the Common Stock held by non-affiliates of the registrant, based upon the last sale price of the Common Stock reported on The Nasdaq Stock Market LLC on June 29, 2018, was $26,514,235,288.(1)

The number of shares of Common Stock outstanding as of January 31, 2019 was 223,469,381.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be used in connection with its 2019 Annual Meeting of Stockholders currently anticipated to be held on May 14, 2019, are incorporated by reference into Part III of this report.

(1) Excludes 9,186,789 shares of common stock held by directors, executive officers and their respective affiliates at June 29, 2018. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, directly or indirectly, to direct or cause the direction of the management or policies of the registrant, or that such person is controlled by or under common control with the registrant.

Alexion Pharmaceuticals, Inc.

Table of Contents

		Page
PART I		
Item 1.	Business	5
Item 1A.	Risk Factors	29
Item 1B.	Unresolved Staff Comments	56
Item 2.	Properties	56
Item 3.	Legal Proceedings	56
Item 4.	Mine Safety Disclosures	56
PART II		
Item 5.	Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	57
Item 6.	Selected Financial Data	59
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	61
Item 7.A	Quantitative and Qualitative Disclosures About Market Risk	85
Item 8.	Financial Statements and Supplementary Data	86
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	86
Item 9A.	Controls and Procedures	86
Item 9A(T).	Controls and Procedures	87
Item 9B.	Other Information	87
PART III		
Item 10.	Directors, Executive Officers and Corporate Governance	88
Item 11.	Executive Compensation	88
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	88
Item 13.	Certain Relationships and Related Transactions, and Director Independence	88
Item 14.	Principle Accounting Fees and Services	88
PART IV		
Item 15.	Exhibits and Financial Statement Schedules	89
Item 16.	Form 10-K Summary	91
SIGNATURES		92

Samsung Bioepis Exhibit No. 1002
Page 12523

19. Segment Information

We operate in a single segment, focusing on serving patients affected by rare diseases through the innovation, development and commercialization of life-changing therapies. Consistent with our operational structure, our chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, results of our operations are reported on a consolidated basis for purposes of segment reporting, consistent with our management reporting. Disclosures about net product sales and long-lived assets by geographic area are presented below.

Net Product Sales

Net product sales by product and geographic region are as follows:

	Year Ended December 31,			% Change	
	2018	2017	2016	2018 compared to 2017	2017 compared to 2016
SOLIRIS					
United States	$ 1,588.4	$ 1,235.0	$ 1,058.5	28.6 %	16.7%
Europe	1,036.7	985.2	939.7	5.2 %	4.8%
Asia Pacific	382.0	328.1	303.8	16.4 %	8.0%
Rest of World	555.9	595.8	541.2	(6.7)%	10.1%
	$ 3,563.0	$ 3,144.1	$ 2,843.2	13.3 %	10.6%
STRENSIQ					
United States	$ 374.3	$ 280.1	$ 177.5	33.6 %	57.8%
Europe	61.7	35.6	15.3	73.3 %	132.7%
Asia Pacific	27.9	18.6	13.0	50.0 %	43.1%
Rest of World	11.2	5.5	3.6	103.6 %	52.8%
	$ 475.1	$ 339.8	$ 209.4	39.8 %	62.3%
KANUMA					
United States	$ 51.3	$ 42.4	$ 20.4	21.0 %	107.8%
Europe	21.6	14.6	6.3	47.9 %	131.7%
Asia Pacific	3.7	2.7	1.3	37.0 %	107.7%
Rest of World	15.4	5.9	1.1	**	**
	$ 92.0	$ 65.6	$ 29.1	40.2 %	125.4%
Total Net Product Sales	4,130.1	$ 3,549.5	$ 3,081.7	16.4 %	15.2%

** Percentages not meaningful

Long-Lived Assets

Long-lived assets consist of property, plant and equipment.

	December 31,	
	2018	2017
United States	$ 468.3	$ 455.9
Europe	1,001.1	864.6
Other	2.1	4.9
	$ 1,471.5	$ 1,325.4

Samsung Bioepis Exhibit No. 1002
Page 12524

Alexion Pharmaceuticals Submits Biologics License Application for Soliris(TM) (eculizumab)

Release Date:
Wednesday, September 20, 2006 8:08 am EDT

Terms:
Product News

- European Application on Track for Submission in 2006 -

Alexion Pharmaceuticals, Inc. (Nasdaq: ALXN) today announced that it has submitted a Biologics License Application (BLA) with the U.S. Food and Drug Administration (FDA) for its lead product candidate Soliris™ (eculizumab) as a treatment for patients diagnosed with paroxysmal nocturnal hemoglobinuria (PNH), a rare life-threatening genetic blood disorder.

"There currently is no treatment specifically available for PNH, which can be a debilitating disease that often shortens lives," said Leonard Bell, M.D., Chief Executive Officer of Alexion. "We believe Soliris represents a significant advance in the management of PNH and in improving the lives of patients diagnosed with the disease. We look forward to working with the FDA as it reviews our application and we remain on track to submit a Marketing Authorization Application (MAA) in Europe by the end of this year."

The BLA submission is based on data from the pivotal Phase III TRIUMPH trial which met all pre-specified primary and secondary endpoints with high levels of statistical significance. Details regarding the TRIUMPH study results are included in an article published today in the New England Journal of Medicine. The BLA submission also includes interim data of at least six months from the open-label Phase III SHEPHERD safety trial. Final 12-month data from the SHEPHERD trial will be submitted to the application. The TRIUMPH trial included 87 PNH patients and the SHEPHERD trial has enrolled 97 PNH patients. An additional 11 PNH patients were enrolled in an earlier pilot study.

Alexion has requested Priority Review designation for this BLA from the FDA. If granted, the FDA has up to six months from submission date to take action on the BLA. Priority Review may be granted to drug products that provide significant improvement compared to existing treatments for a disease. Alexion has already been granted Accelerated Assessment by the EMEA for Soliris™ (eculizumab) in Europe once the MAA is submitted.

PNH, a rare and life-threatening form of hemolytic anemia, is an acquired genetic blood disorder characterized by destruction of red blood cells by the body's complement system (a component of the immune system). Patients with PNH lack naturally-occurring complement inhibitors which normally prevent red blood cell destruction. SolirisTM (eculizumab), a long-acting C5 terminal complement inhibitor, is a monoclonal antibody drug that is designed to selectively block terminal complement activation and thereby restore complement inhibition in the blood of patients with PNH. Soliris™ (eculizumab) has been granted Orphan Drug Status in the PNH indication from both the FDA and European regulatory agencies. There currently is no approved therapy specifically available for treatment of PNH. Based upon scientific investigations and presentations of the prevalence of patients diagnosed with abnormal PNH cells in their blood, it is currently estimated that approximately 8,000 to 10,000 people in North America and Europe suffer from PNH. Patients with PNH may suffer from severe hemolysis, anemia, chronic fatigue, recurrent pain, pulmonary hypertension and intermittent episodes of dark colored urine, known as hemoglobinuria. Importantly, PNH patients are at increased risk of forming life-threatening blood clots, or thromboses, which are a major cause of death in this disease.

About Alexion

Alexion Pharmaceuticals is a biotechnology company working to develop and deliver life-changing drug therapies for patients with serious and life-threatening medical conditions. Alexion is engaged in the discovery and development of therapeutic products aimed at treating patients with a wide array of severe disease states, including hematologic diseases, cancer, and autoimmune disorders. Alexion's lead product candidate, Soliris™ (eculizumab), is currently undergoing evaluation in several clinical development programs, including for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Under the Special Protocol Assessment (SPA) process, the FDA has agreed to the design of protocols for the two phase III trials of Soliris™ (eculizumab) in PNH patients that could, if successful, serve as the primary basis of review for approval of a licensing application for eculizumab in the PNH indication. In January, 2006, Alexion announced that the first of those two PNH trials, the TRIUMPH study, achieved its co-primary endpoints with statistical significance. In June 2006, Alexion announced that interim results from the second of those two PNH trials, the SHEPHERD study, showed that eculizumab appeared to be safe and well tolerated and that all primary and secondary efficacy endpoints were achieved with statistical significance. Alexion is engaged in discovering and developing a pipeline of additional antibody therapeutics targeting severe unmet medical needs. This press release and further information about Alexion Pharmaceuticals, Inc. can be found at: http://www.alexionpharm.com.

This news release contains forward-looking statements, including statements related to potential benefits and commercial potential of Soliris™, clinical trial results, the timing of submission of additional clinical trial results, estimates of the number of PNH patients, and timing for submission of, and regulatory authorities' decisions with respect to, marketing applications for Soliris™ (eculizumab). Forward-looking statements are subject to factors that may cause Alexion's results and plans to

differ from those expected, including delays in completion of the SHEPHERD trial, delays in completion of analysis of clinical trial results, requests by the FDA or other regulatory authorities for additional information or data either prior to their acceptance of our submission for filing or following their review of our applications, timing and evaluation by regulatory agencies of our applications, the need for additional research and testing, decision of the FDA or other regulatory authorities not to approve (or to materially limit) marketing of Soliris™, delays in arranging satisfactory manufacturing capability, inability to acquire funding on timely and satisfactory terms, delays in developing or adverse changes in commercial relationships, the possibility that results of clinical trials are not predictive of the safety and efficacy of Soliris™, the risk that third parties won't agree to license any necessary intellectual property to us on reasonable terms, the risk that third party payors will not reimburse for the use of Soliris™ at acceptable rates or at all, the risk that estimates regarding the number of PNH patients are inaccurate and a variety of other risks set forth from time to time in Alexion's filings with the Securities and Exchange Commission, including but not limited to the risks discussed in Alexion's Quarterly Report on Form 10-Q for the quarter ended June 30, 2006, and in our other filings with the Securities and Exchange Commission. Alexion does not intend to update any of these forward- looking statements to reflect events or circumstances after the date hereof, except when a duty arises under law.

To download further materials related to Alexion and this press release, click here

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Source URL: https://news.alexionpharma.com/press-release/product-news/alexion-pharmaceuticals-submits-biologics-license-application-soliristm-e

Alexion Submits Market Authorization Application for Soliris(TM) (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency

Release Date:
Tuesday, September 26, 2006 8:08 am EDT

Terms:
Product News

- Soliris(TM) (eculizumab) to be reviewed under European Accelerated Assessment Procedure -

CHESHIRE, Conn.--(BUSINESS WIRE)--Alexion Pharmaceuticals, Inc. (Nasdaq: ALXN) today announced that its wholly-owned subsidiary, Alexion Europe, has submitted a Market Authorization Application (MAA) to the European Medicines Evaluation Agency (EMEA) for Soliris(TM) (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), a rare, life-threatening genetic blood disorder. If accepted, Alexion anticipates that the evaluation by the EMEA will commence in the fourth quarter. As reported on September 20, 2006, Alexion has previously submitted a Biologics License Application with the U.S. Food and Drug Administration (FDA) for Soliris(TM) (eculizumab).

"This MAA submission is the second significant regulatory milestone for Soliris this month, following closely behind our U.S. Biologics License Application submitted to the FDA," said Leonard Bell, M.D., Chief Executive Officer of Alexion. "There currently is no treatment specifically available for PNH, which can be a debilitating disease that often shortens lives. We believe Soliris, if approved, would represent an important treatment option in the management of PNH and in improving the lives of patients diagnosed with the disease. We look forward to working with the EMEA as it reviews the Soliris application."

The MAA submission will be reviewed under the centralized licensing procedure, which, if approval is granted, provides a marketing license valid in all 25 member states of the European Community. The EMEA has determined that the Accelerated Assessment Procedure can be utilized for the Soliris(TM) (eculizumab) application review. Accelerated Assessment is given for medicinal products of major therapeutic interest and shortens the timeframe for review by the agency.

The MAA submission includes data from the pivotal Phase III TRIUMPH trial, which met all pre-specified primary and secondary endpoints with high levels of statistical significance. Details regarding the TRIUMPH study results are included in an article published in the September 21, 2006 issue of the New England Journal of Medicine. The Soliris(TM) (eculizumab) application also includes interim six months data from the open-label Phase III SHEPHERD safety trial. Twelve month data from the SHEPHERD trial is expected to be submitted at a later date to the MAA. The TRIUMPH trial included 87 PNH patients and the SHEPHERD trial enrolled 97 PNH patients. An additional 11 PNH patients were enrolled in an earlier pilot PNH study.

PNH, a rare and life-threatening form of hemolytic anemia, is an acquired genetic blood disorder characterized by destruction of red blood cells by the body's terminal complement system (a component of the immune system). Patients with PNH lack naturally-occurring complement inhibitors which normally prevent red blood cell destruction. Soliris(TM) (eculizumab), a long-acting C5 complement inhibitor, is a humanized monoclonal antibody drug that is designed to selectively block terminal complement activation in the blood of patients with PNH. Soliris(TM) (eculizumab) has been granted Orphan Drug Status in the PNH indication from both the FDA and European regulatory agencies. There currently is no approved therapy specifically available for treatment of PNH.

Based upon scientific investigations and presentations of the prevalence of patients diagnosed with abnormal PNH cells in their blood, it is currently estimated that approximately 8,000 - 10,000 people in North America and Europe suffer from PNH. Patients with PNH may suffer from severe hemolysis, anemia, chronic fatigue, recurrent pain, pulmonary hypertension and intermittent episodes of dark colored urine, known as hemoglobinuria. Importantly, PNH patients are at increased risk of forming life-threatening blood clots, or thromboses, which are a major cause of death in this disease.

About Alexion

Alexion Pharmaceuticals is a biotechnology company working to develop and deliver life-changing drug therapies for patients with serious and life- threatening medical conditions. Alexion is engaged in the discovery and development of therapeutic products aimed at treating patients with a wide array of severe disease states, including hematologic diseases, cancer, and autoimmune disorders. Alexion's lead product candidate, Soliris(TM) (eculizumab), is currently undergoing evaluation in several clinical development programs, including for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Under the Special Protocol Assessment (SPA) process, the FDA has agreed to the design of protocols for the two phase III trials of Soliris(TM) (eculizumab) in PNH patients that could, if successful, serve as the primary basis of review for approval of a licensing application for eculizumab in the PNH indication. In January, 2006, Alexion announced that the first of those two PNH trials, the TRIUMPH study, achieved its co-primary endpoints with statistical significance. In June 2006, Alexion announced that interim results from the second of those two PNH trials, the SHEPHERD study, showed that eculizumab appeared to be safe and well tolerated and that all primary and secondary efficacy endpoints were achieved with statistical significance. In September, 2006, Alexion applied for marketing authorization with both the United States Food and Drug Administration and the European Medicines Evaluation Agency for the use of Soliris in PNH patients. Alexion is engaged in discovering and developing a pipeline of additional antibody therapeutics targeting severe unmet medical needs. This press release and further

information about Alexion Pharmaceuticals, Inc. can be found at: http://www.alexionpharm.com.

This news release contains forward-looking statements, including statements related to potential benefits and commercial potential of Soliris(TM), clinical trial results, the timing of submission of additional clinical trial results, estimates of the number of PNH patients, and timing for submission of, and regulatory authorities' decisions with respect to, marketing applications for Soliris(TM) (eculizumab). Forward-looking statements are subject to factors that may cause Alexion's results and plans to differ from those expected, including delays in completion of the SHEPHERD trial, delays in completion of analysis of clinical trial results, requests by the FDA or other regulatory authorities for additional information or data either prior to their acceptance of our submission for filing or following their review of our applications, timing and evaluation by regulatory agencies of our applications, the need for additional research and testing, decision of the FDA or other regulatory authorities not to approve (or to materially limit) marketing of Soliris(TM), delays in arranging satisfactory manufacturing capability, inability to acquire funding on timely and satisfactory terms, delays in developing or adverse changes in commercial relationships, the possibility that results of clinical trials are not predictive of the safety and efficacy of Soliris(TM), the risk that third parties won't agree to license any necessary intellectual property to us on reasonable terms, the risk that third party payors will not reimburse for the use of Soliris(TM) at acceptable rates or at all, the risk that estimates regarding the number of PNH patients are inaccurate and a variety of other risks set forth from time to time in Alexion's filings with the Securities and Exchange Commission, including but not limited to the risks discussed in Alexion's Quarterly Report on Form 10-Q for the quarter ended June 30, 2006, and in our other filings with the Securities and Exchange Commission. Alexion does not intend to update any of these forward-looking statements to reflect events or circumstances after the date hereof, except when a duty arises under law.

Source URL: https://news.alexionpharma.com/press-release/product-news/alexion-submits-market-authorization-application-soliristm-eculizumab-tre

Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product

Release Date:
Thursday, September 25, 2008 8:08 am EDT

Terms:
Company News

Recognizes Scientific Accomplishment in Complement Inhibition and Impact of Soliris on Patients Living with PNH

Alexion Pharmaceuticals, Inc. (NASDAQ: ALXN) has received a Prix Galien USA 2008 Award for Best Biotechnology Product for Soliris® (eculizumab). The Award recognizes the scientific innovation represented by the complement-inhibition technology of Soliris, and the impact the drug is having on the lives of patients with paroxysmal nocturnal hemoglobinuria (PNH), a rare, debilitating and life-threatening blood disorder.

Soliris is a first-in-class complement inhibitor that selectively blocks the formation of terminal complement, a component of the normal immune system. Patients with PNH lack naturally occurring proteins that ordinarily prevent terminal complement from causing the red blood cell destruction (hemolysis) that is central to the serious morbidities and mortality associated with PNH.

"We are living in the midst of a biological revolution and the breakthrough agents honored by the Prix Galien USA illustrate the substantial research and development necessary to bring the fruits of that revolution in molecular medicine to the clinic," said Gerald Weissmann, M.D., Prix Galien USA committee chair, New York University professor emeritus and editor-in-chief of The FASEB Journal.

"We deeply appreciate this honor, which recognizes more than 15 years of dedicated complement-based research. The Prix Galien award is especially gratifying for the scientists, physicians, patients and advocates involved in the discovery and development of Soliris," said Leonard Bell, M.D., Chief Executive Officer of Alexion. "We are committed to making sure that every patient with PNH who can benefit from Soliris will have access to Soliris. We are building on the success of Soliris by increasing our understanding of PNH and by evaluating the promise of complement inhibition for the treatment of other rare and life-threatening kidney, blood, transplant and neurologic disorders."

About the Prix Galien USA Awards

The Prix Galien Award (http://www.prix-galien-usa.com) recognizes the technical, scientific and clinical research skills necessary to develop innovative medicines, and is considered the industry's highest accolade for pharmaceutical research and development -- equivalent to the Nobel Prize.

Prix Galien was first established in 1970 by French pharmacist Roland Mehl and was inaugurated in the United States in September 2007. The Prix Galien USA awards committee of 11 individuals includes seven Nobel Laureates, founders of major biotechnology companies and editors of world-renowned biology journals. The candidates for this year's awards were selected from drugs approved during the past five years.

About PNH

PNH is a rare blood disease that affects an estimated 8,000 to 10,000 people in North America and Europe and, using similar prevalence estimates, potentially 1,000 to 2,000 patients in Japan. (1) PNH often strikes people in the prime of their lives, with an average age of onset in the early 30's. (2) Approximately ten percent of all patients first develop symptoms at 21 years of age or younger. (3) PNH develops without warning and can occur in men and women of all races, backgrounds and ages. PNH often goes unrecognized, with delays in diagnosis often ranging from one to more than 10 years. (4) The estimated median survival for PNH patients is between 10 and 15 years from the time of diagnosis. (2,4)

PNH has been identified more commonly among patients with disorders of the bone marrow, including aplastic anemia (AA) and myelodysplastic syndrome (MDS). (5,6,7,8,9) In patients with thrombosis of unknown origin, PNH may be an underlying cause. (3,9)

Prior to approval of Soliris, there were no therapies specifically available for the treatment of PNH. PNH treatment was limited to symptom management through periodic blood transfusions, non-specific immunosuppressive therapy and, infrequently, bone marrow transplantations -- a procedure that carries considerable mortality risk. (3,9)

About Soliris

Soliris was approved in March 2007 by the U.S. Food and Drug Administration (FDA) as the first treatment for PNH, a rare, debilitating and life-threatening blood disorder defined by hemolysis. In June 2007, the European Commission (EC) also approved the use of Soliris for the treatment of patients with PNH. Soliris is the first drug therapy ever approved under

ALXN2020
IPR2019-00739
Samsung Bioepis Exhibit No. 1002
Page 12529

Priority Review in the U.S. and through the Accelerated Assessment procedure in Europe.

Important Safety Information

Soliris is generally well tolerated. The most frequent adverse events observed in clinical studies were headache, nasopharyngitis (a runny nose), back pain and nausea. Treatment with Soliris should not alter anticoagulant management because the effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established.

The U.S. product label for Soliris also includes a boxed warning: "Soliris increases the risk of meningococcal infections. Vaccinate patients with a meningococcal vaccine at least two weeks prior to receiving the first dose of Soliris; revaccinate according to current medical guidelines for vaccine use. Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary." During clinical studies, two out of 196 vaccinated PNH patients treated with Soliris experienced a serious meningococcal infection.

Prior to beginning Soliris therapy, all patients and their prescribing physicians are enrolled in the Soliris Safety Registry which is part of a special risk management program that involves initial and continuing education and long-term monitoring for detection of new safety findings.

Please see full prescribing information at www.soliris.net.

About Alexion

Alexion Pharmaceuticals, Inc. is a biopharmaceutical company working to develop and deliver life-changing drug therapies for patients with serious and life-threatening medical conditions. Alexion is engaged in the discovery, development and commercialization of therapeutic products aimed at treating patients with a wide array of severe disease states, including hematologic diseases, cancer, and autoimmune disorders. In March 2007, the FDA granted marketing approval for Alexion's first product, Soliris, for all patients with PNH and Alexion began commercial sale of Soliris in the U.S. during April 2007. In June 2007, the EC granted marketing approval for Soliris in the European Union for all patients with PNH. Alexion is evaluating other potential indications for Soliris as well as other formulations of eculizumab for additional clinical indications, and is pursuing development of other antibody product candidates in early stages of development. This press release and further information about Alexion Pharmaceuticals, Inc. can be found at: www.alexionpharm.com.

[ALXN-G]

(1) Hill A, Platts PJ, Smith A et al. The incidence and prevalence of paroxysmal nocturnal hemoglobinuria (PNH) and survival of patients in Yorkshire [abstract]. Blood. 2006;108(11):985.

(2) Socie G, Mary J Yves, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. Lancet 1996; 348:573-577.

(3) Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005;106:3699-3709.

(4) Hillmen P. Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1995; 333:1253-1258.

(5) Johnson RJ, Hillmen P. Paroxysmal nocturnal hemoglobinuria: Nature's gene therapy? Mol Pathol. 2002;55(3):145-52.

(6) Wang, et al. Clinical significance of a minor population of paroxysmal nocturnal hemoglobinuria-type cells in bone marrow failure syndrome. Blood 2002;100:3897-3902.

(7) Iwanga, et al. Paroxysmal nocturnal haemoglobinuria clones in patients with myelodysplastic syndromes. Brit J Haem. 1998; 102:465-474.

(8) Maciejewski, et al. Relationship between bone marrow failure syndromes and the presence of glycophosphatidyl inositol-anchored protein-deficient clones. Brit J Haem. 2001;115:1015-1022.

(9) Hill A, Richards S, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. Brit J Haem. 2007; 137:3, 181-192.

Please see full Prescribing Information and Important Safety Information for Soliris® (eculizumab).

Source URL: https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p

Samsung Bioepis Exhibit No. 1002
Page 12530

Our Pipeline

Inflammation

Oncology

Hematology

ABP 798 (biosimilar rituximab)

ABP 710 (biosimilar infliximab)

ABP 494 (biosimilar cetuximab)

ABP 959 (biosimilar eculizumab)

Monoclonal antibody that specifically binds to the complement protein C5

Reference product primary conditions:

Paroxysmal nocturnal hemoglobinuria

Atypical hemolytic uremic syndrome

Generalized myasthenia gravis

ABP 980 (biosimilar trastuzumab)

(/PRODUCTS/APPROVED-PRODUCTS/) (../CLINICAL-TRIALS/)

PREVIOUS:
APPROVED PRODUCTS

NEXT:
CLINICAL TRIALS

ALXN2088
IPR2019-00740
Samsung Bioepis Exhibit No. 1002
Page 12531

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00739
U.S. Patent No. 9,725,504 B2

AMGEN INC.'S
OBJECTIONS TO EVIDENCE

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Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Petitioner, Amgen Inc. (“Amgen”), objects under the Federal Rules of Evidence (FRE) and 37 C.F.R. § 42.64(b)(1) to the admissibility of Exhibits 2022, 2024, 2026, 2028, 2030, 2031, 2033-2040, 2043, 2044, 2047, 2049-2052, 2054-2056, 2059-2077, 2080-2083, and 2086-2091 (the “Challenged Evidence”), filed by Patent Owner Alexion Pharmaceuticals, Inc. (“Alexion”) on November 22, 2019, with Alexion's Patent Owner Response. Amgen's Objections are timely filed under 37 C.F.R. § 42.64(b)(1), within five business days of the November 22, 2019 Patent Owner Response. Amgen files these Objections to provide notice to Alexion that Amgen may move to exclude the Challenged Evidence under 37 C.F.R. § 42.64(c).

I. IDENTIFICATION OF GROUNDS FOR OBJECTIONS

A. Exhibits 2022, 2024, 2026, and 2056

Amgen objects to part or all of the declarations Alexion has provided as Exhibits 2022, 2024, 2026, and 2056 under FRE 401, 402 and FRE 403:

- Exhibit 2022 purports to be the “Declaration of Arturo Casadeval, M.D., Ph.D.” Amgen objects to paragraphs 1-25, 27-62, 65-67, 69, 72-76, 132-133, 138-139, 154-155, 160, 163-164, 166, 170-175, 177, 184-186, 263-364, 269, 280-282, and 287-288 in Exhibit 2022 under FRE 402 and FRE 403.

- Exhibit 2024 purports to be the "Declaration of Bernhardt L. Trout, Ph.D." Amgen objects to paragraphs 1-38 and 57-63 in Exhibit 2024 under FRE 402 and FRE 403.
- Exhibit 2026 purports to be the "Declaration of Michel C. Nussenzweig, M.D., Ph.D." Amgen objects to the entirety of Exhibit 2026 under FRE 402 and FRE 403.
- Exhibit 2056 purports to be the "Declaration of Daniel Bazarko." Amgen objects to the entirety of Exhibit 2056 under FRE 402 and FRE 403.[1]

Alexion does not cite any of these paragraphs in its Patent Owner Response, rendering the testimony in these paragraphs irrelevant under FRE 401. Amgen therefore objects to these paragraphs under FRE 402. Amgen also objects to these paragraphs under FRE 403 because they have no probative value, create unfair prejudice to Amgen, and will only confuse issues and waste the Board's time.

Amgen also objects to Exhibits 2022, 2024, 2026 and 2056 to the extent that they rely on evidence that is inadmissible under FRE 106, 401, 402, 403, 702, 703,

[1] Alexion's Patent Owner Response contains a single citation to the entirety of EX2056, but does not provide a pin cite to any paragraph within EX2056.

802, 901, 902, 1001(e), 1002, and/or 1003, as described below. Paragraphs that rely on inadmissible evidence include:

Exhibit 2022: ¶¶58, 70-72, 74, 76-80, 83-84, 87, 92-94, 107-108, 113, 116-118, 123, 146, 216, 242, 268, 271-273, 275-276, 280, 285;

Exhibit 2024: ¶¶41-56, 71, 84; EX2026, ¶¶2, 14-17; and

Exhibit 2056: ¶¶6, 9.

B. Exhibits 2028, 2033, 2034, 2037-2040, 2043, 2044, 2047, 2050-2052, 2080-2083, and 2086

Amgen objects to Exhibits 2028, 2033, 2034, 2037-2040, 2043, 2044, 2047, 2050-2052, 2080-2083, and 2086 as lacking authentication under FRE 901. Each of these exhibits is inadmissible under FRE 901 because Alexion has failed to provide sufficient evidence indicating the origin of the documents and has not provided sufficient information regarding their authenticity. Further, these exhibits are not self-authenticating under FRE 902.

Amgen also objects to Exhibits 2033, 2034, 2037-2040, 2043, 2044, 2047, 2050-2052, 2080-2083, and 2086 as irrelevant under FRE 401 through FRE 403. These exhibits are not cited in Alexion's Patent Owner Response. They are, therefore, irrelevant under FRE 401. Amgen therefore objects to these exhibits under FRE 402. Amgen also objects to these exhibits under FRE 403 because they have no probative value, create unfair prejudice to Amgen, and will only confuse

issues and waste the Board's time.

Amgen also objects to Exhibits 2028, 2037, 2040, and 2082 under FRE 1001 through FRE 1003. For example, these documents have stray markings, extra pages, and other indicia that they are not original, or even clean copies of the original document. Amgen objects because the exhibits are not a "duplicate" as defined by FRE 1001(e) insofar as the exhibit is not "a copy . . . which accurately reproduces the original." Further, Amgen objects to these exhibits for failure to comply with the best evidence rule. FRE 1002.

C. Exhibits 2031, 2035, 2036, 2059-2073, and 2091

Amgen objects to Exhibits 2031, 2035, 2036, 2059-2073, and 2091 as incomplete. Each of these exhibits appears to be part of a larger work, rendering each exhibit inadmissible under FRE 106 ("If a party introduces all or part of a writing or recorded statement, an adverse party may require the introduction, at that time, of any other part that in fairness ought to be considered at the same time."). Because each of these exhibits is part of a larger work, each exhibit is inadmissible under FRE 403 because using only a portion of the exhibit risks unfair prejudice, confusing the issues, and misleading the Board.

Amgen also objects to Exhibits 2031, 2035, 2036, and 2091 as irrelevant under FRE 401 through FRE 403. These exhibits are not cited in Alexion's Patent Owner Response. They are, therefore, irrelevant under FRE 401. Amgen therefore

objects to these exhibits under FRE 402. Amgen also objects to these exhibits under FRE 403 because they have no probative value, create unfair prejudice to Amgen, and will only confuse issues and waste the Board's time.

D. Exhibits 2030, 2049, 2054, 2055, and 2088-2090

Amgen objects to Exhibits 2030, 2049, 2054, 2055, and 2088-2090 as lacking authentication under FRE 901. These exhibits purport to be printouts of web pages, but each is inadmissible under FRE 901 because Alexion has failed to provide sufficient evidence indicating the origin and creation of the PDF documents, and accordingly Alexion has not provided sufficient information regarding their authenticity. Further, these exhibits are not self-authenticating under FRE 902.

Amgen also objects to Exhibits 2030, 2049, 2054, 2055, and 2088-2090 under FRE 802 as containing inadmissible hearsay. Alexion and its experts rely on Exhibits 2030, 2049, 2054, 2055, and 2088-2090 for the truth of the matter asserted. *See e.g.*, Alexion's Patent Owner Response, 66; EX2022, ¶¶58, 268, 272-273, 275-276, 280, 285.

Amgen also objects to Exhibits 2030, 2049, 2054, and 2055 as irrelevant under FRE 401 through FRE 403. These exhibits are not cited in Alexion's Patent Owner Response. They are, therefore, irrelevant under FRE 401. Amgen therefore objects to these exhibits under FRE 402. Amgen also objects to these exhibits

under FRE 403 because they have no probative value, create unfair prejudice to Amgen, and will only confuse issues and waste the Board's time.

E. Exhibits 2074-2077, 2087, and 2026

Amgen objects to Exhibits 2074-2077 and 2087 as lacking authentication under FRE 901. These exhibits purport to relate to the sequencing of an antibody produced by hybridoma cell line, but each is inadmissible under FRE 901 because Alexion has failed to provide sufficient evidence indicating the origin and creation of the exhibits, and accordingly Alexion has not provided sufficient information regarding their authenticity. Further, these exhibits are not self-authenticating under FRE 902.

Amgen also objects to Exhibit 2026, which relies throughout on Exhibits 2074-2077 and 2087, under FRE 702 and FRE 703. Exhibit 2026 purports to describe experiments conducted and data generated, but the cited exhibits only provide summaries of the purported methods and data and do not provide the underlying facts or data on which the presented conclusions are based. 37 C.F.R. §42.65(a).

Amgen also objects to Exhibits 2074-2077 and 2087 as irrelevant under FRE 401 through FRE 403. These exhibits are not cited in Alexion's Patent Owner Response. They are, therefore, irrelevant under FRE 401. Amgen therefore objects to these exhibits under FRE 402. Amgen also objects to these exhibits under FRE

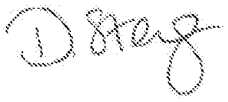
403 because they have no probative value, create unfair prejudice to Amgen, and will only confuse issues and waste the Board's time.

II. CONCLUSION

To the extent Alexion fails to correct the defects associated with the Challenged Evidence in view of Amgen's objections herein, Amgen may file a motion to exclude the Challenged Evidence under 37 C.F.R. § 42.64(c).

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Date: December 2, 2019
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Deborah A. Sterling, Ph.D.
Registration No. 62,732
Lead Attorney for Petitioner

CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned "AMGEN INC.'S OBJECTIONS TO EVIDENCE" was served in its entirety on December 2, 2019, upon the following parties via email:

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Lead Attorney for Petitioner

14217589.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00740
U.S. Patent No. 9,718,880 B2

AMGEN INC.'S
OBJECTIONS TO EVIDENCE

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Alexandria, VA 22313-1450

Petitioner, Amgen Inc. (Amgen), objects under the Federal Rules of Evidence (FRE) and 37 C.F.R. § 42.64(b)(1) to the admissibility of Exhibits 2022, 2024, 2026, 2028, 2030, 2031, 2033-2040, 2043, 2044, 2047, 2049-2052, 2054-2056, 2059-2077, 2080-2083, and 2086-2091 (the Challenged Evidence), filed by Patent Owner Alexion Pharmaceuticals, Inc. (Alexion) on November 22, 2019, with Alexion's Patent Owner Response. Amgen's Objections are timely filed under 37 C.F.R. § 42.64(b)(1), within five business days of the November 22, 2019 Patent Owner Response. Amgen files these Objections to provide notice to Alexion that Amgen may move to exclude the Challenged Evidence under 37 C.F.R. § 42.64(c).

I. IDENTIFICATION OF GROUNDS FOR OBJECTIONS

A. Exhibits 2022, 2024, 2026, and 2056

Amgen objects to part or all of the declarations Alexion has provided as Exhibits 2022, 2024, 2026, and 2056 under FRE 401, 402 and FRE 403:

- Exhibit 2022 purports to be the Declaration of Arturo Casadeval, M.D., Ph.D. Amgen objects to paragraphs 1-25, 27-61, 64-66, 68-69, 71-75, 131-132, 137-138, 153-154, 159-160, 162-163, 169-174, 176, 13-15, 190, 261-262, 267, 279-280, and 285-286 in Exhibit 2022 under FRE 402 and FRE 403.

- Exhibit 2024 purports to be the Declaration of Bernhardt L. Trout, Ph.D. Amgen objects to paragraphs 1-37 and 55-61 in Exhibit 2024 under FRE 402 and FRE 403.
- Exhibit 2026 purports to be the Declaration of Michel C. Nussenzweig, M.D., Ph.D. Amgen objects to the entirety of Exhibit 2026 under FRE 402 and FRE 403.
- Exhibit 2056 purports to be the Declaration of Daniel Bazarko. Amgen objects to the entirety of Exhibit 2056 under FRE 402 and FRE 403.[1]

Alexion does not cite any of these paragraphs in its Patent Owner Response, rendering the testimony in these paragraphs irrelevant under FRE 401. Amgen therefore objects to these paragraphs under FRE 402. Amgen also objects to these paragraphs under FRE 403 because they have no probative value, create unfair prejudice to Amgen, and will only confuse issues and waste the Board's time.

Amgen also objects to Exhibits 2022, 2024, 2026 and 2056 to the extent that they rely on evidence that is inadmissible under FRE 106, 401, 402, 403, 702, 703,

[1] Alexion's Patent Owner Response contains a single citation to the entirety of EX2056, but does not provide a pin cite to any paragraph within EX2056.

802, 901, 902, 1001(e), 1002, and/or 1003, as described below. Paragraphs that rely on inadmissible evidence include:

- Exhibit 2022: ¶¶57, 69-71, 73, 75-79, 82-83, 86, 91-93, 106-107, 112, 115-117, 121-122, 145, 165, 215, 241, 266, 269-271, 273-274, 278, 2083;
- Exhibit 2024: ¶¶38, 41-54, 69, 82;
- Exhibit 2026: ¶¶2, 14-17; and
- Exhibit 2056: ¶¶6, 9.

B. Exhibits 2028, 2033, 2034, 2037-2040, 2043, 2044, 2047, 2050-2052, 2080-2083, and 2086

Amgen objects to Exhibits 2028, 2033, 2034, 2037-2040, 2043, 2044, 2047, 2050-2052, 2080-2083, and 2086 as lacking authentication under FRE 901. Each these exhibits is inadmissible under FRE 901 because Alexion has failed to provide sufficient evidence indicating the origin of the documents and has not provided sufficient information regarding their authenticity. Further, these exhibits are not self-authenticating under FRE 902.

Amgen also objects to Exhibits 2033, 2034, 2037-2040, 2043, 2044, 2047, 2050-2052, 2080-2083, and 2086 as irrelevant under FRE 401 through FRE 403. These exhibits are not cited in Alexion's Patent Owner Response. They are, therefore, irrelevant under FRE 401. Amgen therefore objects to these exhibits

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C. Exhibits 2031, 2035, 2036, 2059-2073, and 2091

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Amgen also objects to Exhibits 2031, 2035, 2036, and 2091 as irrelevant

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Amgen also objects to Exhibits 2030, 2049, 2054, 2055, and 2088-2090 under FRE 802 as containing inadmissible hearsay. Alexion and its experts rely on Exhibits 2030, 2049, 2054, 2055, and 2088-2090 for the truth of the matter asserted. *See e.g.*, Alexion's Patent Owner Response, 67; EX2022, ¶¶57, 121, 266, 270-271, 273-274, 278, 283.

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Amgen objects to Exhibits 2074-2077 and 2087 as lacking authentication under FRE 901. These exhibits purport to relate to the sequencing of an antibody produced by hybridoma cell line, but each is inadmissible under FRE 901 because Alexion has failed to provide sufficient evidence indicating the origin and creation of the exhibits, and accordingly Alexion has not provided sufficient information regarding their authenticity. Further, these exhibits are not self-authenticating under FRE 902.

Amgen also objects to Exhibit 2026, which relies throughout on Exhibits 2074-2077 and 2087, under FRE 702 and FRE 703. Exhibit 2026 purports to describe experiments conducted and data generated, but the cited exhibits only provide summaries of the purported methods and data and do not provide the underlying facts or data on which the presented conclusions are based. 37 C.F.R. §42.65(a).

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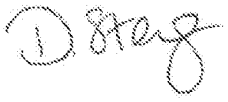
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II. CONCLUSION

To the extent Alexion fails to correct the defects associated with the Challenged Evidence in view of Amgen's objections herein, Amgen may file a motion to exclude the Challenged Evidence under 37 C.F.R. § 42.64(c).

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Date: December 2, 2019
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(202) 371-2600

Deborah A. Sterling, Ph.D.
Registration No. 62,732
Lead Attorney for Petitioner

CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned "AMGEN INC.'S OBJECTIONS TO EVIDENCE" was served in its entirety on December 2, 2019, upon the following parties via email:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00741
U.S. Patent No. 9,732,149 B2

AMGEN INC.'S
OBJECTIONS TO EVIDENCE

Mail Stop "PATENT BOARD"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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- Exhibit 2026 purports to be the "Declaration of Michel C. Nussenzweig, M.D., Ph.D." Amgen objects to the entirety of Exhibit 2026 under FRE 402 and FRE 403.
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[1] Alexion's Patent Owner Response contains a single citation to the entirety of EX2026 and EX2056, but does not provide a pin cite to any paragraph within EX2026 or EX2056.

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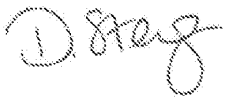
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00739
Patent: 9,725,504

PATENT OWNER RESPONSE PURSUANT TO 37 C.F.R. § 42.120

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TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 9

A. Design of Humanized Monoclonal Antibodies, and Pharmaceutical Compositions of Such Antibodies for Human Therapeutic Use Was a Complex, Unpredictable Art 9

B. Naming of Humanized Monoclonal Antibodies 13

C. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" to be the IgG4 Monoclonal Antibody of Thomas 14

D. The Structure and Sequence of SOLIRIS® Was *Not* Known Prior to March 15, 2007 21

E. Overview of the '504 Patent 28

F. Prosecution History of the '504 Patent and Related Applications 29

III. PERSON OF ORDINARY SKILL IN THE ART OF THE '504 PATENT 31

IV. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF CLAIMS 1-10 OF THE '504 PATENT 32

A. Amgen's Ground 1 Fails Because Amgen Cannot Show that Claims 1-3 and 7-10 Were Anticipated by Hillmen 32

1. Hillmen Did Not Disclose an Antibody "Comprising a Heavy Chain Consisting of SEQ ID NO: 2 and a Light Chain Consisting of SEQ ID NO: 4" 32

2. Hillmen Did Not Inherently Disclose the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claims 1-3 and 7-10 of the '504 Patent 33

B. Amgen's Grounds 2 and 3 Fail Because Amgen Cannot Show that Claims 4 and 5 Were Obvious Over Hillmen and Bell, or that Claim 6 Was Obvious Over Hillmen in Combination with Bell and Wang 35

Table of Contents
(continued)

Page

1. Hillmen and Bell (and Wang), in any Combination, Did Not Teach the Specific Claimed Antibody of Claims 4-6, or its Use in Treating Patients Suffering from PNH.....35

2. The Claimed Pharmaceutical Compositions Were Not Taught by Hillmen and Bell (Claims 4 and 5) or Hillmen, Bell, and Wang (Claim 6).....37

C. Amgen's Grounds 4 and 5 Fail Because Amgen Cannot Show that the '504 Patent Claims Would Have Been Obvious Over Bell, Bowdish and Evans (Claims 1-5, 7-10) or Bell, Wang, Bowdish and Evans (Claim 6).....42

1. Bell (and Wang) Did Not Disclose the Claimed Sequence, and Would Not Have Motivated a POSA to Make the Claimed Antibody.....44

2. A POSA Would Not Have Been Motivated to Combine Bell's Teachings with Bowdish and Evans, or to Make the Specific Claimed Sequence.....47

3. The Combination of Bell, Bowdish and Evans (and Wang) Would Not Have Motivated a POSA to Practice the Claimed Treatment Methods and Pharmaceutical Compositions of the '504 Patent, or Given a POSA a Reasonable Expectation of Success in Doing So.....56

D. Amgen's Grounds 6 and 7 Fail Because Amgen Cannot Show that the '504 Patent Claims Would Have Been Obvious Over the Combination of Bell, Mueller and Evans (Claims 1-5, 7-10) or Bell, Wang, Mueller and Evans (Claim 6).....58

E. The Objective Indicia of Nonobviousness Support Validity.....64

V. CONCLUSION.....67

Samsung Bioepis Exhibit No. 1002
Page 12562

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Amerigen Pharm. Ltd. v. UCB Pharma GmbH
913 F.3d 1076 (Fed. Cir. 2019) 56, 60, 63

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894 F.3d 1374 (Fed. Cir. 2018) 36, 60

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855 F.3d 1356 (Fed. Cir. 2017) 46

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938 F.3d 1324 (Fed. Cir. 2019) 51, 68

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939 F.3d 1375 (Fed. Cir. 2019) 45, 60

Par Pharm., Inc. v. TWI Pharms., Inc.
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Therasense, Inc. v. Becton Dickinson & Co.
593 F.3d 1325 (Fed. Cir. 2010) 34

EXHIBIT LIST

Exh. No.	Description
2001	Declaration of Evan D. Diamond in support of Motion for *Pro Hac Vice*
2002	Evan D. Diamond Biography
2003	Declaration of Vanessa Y. Yen in support of Motion for *Pro Hac Vice*
2004	Vanessa Y. Yen Biography
2005	SOLIRIS® Label
2006	Dmytrijuk *et al.*, FDA Report: Eculizumab (SOLIRIS®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, THE ONCOLOGIST, 13:993-1000 (2008)
2007	Janeway and Travers, *Immunobiology*: The Immune System in Health and Disease (Garland Science, 6th ed. (2005))
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2009	Torres *et al.*, The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917–27 (2007)
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2011	Pritsch *et al.*, Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)
2012	Pritsch *et al.*, Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)
2013	McLean *et al.*, Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379–86 (2002)
2014	Greenspan *et al.*, Complementarity, Specificity and the Nature of Epitopes and Paratopes in Multivalent Interactions, IMMUNOL. TODAY, 16(5): 226-30 (1995)
2015	Radbruch, *et al.*, Drastic Change in Idiotypic but Not Antigen-Binding Specificity of an Antibody by a Single Amino-Acid Substitution, NATURE, 315(6): 506-508 (1985)
2016	U.S. Patent No. 7,482,435, issued to Bowdish *et al.*
2017	Hawkins *et al.*, The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J. MOL. BIO., 234: 958-964 (1993)

Exh. No.	Description
2018	Alexion Pharmaceuticals, Inc. Form 10-K for the fiscal year ending December 31, 2018 (excerpts)
2019	Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)
2020	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p (last visited May 15, 2019)
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I. INTRODUCTION

Claims 1-10 of Alexion's U.S. Patent No. 9,725,504 ("the '504 patent") recite methods of treating a patient suffering from paroxysmal nocturnal hemoglobinuria ("PNH") with a pharmaceutical composition of an antibody comprising the novel, uniquely-engineered amino acid sequence of SOLIRIS®, the groundbreaking, commercially successful anti-C5 monoclonal antibody developed by Alexion. Claim 6 also specifically requires that the composition is a "300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution."

SOLIRIS®, also referred to today by its non-proprietary name "eculizumab," is a first-in-class treatment for patients with the rare, potentially fatal blood disease paroxysmal nocturnal hemoglobinuria ("PNH"), caused by red blood cells losing their normal protection against the "complement" immune pathway. SOLIRIS® works by binding to component 5 ("C5") of the complement pathway and preventing its cleavage into components "C5a" and "C5b," which mediate downstream effects of the complement pathway, including hemolysis in patients with PNH.

Prior to March 15, 2007, the priority date of the '504 patent, the unique amino acid sequence of SOLIRIS® recited in claims 1-10 of the '504 patent (heavy and light chains consisting of SEQ ID NOs: 2 and 4, respectively) was ***not*** publicly known or disclosed in the prior art. While a person of ordinary skill in the art

("POSA") as of that date would have known that Alexion had designed, formulated, and clinically tested an antibody named "eculizumab," the POSA would not have known that "eculizumab" had the amino acid sequence recited in the '504 patent claims. That is because the literature as of March 15, 2007 consistently identified "eculizumab" as the antibody described in the "Thomas" publication (AMG1023), which has a naturally-occurring "***IgG4***" heavy chain constant region. In contrast, the novel antibody in the methods of treatment and pharmaceutical compositions of the '504 patent has a very different, uniquely-engineered, non-naturally occurring constant region. A POSA would not have known of any antibody with the specific sequence recited in claims 1-10 of the '504 patent and would not have reasonably expected that such an antibody would bind C5. Further, a POSA prior to March 15, 2007 would not have known or reasonably expected that such a novel antibody – with no *in vitro* or *in vivo* biological data or formulation information reported in the literature – could be formulated into a pharmaceutical composition suitable for use in treating PNH.

Amgen has not shown how any of the prior art of its Grounds disclosed or would have led a POSA to a method of treating PNH with pharmaceutical compositions comprising an antibody with the uniquely-engineered amino acid sequence recited in claims 1-10 of the '504 patent. Instead, Amgen disregards the perspective of a POSA as of March 15, 2007, and impermissibly uses its ***hindsight***

knowledge of the '504 patent's novel, previously-undisclosed claimed sequence and pharmaceutical compositions to misstate the disclosures of the prior art, pick and choose from those misstated disclosures, and reconstruct the claimed invention using the '504 patent's teachings as a guide. The law forbids such use of hindsight. When that improper hindsight is removed, and the art is viewed from the proper perspective of a POSA, each of Amgen's Grounds fails.

Amgen's Ground 1 – alleging anticipation of claims 1-3 and 7-10 – fails because Amgen incorrectly presumes that a POSA would have understood that the clinical publication Hillmen (AMG1004) disclosed the claimed sequence of the '504 patent by using the name "eculizumab." But nothing within the four corners of Hillmen necessarily disclosed the present-day knowledge that eculizumab has the uniquely-engineered amino acid sequence described and claimed in the '504 patent. Rather, as the Board recognized, Hillmen identified "eculizumab" as the ***IgG4 antibody of Thomas***. (*See, e.g.*, Paper No. 15, 28-29 & n.16, 33-35.)

Amgen's Grounds 2 and 3 – alleging obviousness of claims 4-6 in view of Hillmen in further combination with Bell (AMG1005) (claims 4 and 5) or Bell and Wang (AMG1028) (claim 6) – are based on the same mistaken premise that Hillmen disclosed the specific amino acid sequence claimed in the '504 patent, and fail for at least the same reasons as Ground 1. *See Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014) (in obviousness, as in

anticipation, an alleged inherent element must be "***necessarily present*** in the prior art combination").[1] Bell and Wang, like Hillmen, did not disclose the '504 patent's specific claimed amino acid sequence, or any pharmaceutical compositions of an antibody having that sequence. And Amgen fails to explain why a POSA would have been motivated to make, or would have reasonably expected success with, the specific pharmaceutical compositions recited in claim 6 for an antibody that, as far as a POSA knew, might have never been made or tested for C5 binding, *in vitro* activity, therapeutic effect in treating PNH (as the claims require), or suitability for pharmaceutical formulation.

Amgen's Grounds 4-7, alleging obviousness of claims 1-10, fail because they rely on post-hoc knowledge of the '504 patent's unique claimed sequence to reconstruct that invention from bits and pieces of structurally and functionally distinct compounds in unrelated art. *See Merck Sharpe & Dohme B.V. v. Warner Chilcott Co.*, 711 Fed. App'x 633, 637 (Fed. Cir. 2017) ("[U]sing the [patent-in-suit] as a roadmap to piece together various elements of [the prior art] . . . represents an improper reliance on hindsight."). As Dr. Balthasar conceded at deposition, he was handed his cited prior art by counsel; he read only the portions

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[1] Unless otherwise noted, all emphasis is added, and all internal citations and internal quotation marks are omitted.

of his references that he contends showed obviousness of the claimed invention; he could not testify with any "confidence" as to whether his references did or did not disclose key aspects of the claimed invention; and he assembled his figures based on the claimed sequence of the '504 patent that was not available to a POSA prior to March 15, 2007. (ALXN2032, 64:23-65:14, 74:16-75:5, 77:7-78:2, 85:10-17, 108:17-109:10, 148:24-149:10, 180:8-11, 244:17-245:9, 267:17-268:11.)

For example, Amgen's Grounds 4 and 5 contend that a POSA would have started with Bell (AMG1005), for teaching "eculizumab" as a clinically studied anti-C5 antibody (and for claim 6, Wang (AMG1028) for teaching compositions of "eculizumab") – and then would have turned to Bowdish (AMG1006) and Evans (AMG1007) for the sequence of "eculizumab." But ***nothing*** in Bowdish and Evans suggested to a POSA that the claimed antibody was "eculizumab." Rather, Bell – like Hillmen – informed a POSA that "eculizumab" was Thomas's ***IgG4*** antibody. (Paper No. 15, 29 n.16; IPR2019-00741, Paper No. 15, 21 n.14.) Amgen cannot explain why a POSA would have ignored the unequivocal direction toward Thomas's IgG4 antibody and instead looked to (1) Bowdish, which was not cited in Bell and disclosed neither "eculizumab" nor any other humanized monoclonal antibody that binds C5; and (2) Evans, which did not describe ***any*** full-length humanized antibodies for binding C5 or treating PNH, let alone the antibody of the claimed treatment methods and pharmaceutical compositions of the

'504 patent. There is no support for Amgen's hindsight-driven theory that a POSA trying to determine the structure of Bell's "eculizumab" would have (1) selected Bowdish, rather than Thomas, as a starting point; (2) identified Bowdish's TPO-mimetic compound as relating to a humanized antibody with a hybrid IgG2/IgG4 constant region – even though nothing in Bowdish contains such a statement; and (3) associated the purported IgG2/IgG4 structure of Bowdish's TPO-mimetic compound with "eculizumab" – despite Bell's and many other prior art references' teachings of "eculizumab" as an ***IgG4*** isotype antibody.

Even if Bowdish and Evans were viewed in combination, a POSA without hindsight would not have arrived at the specific sequence in the claimed compositions of the '504 patent. Rather, a POSA would have seen Bowdish and Evans pointing in different directions, with Bowdish referring to a mouse antibody in its reference to "[c]onstruction of 5G1.1" from the "'283 application"; and Evans disclosing only that mouse antibody plus humanized recombinant "fragment" compounds that could not have been used as the "scaffold" to make Bowdish's full-length TPO-mimetic compound.

Amgen's Grounds 6 and 7 start with the disclosure of "eculizumab" by Bell (or Bell and Wang for claim 6), and then use improper hindsight to recreate the claimed sequence of the '504 patent from sequences plucked from Evans and Mueller (AMG1008). Mueller concerned antibodies directed at "VCAM" – a very

different target from C5 – and used the antibody "h5G1.1 CO12 HuG2/G4 mAb" only as an "isotype control" for experiments involving VCAM. As the Board noted, Mueller identified only an ***IgG4*** antibody (*i.e.*, the isotype of Thomas) as an "anti-C5 antibody," and taught nothing about the C5 binding or clinical properties of "h5G1.1 CO12 HuG2/G4 mAb."

Nor would a POSA have been motivated to combine the sequences in Evans and Mueller – neither of which cites to the other – in the exact manner to get the specific claimed antibody sequence of the '504 patent. As the Board recognized, nothing in Evans or Mueller instructed whether or how such a combination should be done, including "precisely those portions of Evans's and Mueller's constructs to create an antibody having exactly the sequences set forth in SEQ ID NOs: 2 and 4." (Paper No. 15, 54.)

Even if sequences from Evans and Bowdish or Mueller were combined in the specific and untaught way that Amgen proposes, the methods of treatment and pharmaceutical compositions recited in claims 1-10 of the '504 patent considered as a whole would still not have been obvious in view of the art asserted in Grounds 4-7. First, a POSA would not have reasonably expected that an antibody with the claimed sequence would be "an antibody that binds C5," as the claims require. Further, a POSA would not have been motivated to use, or reasonably expected success in using, an uncharacterized antibody with the claimed sequence for a

"method of treating a patient suffering from [PNH]," or for inclusion in a "pharmaceutical composition" suitable for such treatment, as claims 1-10 require.

And even if Amgen were correct, as it contends in Grounds 3, 5, and 7, that the "eculizumab" antibody of Bell (AMG1005) and Wang (AMG1028) had the uniquely-engineered sequence recited in the '504 patent claims, it would not have been obvious for a POSA to formulate that composition as "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution," as required by claim 6. Amgen relies on Bell and Wang for allegedly teaching that such a composition would be "sufficiently stable and active to be used as a drug" and would be useful for treating PNH. (*E.g.*, Petition, 42 n.21.) But as Dr. Trout explains, nothing in Bell or Wang disclosed such a composition, or would have motivated a POSA without hindsight to make or use it. In particular, Bell disclosed no composition details at all; and Wang's disclosure of a 30 mg/ml eculizumab solution passed through a nebulizer device would not have motivated a POSA to make the claimed 300 mg single use, 10 mg/ml antibody solution compositions, or have given a POSA a reasonable expectation that such compositions would be suitable for use in treating PNH patients.

II. BACKGROUND

A. Design of Humanized Monoclonal Antibodies, and Pharmaceutical Compositions of Such Antibodies for Human Therapeutic Use Was a Complex, Unpredictable Art

There is no dispute that as of March 15, 2007, a POSA would have understood a "monoclonal" antibody (including a "humanized monoclonal antibody" such as "eculizumab") to be a single, unique antibody with one defined structure, and critically, ***one unique primary amino acid sequence*** for the entire antibody. (ALXN2022 ¶71; ALXN2032, 10:9-22, 11:10-17.) A humanized monoclonal antibody, in turn, was understood = to be a unique antibody with a unique sequence, designed by grafting mouse monoclonal antibody sequences associated with antigen binding into a human monoclonal antibody. (ALXN2022 ¶¶77, 79.) And a POSA would have understood that a humanized monoclonal antibody for therapeutic use – the subject matter of the methods of treatment and pharmaceutical compositions described and claimed in the '504 patent – was a humanized monoclonal antibody intended to bind its target and achieve a desired biological and therapeutic activity when administered to human patients, while maintaining sufficient safety to be suitable for human administration. (*See* ALXN2022 ¶¶77-83, 87-91; ALXN2032, 43:15-22, 46:20-48:2.)

A POSA would have understood that development of a "humanized" antibody intended for human therapeutic use was a complex and unpredictable art.

(ALXN2022 ¶¶77-91.) A particular new humanized monoclonal antibody could not simply be assumed to retain the original mouse antibody's binding affinity and biological activity against its target antigen. Accordingly, a new humanized monoclonal antibody would need to be tested *in vitro* to establish binding properties and biological activity. (ALXN2022 ¶83.) To determine the suitability of a new humanized antibody as a therapeutic agent, additional extensive testing would need to be performed, including "pre-clinical" testing in animals; clinical testing of efficacy, immunogenicity, and overall safety; and pharmaceutical formulation work to determine whether a suitably stable composition could be safely and efficaciously administered to people. (ALXN2022 ¶¶87-91; ALXN2032, 46:20-48:2.)

A POSA could not reasonably extrapolate the *in vitro* or clinical properties of one monoclonal antibody with a unique amino acid sequence to a different antibody with a different sequence. A POSA understood that antibodies were complex three-dimensional structures, and that a monoclonal antibody's specific amino acid sequence was essential to its structure and function. (ALXN202022 ¶¶63-64, 71, 117.) In particular, it was known that even small changes in an antibody's sequence could affect its critical properties. (ALXN2022 ¶¶105-118.)

For example, a POSA would have understood that sequences ***beyond*** a monoclonal antibody's "CDRs" could substantially influence its antigen-binding

properties, including its "affinity" (tightness of binding) for the target antigen, "specificity" for binding the target antigen versus non-targets, and "fine specificity" for binding the target antigen in the particular region ("epitope") needed to provide the desired therapeutic activity. (ALXN2022 ¶¶105-118.) It was well-known that non-CDR amino acids within an antibody's "variable" region (*i.e.*, "framework" residues) could impact antigen binding, either by direct involvement in binding or indirect effects on three-dimensional antibody structure. (ALXN2022 ¶107.) A POSA also would have known that the ***constant regions*** of monoclonal antibodies play an indirect role in antigen binding, and that switching between different constant regions ("isotype switching") could significantly impact antigen binding, even while leaving the variable region unchanged. (ALXN2022 ¶¶108-115.) In particular, the art described how changes to the "CH1" and "hinge" portions of the heavy chain constant region impact antigen affinity and specificity. (ALXN2022 ¶114; ALXN2012, 3388, 3391-92; ALXN2009, 13917-18, 13924.)

Once a suitable humanized monoclonal antibody was designed and tested to show it has its desired *in vitro* activity, it would need to be further studied with clinical tests. (ALXN2022 ¶¶87-89.) A POSA would have been particularly concerned about the unpredictability of a humanized monoclonal antibody for therapeutic use if, in addition to the mouse sequences of the variable region, it contained a non-naturally occurring constant region that was not known to have

been clinically tested and shown to be suitable for human administration (*e.g.*, a hybrid constant region fusing sequences from different isotypes). (ALXN2022 ¶87.)

A POSA would have also understood that truncated antibody-like molecules could be made, containing amino acid sequences that include less than a full-length, intact humanized monoclonal antibody. (ALXN2022 ¶¶92-94.) While commonly called "fragments," these compounds were typically made by recombinant DNA means, rather than "broken off" from a full-length, pre-existing antibody. (ALXN2022 ¶92; ALXN2032, 143:18-22.) For example, a humanized single-chain Fv or "scFv" compound could be made, containing only the variable light and heavy chain regions connected by a linker; or an "Fab" compound could be made, containing a complete light chain but only the variable and CH1 constant region of the heavy chain ("Fd"), with no intact "Fc" region (the stem of the Y-shaped antibody structure). (ALXN2022 ¶¶68, 93; ALXN2032, 143:8-25.) A POSA would have understood that these "fragments" were very different from a full-length humanized antibody, and have different properties (*e.g.*, shorter half-life but greater tissue penetration). (ALXN2022 ¶93.) A POSA would have further understood that because the constant regions of a full-length, intact antibody could impact its antigen-binding properties as well as its immunogenicity, the properties of a "fragment" lacking a full heavy chain constant region could not reliably be

extrapolated to a new, untested full-length humanized monoclonal antibody. (ALXN2022 ¶¶94, 106-118.)

A POSA also understood that developing pharmaceutical compositions of antibodies was an unpredictable art. (ALXN2024 ¶¶41-56; AMG1029, 1, 5.) Antibody compositions (liquid compositions in particular) were at risk for degradation that could cause them to lose effect or even harm patients – and thus would need to be tested to determine suitability for human use. (ALXN2024, ¶¶42-53.)

B. Naming of Humanized Monoclonal Antibodies

A POSA as of March 15, 2007 would have understood that different naming conventions were used for humanized monoclonal antibodies at different stages of development. (ALXN2022 ¶95.) Depending on the convention used and the stage of development, a POSA might understand that a particular name refers to a group of several related antibodies; or in other cases, that a specific non-proprietary name (*e.g.*, "eculizumab") or a brand name (*e.g.*, "SOLIRIS®") refers to a single, unique monoclonal antibody with one defined structure and one primary amino acid sequence. (ALXN2022 ¶¶95-104; ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14.)

At early stages of development of a humanized monoclonal antibody, a POSA would have understood that informal research code names were commonly

used, and typically referenced the original source mouse antibody from which the humanized antibody was generated (*e.g.*, "5G1.1"). (ALXN2022 ¶96; ALXN2032, 98:2-99:8, 202:24-203:14.) A POSA would have understood that, depending on the context, these code names could potentially refer to a number of different structures or sequences. (ALXN2022 ¶96; ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14.)

In contrast, after a specific humanized monoclonal antibody with a single, unique sequence has progressed into clinical development, it may be assigned a "non-proprietary" name (*e.g.*, "eculizumab") by authorities including INN and USAN. (ALXN2022 ¶98.) A POSA would have understood that these non-proprietary names with respect to humanized monoclonal antibodies would refer to one – and only one – specific antibody as defined by its unique amino acid sequence. (ALXN2022 ¶¶101-102, 121; ALXN2032, 10:9-11:17, 98:19-99:8, 100:3-10; ALXN2046, 1; ALXN2045, 1210.) The same would be true when, as the product neared FDA submission, the research sponsor would propose a unique branded trade name (*e.g.*, "SOLIRIS®"). (ALXN2022 ¶103.)

C. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" to be the IgG4 Monoclonal Antibody of Thomas

As of March 15, 2007, a POSA would have understood that a unique humanized monoclonal antibody named "eculizumab," that specifically targets

human C5 and prevents its cleavage, had been developed. (ALXN2022 ¶¶119-124; AMG1047, 2559 (citing Thomas, AMG1023).)

But the POSA as of March 15, 2007 would ***not*** have known that "eculizumab" had the sequence claimed in the '504 patent, including the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2. Rather, a POSA at that time would have believed that "eculizumab" contained an "***IgG4***" constant region – which is very different from the uniquely-engineered heavy-chain constant region recited in claims 1-10 of the '504 patent. (ALXN2022 ¶¶121-124; ALXN2032, 97:7-21.) Specifically, the literature regarding the development of "eculizumab" consistently described "eculizumab" by referencing Thomas (AMG1023). (ALXN2022 ¶¶121-124, 140, 194-196; ALXN2032, 125:13-126:9, 128:20-129:10, 192:13-22, 160:18-162:12.) Thomas, in turn, details the design and testing of a full-length, ***IgG4***-isotype humanized antibody ("humanized 5G1.1") with anti-C5 affinity, specificity, and complement-blocking activity comparable to the original mouse "5G1.1" antibody. (AMG1023, 1396-99; ALXN2022 ¶124; ALXN2032, 242:21-243:4.)

A POSA would have had no doubt that "eculizumab" was Thomas's IgG4-isotype humanized antibody, because the pertinent literature consistently and unambiguously said so:

Table 1: References to "Eculizumab" as Thomas's Humanized IgG4 Antibody

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hillmen (AMG1004) at 553 – Phase II clinical trial for treatment of PNH	"***Eculizumab is*** a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components." (Citing ***Thomas***, Ref. No. 15)
Hill (AMG1047) at 2559 – 52-week extension of Hillmen Phase II clinical trial	"***Eculizumab is*** a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage." (Citing ***Thomas***, Ref. No. 9)
Hillmen 2006 (AMG1012) at 1234 – pivotal Phase III clinical trial for treatment of PNH	"***Eculizumab (Soliris, Alexion Pharmaceuticals) is*** a humanized monoclonal antibody directed against the terminal complement protein C5." (Citing ***Thomas***, Ref. No. 13)
Hill 2007 (ALXN2028) – post-Phase III case report for PNH patient	"***Eculizumab is*** a novel humanized monoclonal antibody directed against the complement protein C5." (Citing ***Thomas***, Ref. No. 6)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Bell (AMG1005) at [0052] – Phase II clinical studies described in Hillmen and Hill	States that "[m]ethods for the preparation of h5G1.1-mAb" are described in ***Thomas***, and that "[t]he antibody h5G1.1-mAb is currently undergoing clinical trials under the name ***eculizumab***."
Kaplan (AMG1021) at 1018	States that "***Eculizumab*** (5G1.1), under development by Alexion Pharmaceuticals Inc. is a humanized C5 inhibitory monoclonal antibody (mAb)," and cites ***Thomas*** for the synthesis and complement-blocking activity of "intact humanized 5G1.1 antibody" or "humanized 5G1.1"
Brekke (AMG1019) at 56	"***Eculizumab*** (5G1.1; Alexion Pharmaceuticals) ***is*** a humanized monoclonal antibody that prevents the cleavage of human complement component C5 . . . ." (citing ***Kaplan***, Ref. No. 31, which in turn cites to ***Thomas***)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Pierangeli (AMG1020) at 2123	Stating that "***eculizumab*** has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH] . . . ." (citing to ***Hillmen***, Ref No. 18, which in turn cites to ***Thomas***)

Looking at this literature, a POSA would have believed that Thomas's IgG4 antibody was the ***only*** full-length humanized antibody shown to bind C5 and prevent its cleavage, tested for safety and efficacy in treating PNH, and submitted to the FDA for marketing approval.[2] In Thomas, a POSA would have seen the extensive work in rationally designing an "intact" humanized monoclonal antibody preserving the anti-C5 activity of the "5G1.1" mouse antibody, using an IgG4 isotype. (AMG1023, 1393-99; ALXN2022 ¶124; ALXN2032, 242:21-243:4.)

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[2] Thomas also does not disclose the specific light chain amino acid sequence recited in SEQ ID NO: 4 of the '504 patent. In particular, the light chain variable region sequence provided by Thomas differs from SEQ ID NO: 4 of the '504 patent at amino acid position 38, flanking light chain CDR1. (*Compare* AMG1023 at 1392, 1396 (identifying position 38 as "R" (arginine)) *with* AMG1001 at col. 35, SEQ ID NO: 4 (identifying position 38 as "Gln" (glutamine).)

And, prior to March 15, 2007, a POSA would have seen that "eculizumab" – consistently identified as Thomas's IgG4 antibody – was shown to be safe and effective in treating PNH, and was submitted for FDA and European approval under the trade name SOLIRIS®. (*See, e.g.*, AMG1004; AMG1047; AMG1012; ALXN2028; AMG1005, ¶¶[0052], [0081-0096]; ALXN2022 ¶¶121-124.)

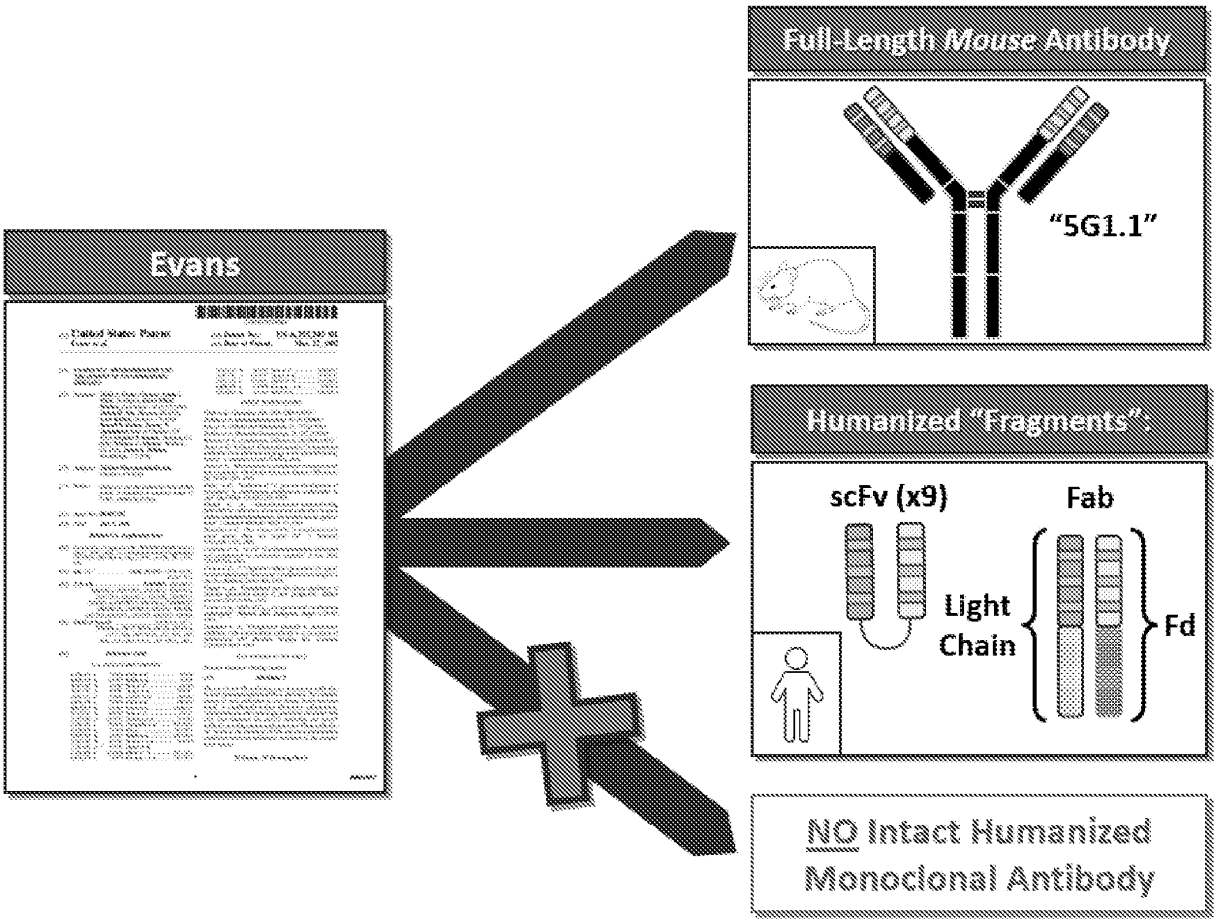
In contrast to Thomas and the literature regarding "eculizumab" that followed Thomas, a POSA would have understood that Evans (AMG1007) did ***not*** disclose "eculizumab." Rather, a POSA would have understood that Evans described an earlier stage of research that predated the design of the intact, full-length humanized antibody "eculizumab." (ALXN2022 ¶¶125-131.) It is undisputed that Evans did ***not*** disclose any full-length humanized antibodies. (ALXN2022 ¶¶125-129, 217, 223-224; ALXN2032, 163:12-15, 169:13-18.) At most, a POSA would have read Evans as a precursor to the research that resulted in "eculizumab."

As Dr. Balthasar agreed at deposition, the only full-length antibody described in Evans (AMG1007) is the "5G1.1" mouse antibody, which Evans obtained from the "5G1.1" hybridoma. (AMG1007, 19:47-49, Figs. 18-19; ALXN2032, 165:5-21, 169:13-18; ALXN2022 ¶¶126-129.) Evans further describes the researchers' characterization of the "5G1.1" mouse antibody, including its binding affinity, *in vitro* complement-blocking activity, and the

sequencing and cloning of the variable regions of the "5G1.1 mouse antibody." (AMG1007, Examples 7-10; ALXN2022 ¶126; ALXN2032, 165:5-169:23.) But Evans provides no such information for a full-length ***humanized*** antibody derived from the "5G1.1" mouse antibody – which a POSA would have understood would have a different amino acid sequence and different clinical properties from the mouse antibody. (ALXN2022 ¶127; ALXN2032, 163:12-15, 169:24-170:4.)

To the extent Evans described "humanization" work based on the "5G1.1" mouse antibody, it was the development of recombinant "fragments" – scFv or Fab – that did ***not*** contain an intact heavy chain constant region, let alone the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2 of the '504 patent. (AMG1007, Example 11; ALXN2022 ¶127.) For example, Evans described nine different humanized "scFv" fragments, which are recombinantly-produced molecules containing two variable regions connected by a linker, with no constant region, (AMG1007, 43:6-14, 43:62-45:4), and humanized "Fab" fragments that also lack the "Fc" portion (regions CH2 and CH3) of an intact antibody (AMG1007, 43:21-61). (ALXN2022 ¶127.) Notably, the humanized Fab fragments of Evans have different heavy chain sequences ("Fd," Evans SEQ ID NOs: 11 and 12) from the non-prior art SEQ ID NO: 2 of the '504 patent, including in "CH1" constant region. (ALXN2022 ¶130.) A POSA would have understood

what Evans did disclose – a mouse antibody and humanized "fragments" – and what Evans did not disclose, *i.e.*, an intact humanized monoclonal antibody.



D. The Structure and Sequence of SOLIRIS® Was *Not* Known Prior to March 15, 2007

Today, but ***not*** before the priority date for the '504 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in claims 1-10 of the '504 patent, namely, "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." A POSA prior to the '504 patent, however, would

not have known of any antibody consisting of SEQ ID NOs: 2 and 4, and would not have reasonably expected that such an antibody would bind to C5, that it would be useful to treat patients suffering from PNH, or that it could be developed into a pharmaceutical composition suitable for human administration.

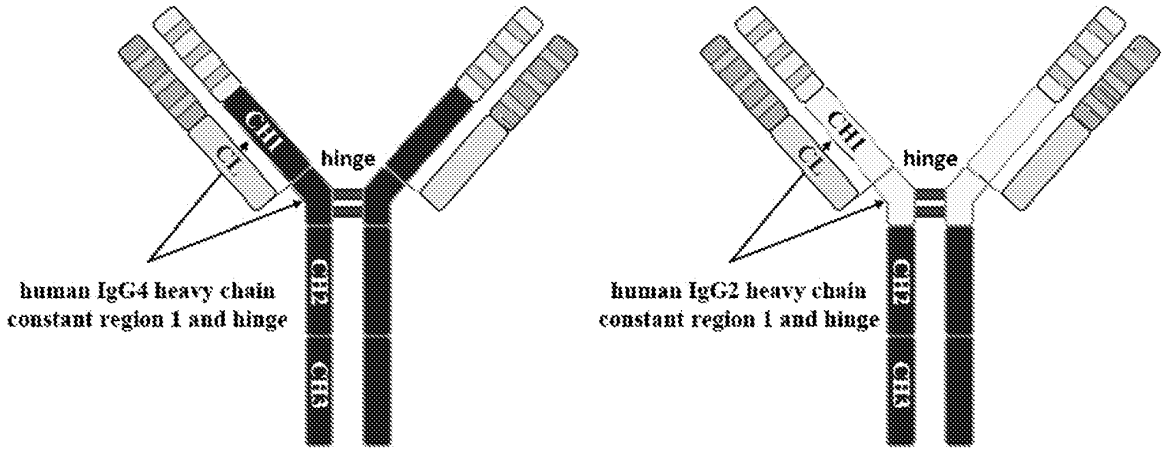
Today, but ***not*** prior to March 15, 2007, it is known that SOLIRIS® is a unique antibody that is ***very different*** from the humanized IgG4 antibody described in Thomas. As understood today, the heavy chain of SOLIRIS® (SEQ ID NO: 2) features a non-naturally occurring, uniquely-engineered constant region – containing sequences from both human IgG2 and IgG4 – that was designed by scientists at Alexion and was tested in human clinical trials. (ALXN2022 ¶¶134-137.)

Notably, SOLIRIS® was the first FDA-approved product containing Alexion's uniquely-engineered heavy chain constant region. A POSA would not have been aware of any published clinical testing showing that an antibody with this uniquely-engineered constant region would be therapeutically useful and suitable for human administration.

The presently-known structure of SOLIRIS® reflected in claims 1-10 of the '504 patent is shown below in comparison to the IgG4 isotype antibody described in Thomas, which the literature prior to March 15, 2007 would have taught a POSA was "eculizumab." The figure depicts how, unlike the IgG4 antibody of

Thomas, the claimed antibody uses the CH1 and "hinge" regions of IgG2, thereby providing a meaningfully different antibody than that identified in the literature citing to Thomas.

Left – Structure of the IgG4 isotype antibody referenced to as "eculizumab" in the literature as of March 15, 2007
Right – Structure of SOLIRIS®, having a non-naturally occurring, protein-engineered isotype



Amgen's and Dr. Balthasar's arguments fail because they are based on the erroneous assumption that a POSA would have understood "eculizumab" to contain "a hybrid IgG2/IgG4 constant region." (*See, e.g.*, Petition, 16-17, 69-70; AMG1002, ¶¶43, 46, 56.) That improperly ignores the overwhelming evidence that directed a POSA back then to look to Thomas for the structure of "eculizumab." (*See* Section II.C above.) Instead, to support its assumption that a POSA would have known that "eculizumab" contained an IgG2/IgG4 constant region, Amgen relies on a ***single***, ambiguous sentence in just one document – Tacken (AMG1034)[3] – regarding an "isotype control antibody." But a POSA looking for the structure of "eculizumab" would not have considered or credited Tacken above the consistent, clear statements in earlier and later publications that expressly identified "eculizumab" as the IgG4 antibody of Thomas.

As Dr. Balthasar admitted, Tacken is the ***only*** document on which he relies dated prior to March 15, 2007 that purportedly associated "eculizumab" with a hybrid IgG2/IgG4 constant region. (ALXN2032, 104:14-20.) But unlike the clinical literature discussed in Section II.C above, Tacken did not concern the study of "eculizumab" in binding C5, blocking C5 cleavage or treating conditions

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[3] Notably, Amgen does not rely on Tacken (AMG1034) as the basis for any of its Grounds alleging anticipation or obviousness of the '504 patent.

such as PNH. (ALXN2022 ¶¶141-151; ALXN2032, 72:23-73:2, 73:12-74:1, 74:16-21.) Rather, Tacken involved the study of an entirely different antibody (the "hD1" antibody) with a wholly different purpose: directing antigens to a dendritic cell receptor for purposes of developing improved vaccinations. (AMG1034, 1278-79, 1283-84.)

Nothing in Tacken contradicted the consistent teaching of the prior art ***as a whole*** that "eculizumab" had an IgG4 constant region. In a single sentence identifying an "isotype control antibody" for use in studies of the "hD1" antibody directed to dendritic cells, Tacken states the following (including a citation to ***Thomas*** as Ref. No. 19):

> An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

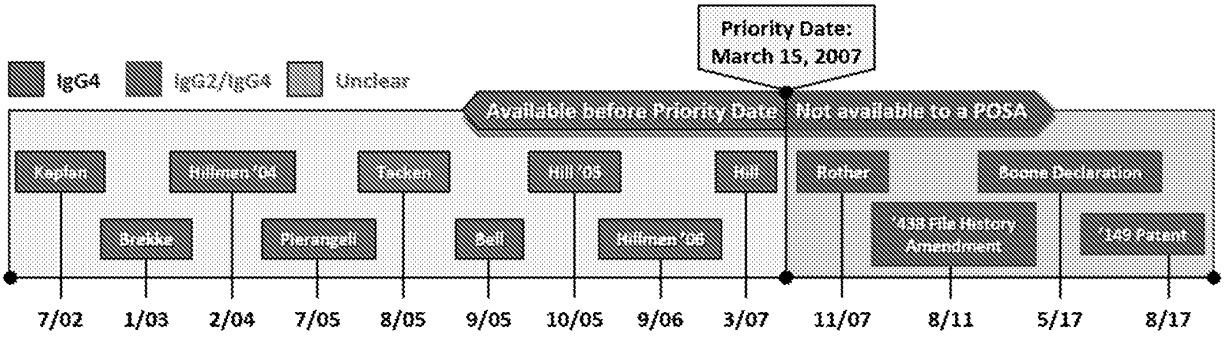
(AMG1034, 1279.) A POSA reading that isolated statement would not have been dissuaded from the consistent, clear teaching in the literature as of March 15, 2007 (both before and after Tacken's publication) identifying "eculizumab" and "SOLIRIS®" as the ***IgG4*** antibody of Thomas. (*See supra* Table 1; ALXN2022 ¶¶141-151.) A POSA would have seen substantial ambiguity in that statement. Not only does Tacken misspell "eculizumab," but it uses multiple conflicting and

undefined terms – including "h5G1.1-mAb," which could refer to a class of various humanized antibodies; and "5G1.1," which can refer to many things, including the original "5G1.1" mouse antibody from the "5G1.1" hybridoma. (ALXN2022 ¶144; ALXN2032, 98:2-99:8, 159:1-10; 202:24-203:14.) Further, a POSA would have seen Tacken's citation to Thomas's IgG4 antibody (Ref. No. 19) for "eculizamab" [sic] as inconsistent with its reference to an IgG2/IgG4 isotype control antibody. On balance, the ambiguous, passing reference in Tacken would not have led a POSA to "understand" that the clinically tested "eculizumab" antibody has an "IgG2/IgG4" constant region.

Amgen's myopic focus on the isotype control antibody of Tacken, to the exclusion of all other prior art information, is also not tenable because at least four prior art documents published ***after*** Tacken confirmed a POSA's belief as of March 15, 2007 that the clinically-tested "eculizumab" antibody was the ***IgG4*** antibody of Thomas. For example, the Hill clinical study was published two months after Tacken in the same journal (Blood), and stated that "[e]culizumab is" the antibody of Thomas. (AMG1047, 2559 (Ref. No. 9); ALXN2032, 113:14-21, 114:19-115:10.) Bell, published a month after Tacken, likewise pointed to Thomas for methods of making "eculizumab," and made no mention of hybrid IgG2/IgG4 antibodies. (AMG1005, ¶[0052]; ALXN2022 ¶¶123, 146; ALXN2032, 160:18-162:11.) The Hillmen 2006 Phase III study, published more than a year after

Tacken in the New England Journal of Medicine, and the Hill 2007 case report, published on March 1, 2007, likewise both stated that "eculizumab is" Thomas's IgG4 isotype antibody. (AMG1012, 1234 (Ref. No. 13); ALXN2028, 31 (Ref. No. 6); ALXN2022 ¶146; ALXN2032, 116:16-117:1.)

As the following timeline figure illustrates, the ***only*** plausible conclusion a POSA could have reached in view of the entire content of the art was that "eculizumab" was the IgG4 antibody of Thomas, and the ambiguous statement in Tacken (a publication having nothing to do with C5 binding) was either supportive of that understanding – as Tacken cites Thomas – or otherwise mistaken. (ALXN2022 ¶¶147, 151.) *See, e.g.*, *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 882-883 (Fed. Cir. 1998) (the "***entire content of the prior art***" must be considered in determining whether the art showed a trend towards the claimed invention).



E. Overview of the '504 Patent

The '504 patent issued on August 8, 2017 from U.S. App. No. 15/260,888, filed on September 9, 2016, and claims priority back to PCT/US2007/006606, filed on March 15, 2007. The '504 patent has ten claims, all directed to methods of treating patients suffering from PNH with a composition of a uniquely-engineered anti-C5 antibody claimed by its amino acid sequence: "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." Claim 1 is the sole independent claim of the '504 patent:

> **1.** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

In addition to the elements of claim 1, claim 2 of the '504 patent recites administration by "intravenous infusion"; claims 3 and 8 recite certain dosing amounts or regimens; and claim 7 additionally recites that "the patient is anemic."

Claim 9 further provides that the treatment results in an immediate and sustained decrease in mean levels of lactate dehydrogenase ("LDH") – a biochemical marker of hemolysis in PNH patients; and claim 10 provides that the immediate decrease in LDH occurs within one week of administration.

Claims 4-6 of the '504 patent also depend from claim 1, and recite additional elements specifying the claimed pharmaceutical composition. Claim 4 recites "a single unit dosage form," which claim 5 provides is "a 300 mg single unit dosage form." Claim 6 depends from claim 1, and recites "a 300 mg single-use formulation" that is "30 ml of a 10 mg/ml sterile, preservative free solution."

The claims of the '504 patent recite the complete amino acid sequence for SOLIRIS®: the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001, cols. 31-33, 35.) The '504 patent discloses that the claimed antibody binds C5, and provides Phase III clinical data from the "TRIUMPH" study confirming that the claimed antibody is safe and effective for treating PNH, and identifying the safe and effective dosing regimen for that use. (AMG1001, abstract, 3:17-19, 19:51-28:45.) The '504 patent also describes pharmaceutical compositions of eculizumab, including a "300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." (AMG1001, 4:21-24, 5:21-25, 16:30-33.)

F. Prosecution History of the '504 Patent and Related Applications

In prosecution leading to issuance of the '504 patent, as well as the prosecution of related U.S. Patent Nos. 9,718,880 ("the '880 patent") and 9,732,149 ("the '149 patent"), the Examiner considered much of the same art that Amgen now asserts. The Examiner made findings undermining Amgen's positions

here, including that (1) none of the art recited an antibody comprising SEQ ID NOs: 2 and 4, (2) a POSA "would not have been easily guided to mak[e] antibodies with these recited sequences," and (3) SOLIRIS® and its unique sequence was not "accessible to the public" as of March 15, 2007. (AMG1014, 790.)

For example, in finding claims 1-10 of the '504 patent to be novel and nonobvious, the Examiner discussed Amgen's asserted references Hillmen (AMG1004), Evans (AMG1007), and Wang (AMG1028) as a basis for rejection before ultimately finding the claims to be allowable over the art. (*See, e.g.*, AMG1014, 557-561, 623-628, 738-743.) The Examiner also considered Amgen's asserted references Hill (AMG1047) and Bell (AMG1005); U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Bowdish (AMG1006); and Mueller II (AMG1031), which is cumulative of Mueller (AMG1008). (*See, e.g.*, AMG1014, 499, 565-566.) Alexion did not mislead the Patent Office or fail to disclose references pertaining to Amgen's arguments here.

Notably, the Examiner confirmed a central fact that Amgen ignores in its Grounds: that Hillmen cites to ***Thomas*** (*i.e.*, "reference number 15" of Hillmen) as "disclosing more information about eculizumab." (AMG1014, 559, 623 (citing AMG1023).) Ultimately, the Examiner agreed that the prior art did not disclose or

suggest the specific claimed antibody sequence of the compositions recited in claims 1-10 of the '504 patent. (AMG1014, 790.)

The Examiner also credited the Declaration of Dr. Laural Boone (AMG1014, 763-770 ("the Boone Declaration") as showing that Alexion's clinical studies of the claimed antibody did not disclose its sequence or render it publicly accessible. (AMG1014, 790-91.) The Examiner relied on, among other things, Dr. Boone's showing that "neither doctors nor patients had any knowledge of the ... claimed sequences of the antibody used in the studies." (AMG1014, 767-770 ¶¶6-13; *id.*, 790.) While it is known ***today*** that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4 (AMG1014, 767, ¶6), a POSA as of March 15, 2007 would have only been guided by the teachings of the published literature that "eculizumab" had the IgG4 structure of Thomas.

III. PERSON OF ORDINARY SKILL IN THE ART OF THE '504 PATENT

Amgen contends that a POSA would have had "an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with **at least two years of experience in the field**"; that POSA would have had "skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics"; and that a POSA could work on a team with others having "specialized skills," including clinicians and formulation chemists. (Petition, 20-21.)

Alexion does not dispute Amgen's POSA definition, except to clarify – as the Board accepted (Paper No. 15, 19-21) – that the POSA would have **at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry**. (ALXN2022 ¶26.)

IV. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF CLAIMS 1-10 OF THE '504 PATENT

A. Amgen's Ground 1 Fails Because Amgen Cannot Show that Claims 1-3 and 7-10 Were Anticipated by Hillmen

Amgen's Ground 1 contends that claims 1-3 and 7-10 of the '504 patent were anticipated by the clinical trial publication Hillmen (AMG1004). As the Board recognized, Amgen's Ground 1 fails because Amgen cannot show how Hillmen disclosed the antibody recited in claims 1-3 and 7-10 of the '504 patent.

1. Hillmen Did Not Disclose an Antibody "Comprising a Heavy Chain Consisting of SEQ ID NO: 2 and a Light Chain Consisting of SEQ ID NO: 4"

Amgen's Ground 1 fails because Hillmen did not expressly or inherently disclose all the elements recited in claims 1-3 and 7-10 of the '504 patent. *See, e.g.*, *Therasense, Inc. v. Becton Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) ("Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim.").

As the Board recognized, Hillmen fails to disclose an antibody comprising the specific amino acid sequence recited in claims 1-3 and 7-10 of the '504 patent. (Paper No. 15, 33-35.) Simply put, there were ***no amino acid sequences*** for

"eculizumab" disclosed anywhere within the four corners of the Hillmen publication. (ALXN2022 ¶¶176, 178-181.) And to the extent Hillmen provided any guidance about the structure of "eculizumab," it identified "eculizumab" by reference to Thomas (AMG1023) – which in turn described a humanized monoclonal antibody with an "***IgG4***" heavy chain constant region having a very different amino acid sequence from the '504 patent's SEQ ID NO: 2. (*See supra* Section II.C.) Dr. Balthasar conceded that Hillmen's statements regarding what "eculizumab is" cited to Thomas; and he was unable to identify ***any*** disclosure within Hillmen or its cited references suggesting that "eculizumab" had a hybrid IgG2/IgG4 constant region, rather than the IgG4 constant region of Thomas. (ALXN2032 123:8-15, 125:13-126:11, 126:19-23, 127:19-128:1, 128:20-129:10, 132:7-12, 134:9-21.)

2. Hillmen Did Not Inherently Disclose the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claims 1-3 and 7-10 of the '504 Patent

To supply the claimed elements of SEQ ID NOs: 2 and 4 that are missing from Hillmen, Amgen admittedly must go ***outside*** the four corners of the references themselves, and turns to a either patent prosecution document created in 2017 that indisputably was not prior art available to a POSA as of March 15, 2007, or to amino acid sequences that Amgen mixes and matches from extraneous

documents (Bowdish, Mueller, and Evans) that were not cited or referenced anywhere in Hillmen. (Petition, 27, 30-32; ALXN2022 ¶¶182-183.)

For example, Amgen alleges inherent anticipation of claims 1-3 and 7-10 on the ground that ***today*** – years after the '504 patent's March 15, 2007 priority date – it is known that the clinical studies underlying Hillmen ***actually*** used an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. (*See, e.g.*, Petition, 27 (citing the May 11, 2017 Declaration of Dr. Laural Boone, AMG1014, 765, 7767).) But Amgen is mistaken on the law. The mere naming of an investigational product (*e.g.*, "eculizumab") in a publication does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as of the priority date. *See, e.g.*, *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018). Likewise, post-filing information showing that the later-claimed antibody sequence was actually used in the studies underlying prior art clinical publications is insufficient to give rise to inherent anticipation, when those publications would have guided a POSA to a different, unclaimed antibody sequence. *See, e.g.*, *id.*; *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018).

B. Amgen's Grounds 2 and 3 Fail Because Amgen Cannot Show that Claims 4 and 5 Were Obvious Over Hillmen and Bell, or that Claim 6 Was Obvious Over Hillmen in Combination with Bell and Wang

Amgen's Grounds 2 and 3 contend that claims 4 and 5 of the '504 patent would have been obvious in view Hillmen and Bell (AMG1005), and Ground 3 contends that claim 6 would have been obvious over Hillmen in combination with Bell and Wang (AMG1028). As Grounds 2 and 3 raise overlapping issues, we address them together.

1. Hillmen and Bell (and Wang), in any Combination, Did Not Teach the Specific Claimed Antibody of Claims 4-6, or its Use in Treating Patients Suffering from PNH

Amgen's Grounds 2 and 3, like its Ground 1, rely upon Hillmen as allegedly disclosing the claimed amino acid sequence of claims 4-6 of the '504 patent. (*See* Petition, 25-31, 37, 41-42.) But nothing in Hillmen expressly or inherently disclosed that claimed sequence. (*See supra* Section IV.A.) As the Board agreed, Hillmen identified "eculizumab" as the ***IgG4*** isotype antibody of Thomas. (*See supra* Sections II.C, IV.A.) Likewise, Bell (AMG1005) and Wang (AMG1028) were silent on the sequence for "eculizumab." (*See, e.g.*, Petition, 45-47; ALXN2032, 146:17-25, 256:15-22.) And Bell, like Hillmen (which corresponds

to one of Bell's described studies), pointed to Thomas as a reference for "eculizumab."[4] (AMG1005, ¶[0052]; ALXN2022 ¶¶188, 196-199.)

Thus, nothing in Hillmen, Bell or Wang would have motivated a POSA to abandon Thomas's IgG4 antibody that they cite as "eculizumab," and instead attempt treating PNH using a different, unknown antibody with the sequence recited in the '504 patent, which was not disclosed anywhere in those documents. (ALXN2022 ¶¶187-190; *supra* Section IV.A.)

Nor would a POSA have reasonably expected success in using such an uncharacterized antibody in a "method of treating patients suffering from [PNH]," as an antibody's therapeutic effects or suitability for human administration could not have been reasonably predicted based on its amino acid sequence alone. (*See supra* Section II.A.) A POSA would have had no way to know, or even expect, that the then-undisclosed, uncharacterized antibody of the '504 patent would have therapeutic effect or be safe for administration. (ALXN2022 ¶¶189, 225-234.)

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[4] While Bell also cited Evans for the disclosure of antibody fragments, a POSA would have understood that Bell's regarding "eculizumab" to refer to Thomas, not Evans, because Evans did not disclose any full-length humanized antibodies. (*See, e.g.*, ALXN2022 ¶¶197-199, ALXN2032, 158:2-8, 159:14-160:3, 160:18-162:11, 163:5-15.)

2. The Claimed Pharmaceutical Compositions Were Not Taught by Hillmen and Bell (Claims 4 and 5) or Hillmen, Bell, and Wang (Claim 6)

With nothing in Hillmen and Bell (or Wang) disclosing an antibody with the specific sequence recited in claims 4-6 of the '504 patent, a POSA would not have been motivated to make, or reasonably expected to succeed in making, a "pharmaceutical composition" of such an uncharacterized antibody, as claims 4-6 require. (ALXN2024, ¶¶64-91.) Nor would a POSA have been motivated to use any such compositions in a "method of treating a patient suffering from [PNH]." (ALXN2024 ¶¶64-91; ALXN2022 ¶¶190-191.)

As of March 15, 2007, antibody formulation was an empirical endeavor, and a POSA could not have reasonably expected that any particular uncharacterized antibody would be capable of development into any pharmaceutical composition suitable for human therapeutic use, or treatment of PNH in particular. (ALXN2024 ¶¶41-56, 71.) That concern would apply at both the commercial scale and the experimental scale, because a POSA would understand that pharmaceutical compositions needed to meet basic stability requirements to avoid harm to patients. (ALXN2024 ¶40.) A POSA particularly would have had no motivation, and no reasonable expectation of success, to formulate an uncharacterized antibody having a novel, hybrid "IgG2/IgG4" constant region

when nothing in the literature reported the formulation of such an antibody, on a commercial or experimental scale. (ALXN2024 ¶¶69-75.)

Nor would Bell or Wang have motivated a POSA to make the specific composition of claim 6 – "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution" – or have given a POSA a reasonable expectation of success in doing so. Bell described no specific pharmaceutical compositions, and only suggested that an undefined composition was used for purposes of administering "eculizumab" by intravenous infusion to treat PNH. (ALXN2024 ¶78; ALXN2022 ¶¶190-191.) A POSA without the benefit of hindsight would not have been motivated to combine Bell's teachings of an undefined composition ***for injection*** with Wang (AMG1028), which broadly concerned administration of a wide range of anti-C5 antibodies and fragments ***by inhalation through a "nebulizer"*** device for treating respiratory diseases. (AMG1028, ¶¶[0169]-[0173]; ALXN2024 ¶¶81-83; ALXN2032 257:24-258:15, 259:6-9.) *See, e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013).

Further, nothing in Wang disclosed a pharmaceutical composition containing a "10 mg/ml antibody solution" of "eculizumab" in a "single-use dosage form." (ALXN2024 ¶80.) Even if a POSA had associated Wang's "eculizumab" with the claimed antibody sequence – which Hillmen, Bell and Wang did ***not*** do – nothing

in Wang would have motivated a POSA to make such a composition of "eculizumab," or given a POSA a reasonable expectation of success in doing so. Wang did not specifically teach "eculizumab formulations of between 1 and 30 mg/ml" as Amgen claims (Petition, 41), but rather disclosed wide ranges including 1-30 mg/ml, 40-200 mg/ml and 1-200 mg/ml that hypothetically might be used ***for nebulization*** of various unrelated "anti-C5" antibodies and derivative compounds. (AMG1028, ¶¶[0067], [0130], [0170]-[0172], Fig. 10; ALXN2024 ¶¶84-86.)

Amgen's hindsight-driven combination of Bell and Wang is based on a misunderstanding of what Wang would have taught a POSA. According to Amgen, a POSA would have been motivated to make this combination, and arrive at the claimed 10 mg/ml concentration, because Wang allegedly taught that "eculizumab, formulated at a concentration of 1 to 30 mg/mL, would be ***sufficiently stable and active*** to be used as a drug." (Petition, 42 n.21; *see also* AMG1002 ¶113 ("[A] POSA would have arrived at a concentration of 10 mg/ml because Wang disclosed that eculizumab could be ***stably formulated*** at a concentration between 1 and 30 mg/ml, a range that encompasses 10 mg/ml.") But there is no such disclosure in Wang. Regarding stability, Wang only contained a highly general, hypothetical statement that compositions of undefined anti-C5 antibodies "may be stable" over a wide concentration range of 1-200 mg/ml

(AMG1028 ¶[0067]) – a statement that a POSA would ***not*** have taken as fact with respect to every specific antibody and concentration point. (ALXN2024 ¶86.)

A POSA would have understood that Wang's data, including the "SDS-PAGE" and "HPLC" studies of an unknown concentration of "eculizumab" that Amgen cites (Petition, 42 n.21), did ***not*** teach anything about stability pertinent to a pharmaceutical composition suitable for human administration, including for PNH. (ALXN2024 ¶¶87-88.) A POSA seeking a pharmaceutical composition of "eculizumab" for treatment of PNH would have been motivated to seek a composition with suitable stability under conditions pertinent to storage and transportation (*e.g.*, stability over time, and under different temperatures) to confirm that the product would not degrade prior to human administration to the point where it loses therapeutic effect or becomes dangerous to patients (*e.g.*, potentially immunogenic). (ALXN2024 ¶¶44-56, 84-88.); AMG1002 ¶107 ("Developing any given dosage form requires testing, validating, manufacturing, storing, and transporting that dosage form.") Wang disclosed no such data. Instead, Wang's studies of an "eculizumab" solution (at 30 mg/ml or an unspecified concentration) were limited to information irrelevant to the '504 patent, such as the formation of inhalable particles, and the "integrity of the nebulized antibody" when passed through various nebulizer mouthpieces – with ***no***

information on degradation over time or under storage conditions.[5] (AMG1028, ¶¶[0171]-[0173]; ALXN2024 ¶¶83-88.)

Bell and Wang also would not have motivated a POSA to make a "300 mg single-usage dosage form." Bell disclosed the administration of 600 mg and 900 mg dosages, but did not describe any particular dosage units or dosage forms. (ALXN2024 ¶91.) Amgen disregards the inconvenience of and greater possibility of provider error from having to use multiple 300 mg vials on each administration; and that antibody compositions were commonly available in multiple dosage forms of different strengths. (ALXN2024 ¶91.)

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[5] Amgen's reliance on other, unrelated antibodies commercially formulated at 10 mg/ml (Petition at 43, citing AMG1029, Table 1; AMG1030, Table 1) is misplaced, because (1) formulations of other antibodies could not reasonably be expected to work for "eculizumab"; (2) only ***one*** commercial product was a full-length humanized antibody in a 10 mg/ml solution; and (3) many commercial antibodies were not sufficiently stable to be formulated in solution in ***any*** concentration. (ALXN2024, ¶¶39-54, 88; AMG1029, 2-5.)

C. Amgen's Grounds 4 and 5 Fail Because Amgen Cannot Show that the '504 Patent Claims Would Have Been Obvious Over Bell, Bowdish and Evans (Claims 1-5, 7-10) or Bell, Wang, Bowdish and Evans (Claim 6)

Amgen's Ground 4 contends that claims 1-5 and 7-10 of the '504 patent would have been obvious over a combination of Bell (AMG1005), Bowdish (AMG1006) and Evans (AMG1007); and Amgen's Ground 5 contends that claim 6 would have been obvious over a combination of Bell, Wang (AMG1028), Bowdish and Evans. As Grounds 4 and 5 raise overlapping issues, we address them together.

Amgen's Grounds 4 and 5 fail because they are founded in an impermissible hindsight-driven premise: that a POSA considering Bell's description of "eculizumab" would have ignored what Bell ***actually*** taught about the structure of "eculizumab" – that it was the full-length IgG4-isotype antibody of Thomas – and would have instead turned to Bowdish and Evans, which make no mention of "eculizumab" or any other full-length humanized monoclonal antibodies known to bind C5 or have any therapeutic utility. (Petition, 45-54, 60-61.)

Without the benefit of hindsight, a POSA as of March 15, 2007 would have ***no reason*** to select and combine the sequences from Bowdish and Evans that Amgen cherry-picks to recreate the unique claimed sequences of the '504 patent; would have had ***no motivation*** to make, and treat PNH patients with, a new, untested antibody with no known or reasonably predictable binding, biological or

therapeutic properties; and would have ***no reasonable expectation*** that such a new untested antibody would be suitable for a "method of treating a patient suffering from [PNH]," or suitable for formulation in a "pharmaceutical composition" for such treatment. (ALXN2022 ¶¶192-234; ALXN2024 ¶¶64-91.)

Even if Bowdish and Evans in combination disclosed amino acid sequences corresponding to SEQ ID NOs: 2 and 4 – which they did not – the combination of Bell, Bowdish and Evans did not motivate a POSA to use an uncharacterized antibody having that sequence in a "method of treating a patient suffering from [PNH]," or provide them with a reasonable expectation of success in doing so. There was no evidence that an antibody with SEQ ID NOs: 2 and 4 had ***ever*** been tested in people for therapeutic effect and tolerability, or even *in vitro* activity in binding C5 and blocking complement. *See, e.g.*, *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1383 (Fed. Cir. 2019) (finding no reasonable expectation of success for a method of treatment where "the asserted references do not disclose ***any*** data" regarding the effect of the claimed drug on the claimed disease) (emphasis in original). Nor would Bell, Bowdish, Evans, or Wang have taught a POSA to make pharmaceutical compositions of such an uncharacterized antibody – particularly with respect to the specific composition of claim 6.

The *Helsinn* decision cited by the Board (Paper No. 15, 46) confirms Amgen's failure to support Grounds 4-5 with any evidence prior to March 15,

2007 that the claimed antibody would be suitable for use in a pharmaceutical composition to treat PNH (as claim 1 requires), or any other condition. In *Helsinn*, the Court found that claims to pharmaceutical compositions for a clinical use ("reducing the likelihood of emesis") were ready for patenting even though Phase III clinical trials were not complete before the critical date, because there was "***overwhelming evidence . . . the patented invention would work for its intended purpose***," including full Phase II and preliminary Phase III clinical trial results for the claimed composition over a seven year period. *See Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 855 F.3d 1356, 1372-1375 (Fed. Cir. 2017). With respect to the claimed methods of treatment and compositions of the '504 patent, however, a POSA would have seen no clinical studies, no formulation studies, no animal studies, no *in vitro* studies of complement-blocking activity, and no C5 binding studies. (*See supra* Section II.D.)

1. Bell (and Wang) Did Not Disclose the Claimed Sequence, and Would Not Have Motivated a POSA to Make the Claimed Antibody

In Ground 4, Amgen relies on Bell (AMG1005) for its disclosure of "eculizumab" – which Bell identifies by name – as allegedly supplying every element of claims 1-5 and 7-10 of the '504 patent except the claimed amino acid sequence. (Petition, 45; AMG1002 ¶¶120, 130.) According to Amgen, a POSA would have specifically been motivated to make and use pharmaceutical

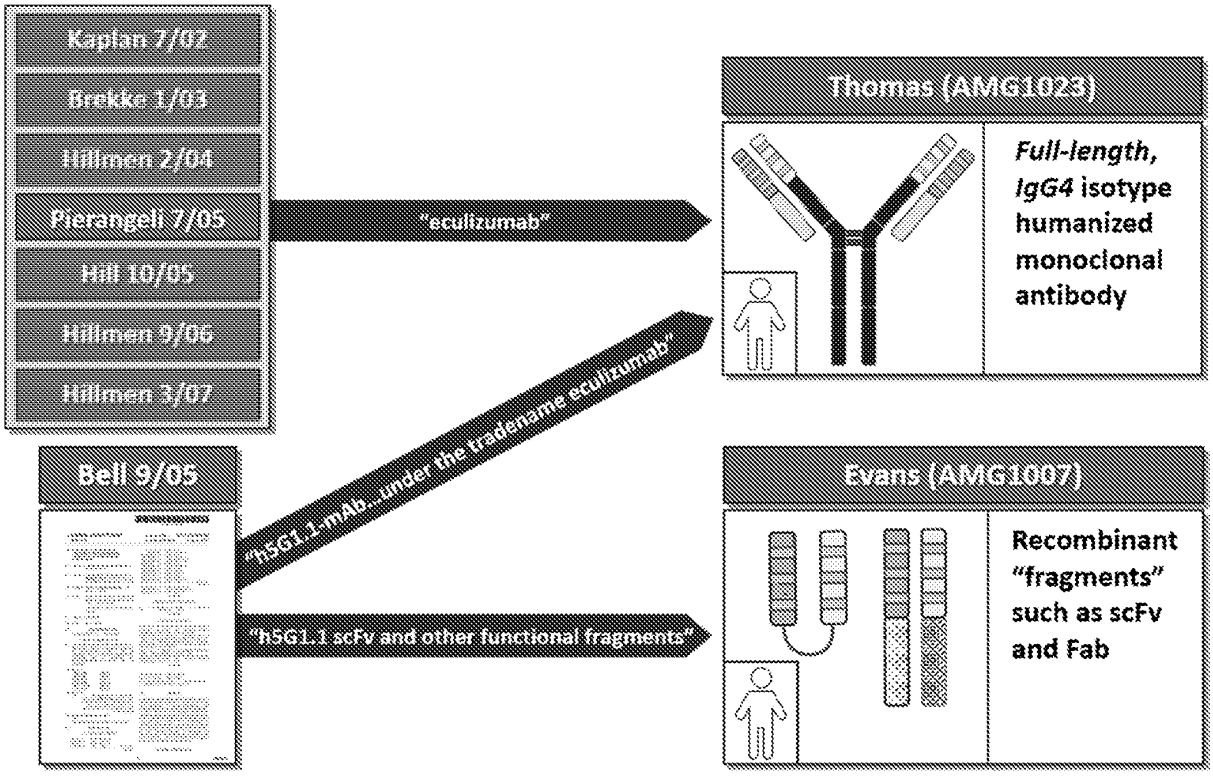
compositions of Bell's "eculizumab" antibody, in view of Bell's teaching that "eculizumab" binds C5, blocks its cleavage, and successfully treats PNH. (*See, e.g.*, AMG1002, ¶¶129-32; ALXN2032, 152:13-154: 7; ALXN2022 ¶¶196-196, 200.) For example, Dr. Balthasar admitted that Bell, along with Hillmen and Hill, motivated a POSA as of March 15, 2007 to "make and use the eculizumab antibody that they describe" (ALXN2032, 154:1-7.)

Amgen further concedes that – just like Hillmen – ***nothing*** in Bell (or Wang) disclosed the amino acid sequence for "eculizumab," or provided the specific amino acid sequence recited in claims 1-10 of the '504 patent. (Petition, 45-47; AMG1002, ¶130 (admitting that Bell did not disclose "the requirement that the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4"); ALXN2032, 146:17-25, 257:13-18; ALXN2022 ¶¶194-197.) And, as Dr. Balthasar admitted, nothing in Bell disclosed or suggested to a POSA that "eculizumab" had a hybrid IgG2/G4 heavy chain constant region. (*See, e.g.*, ALXN2032, 151:4-12, 160:7-9; ALXN2022 ¶¶194-197, 204.)

Rather, as the Board recognized, to the extent Bell disclosed anything about the structure of "eculizumab," it would have directed a POSA towards an antibody with an ***IgG4*** heavy chain constant region – as did Hillmen and the many other references prior to March 15, 2007 pointing to Thomas (AMG1023) for disclosure

of "eculizumab." (ALXN2022 ¶¶119-124; *supra* Section II.C.) Accordingly, a POSA reading Bell would have envisioned "eculizumab" to have a different structure and amino acid sequence from an antibody consisting of SEQ ID NOs: 2 and 4 as claimed in the '504 patent – which again, Amgen concedes was not disclosed anywhere in Bell. (ALXN2022 ¶¶194-95.)

Specifically, paragraph [0052] of Bell cited two documents – Thomas (AMG1023) and Evans (AMG1007) – for disclosing "[m]ethods for the preparation of h5G1.1-mAb, h5G1.1-scFv, and other functional fragments," and further identified "[t]he antibody h5G1.1-mAb" in this context as "eculizumab." (AMG1005 ¶[0052]; ALXN2022 ¶¶196-199; ALXN2032, 160:18-162:11.) As Dr. Casadevall's **Figure 9** illustrates, a POSA as of March 15, 2007 reading Bell would have understood that, between Thomas and Evans, only Thomas could have disclosed "eculizumab," because only Thomas disclosed an intact, full-length humanized "h5G1.1" antibody, while Evans disclosed scFvs and other "fragments." (ALXN2022 ¶¶196-199; ALXN2032, 163:5-15, 163:25-164:5, 164:12-16; 169:13-18; *see supra* 5-6, Section IV.B.1.)



2. A POSA Would Not Have Been Motivated to Combine Bell's Teachings with Bowdish and Evans, or to Make the Specific Claimed Sequence

For the same reason Amgen contends that Bell would have motivated a POSA to make the specific monoclonal antibody "eculizumab" – a C5-binding, clinically-tested antibody that Bell and other clinical literature consistently described as having an ***IgG4*** isotype – a POSA would ***not*** have been motivated to disregard Bell's teachings, and instead make a different antibody with the uniquely-engineered amino acid sequence of the methods claimed in the '504 patent.

A POSA would not have known of an antibody having the specific sequence claimed in the '504 patent – which differs from Thomas's antibody that Bell identifies as "eculizumab" – and would not have been aware that an antibody with the claimed sequence had ever been tested *in vitro* or clinically. (ALXN2022 ¶¶152-153, 194-195, 207; *see supra* Section II.B.) In view of the unpredictability of therapeutic antibody design, a POSA knowing of the clinically-proven anti-C5 antibody "eculizumab" would not have been motivated to make an antibody with a different, unstudied amino acid sequence – which might neither bind C5, nor be therapeutically useful or suitable for human administration. (ALXN2022 ¶¶225-234.)

Amgen agrees, arguing in Ground 4 that POSA as of March 15, 2007 reading Bell would have been specifically motivated to make "eculizumab," and not other, different antibodies. (Petition, 45-47; AMG1002, ¶119-124; *see also* ALXN2032, 154:1-7.) But then, Amgen disregards what Bell and other literature ***actually*** taught actually about "eculizumab" – that it was an IgG4 isotype antibody as described in Thomas. Instead, Amgen implausibly contends that a POSA seeking the sequence of "eculizumab" would have turned to ***Bowdish*** – a document that a POSA would have had no reason to associate with "eculizumab." There is no reason why a POSA without the benefit of hindsight would have jumped from Bell to Bowdish for an understanding of "eculizumab," as Amgen

contends. *See, e.g.*, *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Amgen's hindsight-driven rationale for combining Bell (regarding the anti-C5 antibody "eculizumab") with Bowdish (regarding a TPO-mimetic fusion compound) falls apart under scrutiny, because it depends on assumptions that lack support or even expressly contradict the art's teachings as of March 15, 2007. For example, Amgen asserts that Bowdish was an "eculizumab teaching[] in the art." (Petition, 55.) But, like Hillmen and Hill, Bell did ***not*** cite to Bowdish (for "eculizumab" or otherwise), and Bowdish itself made no mention of "eculizumab." (ALXN2022 ¶¶200-203; ALXN2032, 170:5-10, 199:9-12.) Bowdish did not concern the development of anti-C5 antibodies at all, but rather focused on generating peptide-mimetic fusion compounds having nothing to do with C5 binding or treatment of PNH. (*See, e.g.*, AMG1006 ¶[0006]; ALXN2022 ¶¶161-162, 165, 202-203; ALXN2032, 174:2-12, 175:22-176:6, 180:8-11, 181:5-15.)

Dr. Balthasar's only stated "reason" for a POSA to "look to Bowdish" and "link" Bowdish to Bell (AMG1002, ¶¶140, 169) further reveals his use of improper hindsight. (ALXN2022 ¶¶200-208.) As Dr. Balthasar contends, a POSA would have connected Bell and Bowdish because (1) Bell's "eculizumab was . . . known to be [a] humanized 5G1.1 with a hybrid IgG2/IgG4 constant region," and (2) "Bowdish . . . provides most of the sequence of humanized 5G1.1 with a hybrid

IgG2/IgG4 constant region." (AMG1002, ¶140; ALXN2032, 196:15-23, 197:15-25; *see also* Petition, 45-46.) That "reason" falls apart under scrutiny.

First, Amgen and Dr. Balthasar are wrong to suggest that Bowdish identified its TPO-mimetic compound as relating to "humanized 5G1.1" or "h5G1.1." (*See, e.g.*, Petition, 46 (claiming that Bowdish "explicitly direct[ed]" a POSA to look to Evans for "information" on the "h5G1.1 antibody" used to generate Bowdish's TPO-mimetic compound).) As Dr. Balthasar admitted, Bowdish used the term "5G1.1," not "h5G1.1" or "humanized 5G1.1"; and nothing in Bowdish said that the "scaffold" antibody used to generate its TPO-mimetic compound was a "humanized antibody." (ALXN32, 199:19-23, 200:24-200:2; ALXN2022 ¶¶165, 205, 223.) Rather, Bowdish references the '283 application (issued as Evans) for "[c]onstruction of 5G1.1" – a term that, as discussed above, refers a ***mouse*** antibody when used in Evans. (*See supra* Section IV.B.1.) Even if a POSA did understand Bowdish to be referencing Evans for disclosure of an "h5G1.1 antibody" that was used as Bowdish's "scaffold," they would have found none, because Evans did not disclose ***any*** full length humanized antibodies derived from "5G1.1." **(**ALXN2032, 163:5-15**;** ALXN2022 ¶224.)

Second, Bell suggested that "eculizumab" had an ***IgG4*** constant region, and nothing in Bell pointed towards a hybrid IgG2/IgG4 constant region. (*See,* ALXN2032, 146:17-25, 151:3-12, 160:7-9.) Amgen's attempt to associate

"eculizumab" with a hybrid IgG2/IgG4 structure ignores Bell entirely, and instead relies on ***non-prior art*** information, and Mueller (AMG1008), which does not mention "eculizumab" at all. (ALXN2032, 55:5-57:1, 58:23-59:3, 59:23-60:6, 60:13-16, 61:13-62:4, 63:5-64:19.) For example, Amgen relies on out-of-context statements made in 2011 from the file history of U.S. App. No. 11/127,438 ("the '438 application") – which is not related to the '504 patent.[6] (*See, e.g.*, Petition, 12 (citing AMG1049, 838-39, 855).) These non-prior art statements cite ***nothing*** dated prior to March 15, 2007 identifying "eculizumab" as having a hybrid IgG2/IgG4 constant region. Instead, they cite Mueller II (AMG1031) – a document that makes no mention of "eculizumab," and merely identified "h5G1.1 HuG4" and "h5G1.1 HuG2/G4" as experimental controls – of which ***only*** the "HuG4" antibody was described as an "anti-C5 antibody." (AMG1031, 442-44; *see also* AMG1008, 11:36-12:32; ALXN2022 ¶¶167, 240; ALXN2032, 235:6-19, 237:8-15, 237:25-238:5, 238:13-19.) The prior art must be viewed "***without the***

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[6] Amgen and Dr. Balthasar also rely on a non-prior art publication from November 2007 (AMG1033), and a 2017 submission from an Alexion employee during prosecution of the '504 patent (AMG1014, 763-770.) (*See* Petition at 13, 27, 38 n. 17, 50 n. 24; AMG1002, ¶¶11, 56; ALXN2032, 55:5-20, 56:24-57:1, 58:23-59:3, 64:8-14.)

benefit of the invention" – and Amgen failed to do so by disregarding the overwhelming teaching by Bell and the other art prior to March 15, 2007 that "eculizumab" was described as the IgG4 antibody of Thomas. *See Neptune Generics, LLC v. Eli Lilly & Co.*, IPR2016-00237, Paper 84 at 74-77 (Oct. 5, 2017), *aff'd*, 921 F.3d 1372 (Fed. Cir. 2019).

Third, Dr. Balthasar admits that nothing in Bowdish referred to its TPO-mimetic compound as having an "IgG2/IgG4" constant region structure. (ALXN2032, 212:22-213:2, 214:2-7.) And Dr. Balthasar fails to prove his contention that a POSA would have identified the hybrid IgG2/IgG4 structure of Bowdish's TPO-mimetic compound using "BLAST or a similar search tool." (ALXN2032, 212:22-213:2, 214:2-7.) Bowdish itself did not guide a POSA to apply such "search tools" to its peptide-mimetic compounds. (ALXN2022 ¶205; ALXN2032, 214:19-24.) Further, Amgen presents ***no evidence*** of "the search results that a POSA would have gotten if, prior to March 15, 2007, they had tried to evaluate the sequences in Bowdish Figures 13A and 13B using 'BLAST or a similar search tool.'" (ALXN2032, 214:25-215:8.)

A POSA also would not have connected Bell and Bowdish simply because Bowdish used the term "5G1.1." (ALXN2022 ¶207.) As Dr. Balthasar testified, a POSA would have understood that the term "5G1.1" alone was ***not*** limited to "eculizumab," and depending on the context, could refer to the original "5G1.1"

hybridoma, the "5G1.1" mouse antibody from the hybridoma (as used in Evans), as well as many possible "variants" of that antibody with different structures and sequences. (ALXN2032, 98:22-99:8, 100:16-24, 165:5-21; 169:6-18; 202:24-203:16; ALXN2022 ¶¶96-97.) In contrast, the term "eculizumab" as used in Bell referred to only one humanized monoclonal antibody, having a specific (but unknown) amino acid sequence. (*See supra* Section II.B.) A POSA looking for more information on "eculizumab" thus would have considered the art's pertinent teachings regarding "***eculizumab*" – *not*** the far broader term ***"5G1.1."*** (ALXN2022 ¶207.) And a POSA certainly would not have focused on Bowdish, which contained no data showing that its TPO-mimetic compound or its "scaffold" antibody would bind C5 or treat complement-mediated conditions such as PNH. (ALXN2022 ¶¶203, 233-234.)

Amgen's Grounds 4 and 5 improperly use the '504 patent as a ***reference point*** for reconstructing the uniquely-engineered amino acid sequence of the claimed antibody, from sequences selectively combined from Bowdish and Evans. (*See, e.g.*, AMG1002 Figs. 4-7, 13 (hindsight sequence comparisons between the '504 patent and select sequences from Bowdish or Evans), and Figs. 3, 10, 11 and 12 (using green coloration to signify sequences corresponding in hindsight to the '504 patent).) As Dr. Balthasar concedes, a POSA could not have made any of these comparisons, because a POSA would not have had access to the sequence of

the '504 patent. (ALXN2032, 222:7-224:24.) Further, Amgen and Dr. Balthasar disclose ***only*** the carefully-selected prior art sequences from Bowdish and Evans that they knew ***in hindsight*** would "align[] perfectly" with the '504 patent sequence that was not available to a POSA prior to March 15, 2007. (*See, e.g.*, AMG1002, ¶¶52-53, 55, 80.) But "working backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019).

For example, Amgen presented hindsight alignments between the '504 patent and portions of Evans SEQ ID NO: 20 – a humanized scFv compound (AMG1002, ¶55) – but withheld from the Board the many other disclosures in Evans that would ***not*** have aligned with the claimed sequence, including:

- Evans Figures 18 and 19 – the variable regions of the mouse antibody that Bowdish references (with respect to the '283 application) for "[c]onstruction of 5G1.1" (ALXN2022 ¶¶215-216; ALXN2032, 169:19-170:4) ;
- The "Fd" molecules of Evans SEQ ID NOs: 11, and 12, which a POSA would have understood were more "complete" fragments of a humanized antibody than an scFv, and provide sequences in the constant

region (and for SEQ ID NO:11, the variable region) that do not align with the'504 patent sequence (ALXN2022 ¶¶130, 159); and

- The eight other humanized "scFv" molecules of Evans, which Dr. Balthasar admits were different from SEQ ID NO: 20 (*see* AMG1007, 42:56-45:4; ALXN2022 ¶158; ALXN2032, 222:22-223:9)

Even if Bowdish and Evans were fully combined, a POSA would not have been directed to the complete amino acid sequence recited in claims 1-10 of the '504 patent. Among other things, a POSA would not have reasonably assumed that "heavy chain CDR3" referenced in Bowdish was the same as the heavy chain CDR3 described in Evans for humanized scFv compounds, which are ***not*** full-length structures like the TPO-mimetic compound of Evans. (ALXN2022 ¶¶217-221.) Even if a POSA reading Bowdish were to consider Evans for its disclosure of heavy chain CDR3 sequences, Evans allows for multiple options, and nothing in Bowdish or Evans indicates which, if any, were used in the "scaffold" antibody used to produce Bowdish's TPO-mimetic peptide. (AMG1006, [0005]-[0006], [0191]-[0192]; [ALXN2022 ¶¶217-221.)

Amgen further uses improper hindsight by ignoring the disclosure of variable region sequences in ***Thomas*** (AMG1023), which Bell cites alongside Evans. If a POSA reading Bell were to have followed its reference to Thomas for "eculizumab," they would have been directed to variable region sequences that

would ***not*** "align perfectly" with the non-prior art '504 patent sequence. (ALXN2022 ¶251.) For example, all of the light chain regions disclosed for "5G1.1" and various mouse and humanized compounds derived from "5G1.1" disclosed in Thomas have an arginine ("R") at light chain position 38, whereas the claimed sequence of the '504 patent has a glutamine ("Gln"). (AMG1023, 1392, 1396; ALXN2022 ¶251.)

3. The Combination of Bell, Bowdish and Evans (and Wang) Would Not Have Motivated a POSA to Practice the Claimed Treatment Methods and Pharmaceutical Compositions of the '504 Patent, or Given a POSA a Reasonable Expectation of Success in Doing So

Even if the claimed amino acid sequence of the '504 patent was disclosed by Bowdish and Evans – which Amgen has not shown – Amgen still cannot show that the claimed methods of treatment and pharmaceutical compositions of the '504 patent would have been obvious. First, nothing in Bowdish and Evans would have motivated a POSA to "treat[] a patient suffering from PNH" with the claimed antibody, or that the claimed antibody "binds C5." As discussed above, a POSA would not have understood Bowdish and Evans to disclose "eculizumab" or any full-length humanized anti-C5 antibody. (*See supra* Section IV.C.2.)

Second, nothing in Bowdish, Evans, or any other published literature report that an antibody having the claimed sequence of the '504 patent had been clinically tested. (ALXN2022 ¶¶134-135.) The only antibody identified in the pre-March

15, 2007 literature as having been tested in clinical trials for safety and efficacy in treating PNH, was the ***IgG4*** antibody of Thomas. (*See supra* Section II.C.) With no binding data, *in vitro* or animal testing, or clinical testing of the claimed antibody that Amgen assembles in hindsight from Bowdish and Evans, a POSA would have had no motivation to use that antibody in the claimed methods of treating PNH or pharmaceutical compositions for that use. (ALXN2022 ¶¶78-91, 134-137.) *See, e.g.*, *Endo*, 894 F.3d at 1380. And given the unpredictability of humanized monoclonal antibody design and development, a POSA would have had no reasonable expectation of success in practicing the claimed methods of treating patients suffering from PNH. (ALXN2022 ¶¶78-91, 134-137, 227-228, 257-259.) *OSI Pharms.*, 939 F.3d at 1383.

A POSA also would not have been motivated to make a "IgG2/IgG4" isotype – which Bowdish and Evans did not disclose – based on references that Amgen cites regarding purported benefits of that hybrid (*e.g.*, reduced immunogenicity). (Petition, 17, 52-54.) A POSA "would not have turned to a [hybrid isotype] approach to solve an undefined problem," when a POSA would have seen clinical literature pointing Thomas's IgG4 antibody as safe and effective to treat PNH, and understood the purported benefits of IgG2/IgG4 hybrids to be speculative and clinically untested. (ALXN2022 ¶¶78-91, 134-137, 227-228, 242, 257-258.) *See Amerigen Pharms.*, 913 F.3d at 1087.

Nor would Bowdish, Evans, Bell and Wang have motivated a POSA to make any pharmaceutical composition of the claimed antibody for use in treating patients suffering from PNH. A POSA would not have reasonably expected that an uncharacterized antibody would be suitable for formulation at all – particularly if it were thought to have a new hybrid isotype like IgG2/G4. (ALXN2024 ¶¶68-75; *see supra* Section IV.B.2.) Nothing in Bowdish, Evans, Bell or Wang would have motivated a POSA to make the specific claimed composition of claim 6: a "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." (ALXN2044 ¶¶76-91; *see supra* Section IV.B.2.)

D. Amgen's Grounds 6 and 7 Fail Because Amgen Cannot Show that the '504 Patent Claims Would Have Been Obvious Over the Combination of Bell, Mueller and Evans (Claims 1-5, 7-10) or Bell, Wang, Mueller and Evans (Claim 6)

Amgen's Ground 6 contends that claims 1-5 and 7-10 of the '504 patent would have been obvious over a combination of Bell (AMG1005), Mueller (AMG1008) and Evans (AMG1007); and Amgen's Ground 7 contends that claim 6 would have been obvious over a combination of Bell, Wang (AMG1028), Mueller and Evans. As Grounds 6 and 7 raise overlapping issues and both Grounds fail for at least the same reasons, we address both Grounds together.

As the Board found, Amgen's Grounds 6 and 7 fail, because they rely upon Amgen's present-day knowledge of the antibody sequence recited in claims 1-10 of the '504 patent, which Amgen uses as a guide to pick and combine sequences

that it knows in hindsight will align it. Without the benefit of hindsight, a POSA would have had ***no motivation*** to combine Evans with Mueller to obtain the claimed antibody of the '504 patent; would have had ***no reason*** to pick and combine the specific sequences that Amgen selects from Evans and Mueller to reconstruct the claimed antibody of the '504 patent; and would have had ***no reasonable expectation*** that such a new untested antibody would be suitable for a "method of treating a patient suffering from [PNH]," or for formulation in a pharmaceutical composition for such treatment, as claims 1-10 all require. (ALXN2022 ¶¶235-261.) As stated above, even if Amgen's combination of Evans and Mueller were made, a POSA would not have been motivated to practice, or reasonably expected success in practicing, the specific method of treating PNH and pharmaceutical compositions of the '504 patent. (*See supra* Section II.A.)

As with Ground 4, Amgen's Ground 6 relies on Bell (AMG1005) for its disclosure of "eculizumab," as allegedly supplying every element of claims 1-5 and 7-10 except the claimed amino acid sequence. (Petition, 62; AMG1002 ¶¶172, 176.) As stated above, Bell and the overwhelming weight of the other art would have directed a POSA towards the IgG4 antibody of Thomas. (*See supra* Section II.C.)

Amgen cannot explain why a POSA would have leapt from Bell to Mueller, which Bell does not cite. Amgen states that a POSA would have been motivated to

do so by Mueller's teachings regarding whether its hybrid "G2/G4" constant regions would "activate the complement system." (Petition, 64.) But a POSA would have understood Thomas's antibody, cited for "eculizumab," to have been proven safe and effective in Phase II and Phase III clinical trials for treatment of PNH. (ALXN2022 ¶¶122-124.) A POSA with the proven clinical evidence pointing towards Thomas's antibody would have had no motivation to change it. *See Amerigen Pharms.*, 913 F.3d at 1087.

A POSA also would not have combined Bell and Mueller simply because they both reference "h5G1.1" – a broad term that could potentially refer to a number of different antibody structures. (ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14.) The only full-length "h5G1.1" antibody referenced in Bell is the IgG4 isotype antibody of Thomas that Bell cites as describing "eculizumab." (*See supra* 48-49.)

Nor would a POSA have been motivated to combine Evans with Mueller, when neither document cited to the other (Paper No. 15, 57; ALXN2022 ¶240; ALXN2032 170:21-171:20, 243:16-20), and they addressed very different technological problems. *See, e.g.*, *Broadcom*, 732 F.3d at 1334. While Evans characterized and tested the complement-blocking activity of the anti-C5 mouse "5G1.1" antibody and certain derivative compounds, Mueller studied antibodies to the porcine "VCAM" protein for treating or diagnosing human rejection of

transplanted animal tissue, and did not include any experiments or data on C5 binding or blocking C5 cleavage. (AMG1008, 1:4-19, 7:21-28, 8:34-13:16; ALXN2022 ¶¶167, 240.) Insofar as Mueller described two "h5G1.1" antibodies – "h5G1.1 CO12 HuG4" and "h5G1.1 CO12 HuG2/G4" – these were exclusively used as "controls" for Mueller's study of its anti-VCAM antibodies. (AMG1008, 12:27-30; ALXN2022 ¶240; ALXN2032, 232:6-16.)

Amgen is incorrect a POSA "would have readily understood" Mueller's "h5G1.1 CO12 HuG2/G4 mAb" to be "eculizumab." (Petition, 69-70; *see also* Petition, 66; AMG1002, ¶179.) Neither Evans nor Mueller mentioned "eculizumab." (ALXN2032, 199:15-17, 102:10-14; ALXN2022 ¶168.) And, contrary to Amgen's assertions, the "overwhelming evidence in the art" was that the C5-binding, clinically proven antibody "eculizumab" antibody was Thomas's ***IgG4*** isotype antibody. (*See supra* Section II.C.) Consistent with that teaching, Mueller identified ***only*** the "h5G1.1 CO12 HuG4" antibody as an "anti-C5" antibody. (AMG1008, 12:1-3; ALXN2022 ¶168; *see supra* 55-56, 64.)

Further, as the Board recognized, Amgen fails to show how a POSA without hindsight would have been motivated to combine specifically-selected sequences from Evans and Mueller, in the specific manner required to get the specific amino acid sequence claimed in the '504 patent. (*See* Paper No. 15, 52-54.) Amgen's figures illustrate its use of improper hindsight. For example, Amgen's Figure 14

mistakenly suggests that a POSA would have understood that Mueller and Evans disclosed the same single antibody, with part of the sequence being provided in Evans, and part of the sequence being provided in Mueller. (Petition, 63, Fig. 14; AMG1002, ¶173.) But, as Dr. Balthasar admits, Mueller did ***not*** disclose the amino acid sequences of any full-length "h5G1.1" antibodies. (ALXN2032, 232:17-21; ALXN2022 ¶169.) Nor did Evans provide a partial sequence for a full-length humanized antibody, as Amgen's Figure 16 suggests. Rather, a POSA would have seen that Evans disclosed only a full-length "mouse" antibody, and truncated compounds like scFvs and Fabs that were ***not*** fragmented off a full-length antibody, but rather were produced from scratch using recombinant DNA technology. (ALXN2022 ¶244; *see supra* 20-23.)

Neither Mueller nor Evans provided any ***guidance*** on how to combine their various sequences. As with Grounds 4 and 5, Amgen's Ground 6 and 7 use Amgen's present-day knowledge of the '504 patent to justify its selection and combination of sequences, by showing carefully curated sequence alignments that Amgen knows in hindsight will match with the claimed sequence. (AMG1002 Figs. 10, 14-16; ALXN2022 ¶¶246-254.)

Even if a POSA were to have combined sequences from Evans and Mueller in the exact way that Amgen does to reconstruct the claimed antibody, a POSA would not have (1) reasonably expected that the claimed antibody could be used

for "treating a patient suffering from [PNH]" or would even be "bind C5" (claims 1-10); (2) been motivated to make, or reasonably expected to succeed in making, a "pharmaceutical composition" of the claimed antibody for use in the claimed methods of treating PNH (claims 1-10); or (3) been motivated to make, or reasonably expected to succeed in making, a "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution" using the claimed antibody (claim 6). (*See supra* Section IV.B.2.)

As Dr. Balthasar conceded, nothing in Mueller disclosed that its "h5G1.1 CO12 HuG2/G4" antibody binds to C5; and nothing in Evans disclosed the binding properties of any full-length humanized antibodies, let alone one with a hybrid "IgG2/IgG4" constant region (which Evans also does not disclose). (ALXN2032, 247:13-18, 163:12-15; 163:25-164:5; 169:6-170:4; (ALXN2022 ¶¶156-157.) Further, Mueller contained no data providing any information on the efficacy or even safety of its "HuG2/G4" isotype control antibody, or suggested that it was ever formulated into a pharmaceutical composition. (ALXN2032, 247:20-248:6; ALXN2022 ¶¶255-262.) With such an uncharacterized antibody, a POSA would have had no motivation or reasonable expectation of success in using it to treat PNH patients, or to include it in any pharmaceutical formulation suitable for administration. (*See supra* Section II.A.) Nor would Bell or Wang have motivated

a POSA to make the specific claimed composition of claim 6: "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." (*See supra* Section IV.B.2.)

E. The Objective Indicia of Nonobviousness Support Validity

Objective indicia of nonobviousness, including commercial success, long-felt but unmet need, and industry praise, further support the validity of the claims 1-10 of the '504 patent.

There is no question that SOLIRIS® (eculizumab) is the commercial embodiment of the '504 patent, and that the objective evidence regarding SOLIRIS® and its commercial and therapeutic success has a direct nexus to the '504 patent. The '504 patent claims "[a] method of treating a patient suffering from [PNH]" that corresponds to the groundbreaking SOLIRIS® indication for "[t]he treatment of patients with [PNH] to reduce hemolysis." (ALXN2053, 1; ALXN2022 ¶267.) Further, the '504 patent claims recite pharmaceutical compositions of the sole active ingredient in SOLIRIS®: the uniquely-engineered, non-naturally occurring antibody comprising SEQ ID NOs: 2 and 4, which is responsible for the remarkable clinical properties of SOLIRIS®, and consequently, its commercial success as a treatment for PNH. (ALXN2022 ¶¶265-268; ALXN2032, 262:2-19.) *See, e.g., Henny Penny,* 938 F.3d at 1332; *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392-93 (Fed. Cir. 1988).

Claim 6 claims the pharmaceutical composition of SOLIRIS®, which is supplied as a 300 mg single-dose vial containing 30 mg of a 10 mg/ml solution of the claimed antibody. (ALXN2053, 1; ALXN2022 ¶267.)

SOLIRIS® is unquestionably a huge commercial success. The annual net product sales for SOLIRIS® have grown consistently since launch, including total U.S. sales of $1 billion over the past three years, continuing to grow to over $1.588 billion in 2018 (a 28.6% increase from 2017). (ALXN2056; ALXN2059-ALXN2073.)

The invention of the '504 patent, in its commercial embodiment of SOLIRIS®, also fulfilled a long-felt, unmet need for a safe and effective treatment for PNH, a rare and potentially fatal blood disease. ALXN2022 ¶¶270-279.) *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994, 997-998 (Fed. Cir. 2009). Before SOLIRIS®, PNH patients had to suffer with debilitating symptoms and life-threatening thrombosis, and were often dependent on frequent blood transfusions for survival. (AMG1047, 2559; AMG1012, 1234; ALXN2022 ¶¶273-274.) SOLIRIS® was the ***first*** FDA-approved treatment to reduce hemolysis in patients with PNH – transforming patients' quality of life and reducing their transfusion dependency. (ALXN2022 ¶¶275-277.) While other researchers were interested in developing anti-C5 antibodies for treating PNH and other untreated complement-mediated conditions, only the inventors of SOLIRIS® succeeded in

doing so. (ALXN2022 ¶¶278-279; ALXN2032, 262:23-263:3, 263:23-264:13; AMG1039.)

SOLIRIS® has also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade for pharmaceutical research and development), including the Prix Galien USA 2008 Award for Best Biotechnology Product, and the Prix Galien France 2009 Award for Most Innovative Drug for Rare Disease. (ALXN2020; ALXN2021; ALXN2022 ¶¶283-284.)

The substantial efforts by Amgen and other companies to copy SOLIRIS® with its their proposed biosimilar eculizumab products – which would necessarily include the claimed antibody of the '504 patent – is further strong evidence of the nonobviousness of the '504 patent. (ALXN2088; ALXN2090; ALXN2089; ALXN2022 ¶¶285-286.) That Amgen and at least three others have chosen to copy the specific amino acid sequence of the '504 patent, rather than make a different anti-C5 antibody with a different amino acid sequence, evidences the significant impact of the '504 patent's invention. *See Liqwd, Inc. v. L'Oreal USA, Inc.*, --- F.3d ---, 2019 WL 5587047, at *2 (Fed. Cir. Oct. 17, 2019).

V. CONCLUSION[7]

Alexion respectfully submits that the Board confirm the patentability of claims 1-10.

[7] Alexion provides this Patent Owner Response without prejudice to its right to raise a further constitutional challenge on appeal, including but not limited to challenges to the Board's institution decision and final written decision, based on the Federal Circuit's resolution of pending challenges. *Arthrex, Inc. v. Smith & Nephew, Inc.*, 2019 WL 5616010, at *11 (Fed. Cir. Oct. 31, 2019).

Respectfully submitted,

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The undersigned hereby certifies that the portions of the above-captioned **PATENT OWNER RESPONSE** specified in 37 C.F.R. § 42.24 has 13,746 words, in compliance with the 14,000 word limit set forth in 37 C.F.R. § 42.24.

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Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00740
Patent: 9,718,880

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TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 9

A. Design of Humanized Monoclonal Antibodies, and Pharmaceutical Compositions of Such Antibodies for Human Therapeutic Use Was a Complex, Unpredictable Art 9

B. Naming of Humanized Monoclonal Antibodies 13

C. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" to be the IgG4 Monoclonal Antibody of Thomas 15

D. The Structure and Sequence of SOLIRIS® Was *Not* Known Prior to March 15, 2007 21

E. Overview of the '880 Patent 28

F. Prosecution History of the '880 Patent and Related Applications 29

III. PERSON OF ORDINARY SKILL IN THE ART OF THE '880 PATENT 31

IV. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF CLAIMS 1-3 OF THE '880 PATENT 32

A. Amgen's Grounds 1 and 2 Fail Because Amgen Cannot Show that Claim 2 Was Anticipated by Hillmen or Hill 32

1. Hillmen and Hill Did Not Disclose an Antibody "Comprising a Heavy Chain Consisting of SEQ ID NO: 2 and a Light Chain Consisting of SEQ ID NO: 4" 32

2. Neither Hillmen nor Hill Inherently Disclosed the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claim 2 of the '880 Patent 33

B. Amgen's Grounds 3 and 4 Fail Because Amgen Cannot Show that Claims 1 and 3 Would Have Been Obvious Over Hillmen or Hill in Combination with Bell and Wang 35

1. Hillmen, Hill, Bell, and Wang, In Any Combination, Did Not Teach the Specific Claimed Antibody of Claims 1 and 3 35

Table of Contents
(continued)

Page

2. Hillmen, Hill, Bell, and Wang Did Not Teach the Specific Pharmaceutical Compositions of Claims 1 and 3 37

C. Amgen's Ground 5 Fails Because Amgen Cannot Show that Claims 1-3 Would Have Been Obvious Over the Combination of Bell, Wang, Bowdish and Evans 42

1. Bell and Wang Did Not Disclose the Claimed Sequence, and Would Not Have Motivated a POSA to Make the Claimed Antibody 44

2. A POSA Would Not Have Been Motivated to Combine Bell's Teachings with Bowdish and Evans, or to Make the Specific Claimed Sequence 47

3. The Combination of Bell, Wang, Bowdish and Evans Would Not Have Motivated a POSA to Make the Claimed Pharmaceutical Compositions, or Given a POSA a Reasonable Expectation of Success in Doing So 56

D. Amgen's Ground 6 Fails Because Amgen Cannot Show that Claims 1-3 Would Have Been Obvious Over the Combination of Bell, Wang, Evans and Mueller 59

E. The Objective Indicia of Nonobviousness Support Validity 64

V. CONCLUSION 67

Samsung Bioepis Exhibit No. 1002
Page 12642

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2091	Harlow and Lane, Chapter 15: Antibody Molecules, in Antibodies, A Laboratory Manual, 622-25 (1988)

I. INTRODUCTION

Claims 1-3 of Alexion's U.S. Patent No. 9,718,880 ("the '880 patent") recite pharmaceutical compositions of an antibody comprising the novel, uniquely-engineered amino acid sequence of SOLIRIS®, the groundbreaking, commercially successful anti-C5 monoclonal antibody developed by Alexion. Claim 1 expressly requires that the composition is "for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria." Claims 1 and 3 also specifically require that the composition is a "sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml [anti-C5] antibody solution."

SOLIRIS®, also referred to today by its non-proprietary name "eculizumab," is a first-in-class treatment for patients with the rare, potentially fatal blood disease paroxysmal nocturnal hemoglobinuria ("PNH"), caused by red blood cells losing their normal protection against the "complement" immune pathway. SOLIRIS® works by binding to component 5 ("C5") of the complement pathway and preventing its cleavage into components "C5a" and "C5b," which mediate downstream effects of the pathway, including hemolysis in patients with PNH.

Prior to March 15, 2007, the priority date of the '880 patent, the amino acid sequence of SOLIRIS® recited in claims 1-3 of the '880 patent (heavy and light chains consisting of SEQ ID NOs: 2 and 4, respectively) was ***not*** publicly known or disclosed in the prior art. While a person of ordinary skill in the art ("POSA")

as of that date would have known that Alexion had designed and clinically tested an antibody named "eculizumab," the POSA would not have known that "eculizumab" had the uniquely-engineered amino acid sequence recited in the '880 patent claims. That is because the literature as of March 15, 2007 consistently identified "eculizumab" as the antibody described in the "Thomas" publication (AMG1023), which has a naturally-occurring "***IgG4***" heavy chain constant region. In contrast, the novel antibody in the claimed compositions of the '880 patent has a very different, uniquely-engineered, non-naturally occurring constant region. A POSA would not have known of any antibody with the specific sequence recited in claims 1-3 of the '880 patent and would not have reasonably expected that such an antibody would bind C5. Further, a POSA prior to March 15, 2007 would not have known or reasonably expected that such a novel antibody – with no *in vitro* or *in vivo* biological data or formulation information reported in the literature – could be formulated into a pharmaceutical composition suitable for use in treating PNH or any other complement-mediated condition.

Amgen has not shown how any of the prior art of its Grounds disclosed or would have led a POSA to pharmaceutical compositions comprising an antibody with the uniquely-engineered amino acid sequence recited in claims 1-3 of the '880 patent. Instead, Amgen disregards the perspective of a POSA as of March 15, 2007, and impermissibly uses its ***hindsight knowledge*** of the '880 patent's novel,

previously-undisclosed claimed sequence and pharmaceutical compositions to misstate the disclosures of the prior art, pick and choose from those misstated disclosures, and reconstruct the claimed invention using the '880 patent's teachings as a guide. When the art is viewed from the proper perspective of a POSA, each of Amgen's Grounds fails.

Amgen's Grounds 1 and 2 – alleging anticipation of claim 2 – fail because Amgen incorrectly presumes that a POSA would have understood that the clinical publications Hillmen (AMG1004) and Hill (AMG1047) somehow disclosed the claimed sequence of the '880 patent by using the name "eculizumab." But nothing within the four corners of the Hillmen and Hill publications necessarily disclosed the present-day knowledge that eculizumab has the uniquely-engineered amino acid sequence described and claimed in the '880 patent. Rather, as the Board recognized, both Hillmen and Hill identified "eculizumab" as the ***IgG4 antibody of Thomas***. (*See, e.g.*, Paper No. 15, 28-29 & n.16, 33-35, 37.)

Amgen's Grounds 3 and 4 – alleging obviousness of claims 1 and 3 in view of Hillmen or Hill in further combination with Bell (AMG1005) and Wang (AMG1028) – are based on the same mistaken premise that Hillmen and Hill disclosed the specific amino acid sequence claimed in the '880 patent, and fail for at least the same reasons as Grounds 1 and 2. *See Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014) (in obviousness, as in

anticipation, an alleged inherent element must be "***necessarily present*** in the prior art combination").[1] Bell and Wang, like Hillmen and Hill, did not disclose the '880 patent's specific claimed amino acid sequence, or any pharmaceutical compositions of an antibody having that sequence. And Amgen fails to explain why a POSA would have been motivated to make, or would have reasonably expected success with, the specific pharmaceutical compositions recited in claims 1 and 3 for an antibody that, as far as a POSA knew, might have never been made or tested for C5 binding, *in vitro* activity, therapeutic effect, ability to treat PNH (as recited in claim 1), or suitability for pharmaceutical formulation.

Amgen's Grounds 5 and 6, alleging obviousness of claims 1-3, fail because they rely on post-hoc knowledge of the '880 patent's claimed sequence to reconstruct that invention from bits and pieces of structurally and functionally distinct compounds in unrelated art. *See Merck Sharpe & Dohme B.V. v. Warner Chilcott Co.*, 711 Fed. App'x 633, 637 (Fed. Cir. 2017) ("[U]sing the [patent-in-suit] as a roadmap to piece together various elements of [the prior art] ... represents an improper reliance on hindsight."). As Dr. Balthasar conceded at deposition, he

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[1] Unless otherwise noted, all emphasis is added, and all internal citations and internal quotation marks are omitted.

was handed his cited prior art by counsel; he read only the portions of his references that he contends showed obviousness of the claimed invention; he could not testify with any "confidence" as to whether his references did or did not disclose key aspects of the claimed invention; and he assembled his figures using the claimed sequence of the '880 patent, which was not available to a POSA prior to March 15, 2007, as a guide. (ALXN2022, 64:23-65:14, 74:16-75:5, 77:7-78:2, 85:10-17, 108:17-109:10, 148:24-149:10, 180:8-11, 244:17-245:9, 267:17-268:11.)

For example, Amgen's Ground 5 contends that a POSA would have started with Bell (AMG1005), for teaching "eculizumab" as a clinically studied anti-C5 antibody, and Wang (AMG1028) for pharmaceutical compositions of "eculizumab" – and then would have turned to Bowdish (AMG1006) and Evans (AMG1007) for the sequence of "eculizumab." But ***nothing*** in Bowdish – which addressed TPO-mimetic peptide compounds but purportedly incorporated a mouse "5G1.1" antibody by reference – and Evans – which disclosed various humanized anti-C5 antibody fragments, though no full-length humanized antibody – suggested to a POSA that the claimed antibody was "eculizumab." Rather, Bell – like Hillmen and Hill – informed a POSA that "eculizumab" was Thomas's ***IgG4*** antibody. (Paper No. 15, 29 n.16; IPR2019-00741, Paper No. 15, 21 n.14.) Amgen cannot explain why a POSA would have ignored the unequivocal direction toward Thomas's IgG4 antibody and instead looked to (1) Bowdish, which was not

cited by Bell, Wang or Evans and disclosed neither "eculizumab" nor any other humanized monoclonal antibody that binds C5; and (2) Evans, which did not describe ***any*** full-length humanized antibodies for binding C5 or treating PNH, let alone the specific antibody of the claimed pharmaceutical compositions of '880 patent. There is no support for Amgen's hindsight-driven theory that a POSA considering the structure of Bell's "eculizumab" would have (1) selected Bowdish, rather than Thomas, as a starting point; (2) identified Bowdish's TPO-mimetic compound as relating to a humanized antibody with a hybrid IgG2/IgG4 constant region – even though nothing in Bowdish contains such a statement; and (3) associated the purported IgG2/IgG4 structure of Bowdish's TPO-mimetic compound with "eculizumab" – despite Bell's teaching of "eculizumab" as an ***IgG4*** isotype antibody.

Even if Bowdish and Evans were viewed in combination, a POSA without hindsight would not have arrived at the amino acid sequence in the claimed compositions of the '880 patent. Rather, a POSA would have seen Bowdish and Evans pointing in different directions, with Bowdish referring to a ***mouse*** antibody in its reference to "[c]onstruction of 5G1.1" from the "'283 application"; and Evans disclosing only that mouse antibody plus humanized recombinant "fragment" compounds that could not have been used as the "scaffold" to make Bowdish's full-length TPO-mimetic compound.

Amgen's Ground 6 starts with the disclosure of "eculizumab" by Bell (AMG1005) and Wang (AMG1028), and then uses improper hindsight to recreate the claimed sequence of the '880 patent from sequences plucked from Evans and Mueller (AMG1008). Mueller concerned antibodies directed at "VCAM" – a very different target from C5 – and used the antibody "h5G1.1 CO12 HuG2/G4 mAb" only as an "isotype control" for experiments involving VCAM. As the Board noted, Mueller identified only an ***IgG4*** isotype antibody (*i.e.*, the isotype of Thomas) as an "anti-C5 antibody," and taught nothing about the C5 binding or clinical properties of "h5G1.1 CO12 HuG2/G4 mAb."

Nor would a POSA have been motivated to combine the sequences in Evans and Mueller – neither of which cites to the other – in the exact manner to get the specific claimed antibody sequence of the '880 patent. As the Board correctly recognized, nothing in Evans or Mueller instructed whether or how such a combination should be done, including "precisely those portions of Mueller's and Evans's constructs to create an antibody having exactly the sequences set forth in SEQ ID NOs: 2 and 4." (Paper No. 15, 57.)

Even if sequences from Evans and Bowdish or Mueller were combined in the specific and untaught way that Amgen proposes, the pharmaceutical compositions recited in claims 1-3 of the '880 patent considered as a whole would still not have been obvious in view of the art asserted in Grounds 5 or 6. First, a

POSA would not have reasonably expected that an antibody with the claimed sequence would be "an anti-C5 antibody" as claims 2 and 3 of the '880 patent require. A POSA would also not have been motivated to formulate a "pharmaceutical composition" of an uncharacterized antibody with the claimed sequence of the '880 patent, as claims 1-3 require, and would not have reasonably expected that such a composition would be suitable for "use in treating a patient afflicted with [PNH]," as claim 1 requires.

And even if Amgen were correct, as it contends in Grounds 3-6, that a POSA would have understood the "eculizumab" antibody of Bell (AMG1005) and Wang (AMG1028) to have had the sequence recited in the '880 patent claims, it would not have been obvious for a POSA to formulate that composition as "a sterile, preservative free, 300 mg single-use dosage form comprising 30 mg of a 10 mg/ml antibody solution," as required by claims 1 and 3. Amgen relies on Bell and Wang for allegedly teaching that such a composition would be "sufficiently stable and active to be used as a drug" and would be useful for treating PNH. (*E.g.*, Petition, 41, n.19.) But as Dr. Trout explains, nothing in Bell or Wang disclosed such a composition, or would have motivated a POSA without hindsight to make or use it. In particular, Bell disclosed no composition details at all; and Wang's disclosure of a 30 mg/ml eculizumab solution passed through a nebulizer device would not have motivated a POSA to make the claimed 300 mg single use, 10

mg/ml antibody solution compositions, or have given a POSA a reasonable expectation that such compositions would be suitable for use in treating PNH patients.

II. BACKGROUND

A. Design of Humanized Monoclonal Antibodies, and Pharmaceutical Compositions of Such Antibodies for Human Therapeutic Use Was a Complex, Unpredictable Art

There is no dispute that as of March 15, 2007, a POSA would have understood a "monoclonal" antibody (including a "humanized monoclonal antibody" such as "eculizumab") to be a single, unique antibody with one defined structure, and critically, ***one unique primary amino acid sequence*** for the entire antibody. (ALXN2022, ¶70; ALXN2032, 10:9-22, 11:10-17.) A humanized monoclonal antibody, in turn, was understood to be a unique antibody with a unique sequence, designed by grafting mouse monoclonal antibody sequences associated with antigen binding into a human monoclonal antibody. (ALXN2022, ¶¶76, 78.) And a POSA would have understood that a humanized monoclonal antibody for therapeutic use – the subject matter of the pharmaceutical compositions described and claimed in the '880 patent – was intended to bind its target and achieve a desired biological and therapeutic activity when administered to human patients, while maintaining sufficient safety to be suitable for human

administration. (*See* ALXN2022, ¶¶76-82, 86-90; ALXN2032, 43:15-22, 46:20-48:2.)

A POSA would have understood that development of a "humanized" antibody intended for human therapeutic use was a complex and unpredictable art. (ALXN2022, ¶¶76-90.) A particular new humanized monoclonal antibody could not simply be assumed to retain the original mouse antibody's binding affinity and biological activity against its target antigen. Accordingly, a new humanized monoclonal antibody would need to be tested *in vitro* to establish its binding properties and its biological activity. (ALXN2022, ¶82.) To determine the suitability of a new humanized antibody as a therapeutic agent, additional extensive testing would need to be performed, including "pre-clinical" toxicology testing in animal species; clinical testing of efficacy, immunogenicity, and overall safety; and pharmaceutical formulation work to confirm that a suitably stable composition could be safely and efficaciously administered to people. (ALXN2022, ¶¶87-90; ALXN2032, 46:20-48:2.)

Further, a POSA as of March 15, 2007 could not reasonably extrapolate the *in vitro* or clinical properties of one monoclonal antibody with a unique amino acid sequence to a different antibody with a different sequence. A POSA would have understood that antibodies were complex three-dimensional structures, and that a monoclonal antibody's specific amino acid sequence was essential to its structure

and function. (ALXN2022, ¶¶62-63, 70, 116.) In particular, it was known that even small changes in an antibody's sequence could affect its critical properties. (ALXN2022, ¶¶104-117.)

For example, a POSA would have understood that sequences ***beyond*** a monoclonal antibody's "CDRs" could substantially influence its antigen-binding properties, including its "affinity" (tightness of binding) for the target antigen, "specificity" for binding the target antigen versus non-targets, and "fine specificity" for binding the target antigen in the particular region ("epitope") needed to provide the desired therapeutic activity. (ALXN2022, ¶¶104-117.) It was well-known that non-CDR amino acids within an antibody's "variable" region (*i.e.*, "framework" residues) could impact antigen binding, either by direct involvement in binding or indirect effects on three-dimensional antibody structure. (ALXN2022, ¶106.) A POSA also would have known that the ***constant regions*** of monoclonal antibodies play an indirect role in antigen binding, and that switching between different constant regions ("isotype switching") could significantly impact antigen binding, even while leaving the variable region unchanged. (ALXN2022, ¶¶107-114.) In particular, the art described how changes to the "CH1" and "hinge" portions of the heavy chain constant region impact antigen affinity and specificity. (ALXN2022, ¶¶113; ALXN2012, 3388, 3391-92; ALXN2009, 13917-18, 13924.)

Once a suitable humanized monoclonal antibody was designed and tested to show it has its desired *in vitro* activity, it would need to be further studied with clinical tests. (ALXN2022[CasadevallDecl], ¶86-88.) A POSA would have been particularly concerned about the unpredictability of a humanized monoclonal antibody for therapeutic use if, in addition to the mouse sequences of the variable region, it contained a non-naturally occurring constant region that was not known to have been clinically tested and shown to be suitable for human administration (*e.g.*, a hybrid constant region fusing sequences from different isotypes). (ALXN2022, ¶86.)

A POSA would have also understood that truncated antibody-like molecules could be made, containing amino acid sequences that include less than a full-length, intact humanized monoclonal antibody. (ALXN2022, ¶¶91-93.) While commonly called "fragments," these compounds were typically made by recombinant DNA means, rather than "broken off" from a full-length, pre-existing antibody. (ALXN2022, ¶91; ALXN2032, 143:18-22.) For example, a humanized single-chain Fv or "scFv" compound could be made, containing only the variable light and heavy chain regions connected by a linker; or an "Fab" compound could be made, containing a complete light chain but only the variable and CH1 constant region of the heavy chain ("Fd"), with no intact "Fc" region (the stem of the Y-shaped antibody structure). (ALXN2022, ¶¶67, 92; ALXN2032, 143:8-25.) A

POSA would have understood that these "fragments" were very different from a full-length humanized antibody, and have different properties (*e.g.*, shorter half-life but greater tissue penetration). (ALXN2022, ¶93.) A POSA would have further understood that because the constant regions of a full-length, intact antibody could impact its antigen-binding properties as well as its immunogenicity, the properties of a "fragment" lacking a full heavy chain constant region could not reliably be extrapolated to a new, untested full-length humanized monoclonal antibody. (ALXN2022, ¶¶93, 105-117.)

A POSA also understood that developing pharmaceutical compositions of antibodies was an unpredictable art. (ALXN2024, ¶¶39-54; AMG1029, 1, 5.) Antibody compositions (liquid compositions in particular) were at risk for degradation that could cause them to lose effect or even harm patients – and thus would need to be tested to determine suitability for human use. (ALXN2024, ¶¶40-51.)

B. Naming of Humanized Monoclonal Antibodies

A POSA as of March 15, 2007 would have understood that different naming conventions were used for humanized monoclonal antibodies at different stages of development. (ALXN2022[CasadevallDecl], ¶94.) Depending on the convention used and the stage of development, a POSA might understand that a particular name refers to a group of several related antibodies; or in other cases, that a

specific non-proprietary name (*e.g.*, "eculizumab") or a brand name (*e.g.*, "SOLIRIS®") refers to a single, unique monoclonal antibody with one defined structure and one primary amino acid sequence. (ALXN2022, ¶¶94-103; ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14.)

At early stages of development of a humanized monoclonal antibody, a POSA would have understood that informal research code names were commonly used, and typically referenced the original source mouse antibody from which the humanized antibody was generated (*e.g.*, "5G1.1"). (ALXN2022, ¶95; ALXN2032, 98:2-99:8, 202:24-203:14.) A POSA would have understood that, depending on the context, these code names could potentially refer to a number of different structures or sequences. (ALXN2022, ¶95; ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14.)

In contrast, after a specific humanized monoclonal antibody with a single, unique sequence has progressed into clinical development, it may be assigned a "non-proprietary" name (*e.g.*, "eculizumab") by authorities including INN and USAN. (ALXN2022, ¶97.) A POSA would have understood that these non-proprietary names with respect to humanized monoclonal antibodies would refer to one – and only one – specific antibody as defined by its unique amino acid sequence. (ALXN2022, ¶¶100-101, 120; ALXN2032, 10:9-11:17, 98:19-99:8, 100:3-10; ALXN2046, 1; ALXN2045, 1210.) The same would be true when, as

the product neared FDA submission, the research sponsor would propose a unique branded trade name (*e.g.*, "SOLIRIS®"). (ALXN2022, ¶102.)

C. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" to be the IgG4 Monoclonal Antibody of Thomas

As of March 15, 2007, a POSA would have understood that a unique humanized monoclonal antibody named "eculizumab," that specifically targets human C5 and prevents its cleavage, had been developed. (ALXN2022, ¶¶118-123; AMG1047, 2559 (citing Thomas, AMG1023).)

But the POSA as of March 15, 2007 would ***not*** have known that "eculizumab" had the sequence claimed in the '880 patent, including the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2. Rather, a POSA at that time would have believed that "eculizumab" contained an "***IgG4***" constant region – which is very different from the uniquely-engineered heavy-chain constant region recited in claims 1-3 of the '880 patent. (ALXN2022, ¶¶120-123; ALXN2032, 97:7-21.) Specifically, the literature regarding the development of "eculizumab" consistently described "eculizumab" by referencing Thomas (AMG1023). (ALXN2022, ¶¶120-123, 139, 193-195; ALXN2032, 125:13-126:9, 128:20-129:10, 192:13-22, 160:18-162:12.) Thomas, in turn, detailed the design and testing of a full-length, ***IgG4***-isotype humanized antibody ("humanized 5G1.1") with anti-C5 affinity, specificity, and complement-blocking activity

comparable to the original mouse "5G1.1" antibody. (AMG1023, 1396-99; ALXN2022, ¶123; ALXN2032, 242:21-243:4.)

A POSA would have had no doubt that "eculizumab" was Thomas's IgG4-isotype humanized antibody, because the pertinent literature consistently and unambiguously said so:

Table 1: References to "Eculizumab" as Thomas's Humanized IgG4 Antibody

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hillmen (AMG1004) at 553 – Phase II clinical trial for treatment of PNH	"***Eculizumab is*** a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components." (Citing ***Thomas***, Ref. No. 15)
Hill (AMG1047) at 2559 – 52-week extension of Hillmen Phase II clinical trial	"***Eculizumab is*** a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage." (Citing ***Thomas***, Ref. No. 9)
Hillmen 2006 (AMG1012) at 1234 – pivotal Phase III clinical trial for treatment of PNH	"***Eculizumab (Soliris, Alexion Pharmaceuticals) is*** a humanized monoclonal antibody directed against the terminal complement protein C5." (Citing ***Thomas***, Ref. No. 13)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hill 2007 (ALXN2028) – post-Phase III case report for PNH patient	"***Eculizumab is*** a novel humanized monoclonal antibody directed against the complement protein C5." (Citing ***Thomas***, Ref. No. 6)
Bell (AMG1005) at [0052] – Phase II clinical studies described in Hillmen and Hill	States that "[m]ethods for the preparation of h5G1.1-mAb" are described in ***Thomas***, and that "[t]he antibody h5G1.1-mAb is currently undergoing clinical trials under the name ***eculizumab***."
Kaplan (AMG1021) at 1018	States that "***Eculizumab*** (5G1.1), under development by Alexion Pharmaceuticals Inc. is a humanized C5 inhibitory monoclonal antibody (mAb)," and cites ***Thomas*** for the synthesis and complement-blocking activity of "intact humanized 5G1.1 antibody" or "humanized 5G1.1"
Brekke (AMG1019) at 56	"***Eculizumab*** (5G1.1; Alexion Pharmaceuticals) ***is*** a humanized monoclonal antibody that prevents the cleavage of human complement component C5 ... ." (citing ***Kaplan***, Ref. No. 6, which in turn cites to ***Thomas***)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Pierangeli (AMG1020) at 2123	Stating that "***eculizumab*** has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH] ... ." (citing to ***Hillmen***, Ref No. 18, which in turn cites to ***Thomas***)

Looking at this literature, a POSA would have believed that Thomas's IgG4 antibody was the ***only*** full-length humanized antibody shown to bind C5 and prevent its cleavage, tested for safety and efficacy in treating PNH, and submitted to the FDA for marketing approval.[2] In Thomas, a POSA would have seen the extensive work in rationally designing an "intact" humanized monoclonal antibody preserving the anti-C5 activity of the "5G1.1" mouse antibody, using an IgG4

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[2] Thomas also does not disclose the specific light chain amino acid sequence recited in SEQ ID NO: 4 of the '880 patent. In particular, the light chain variable region sequence provided by Thomas differs from SEQ ID NO: 4 of the '880 patent at amino acid position 38, flanking light chain CDR1. (*Compare* AMG1023 at 1392, 1396 (identifying position 38 as "R" (arginine)) *with* AMG1001, col. 35, SEQ ID NO 4 (identifying position 38 as "Gln" (glutamine).)

isotype. (AMG1023, 1393-99; ALXN2022, ¶123; ALXN2032, 242:21-243:4.) And, prior to March 15, 2007, a POSA would have seen that "eculizumab" – consistently identified as Thomas's IgG4 antibody – was shown to be safe and effective in treating PNH, and was submitted for FDA and European approval under the trade name SOLIRIS®. (*See, e.g.*, AMG1004; AMG1047; AMG1012, ALXN2028; AMG1005 ¶¶[0052], [0081-0096]; ALXN2022, ¶¶121-123.)

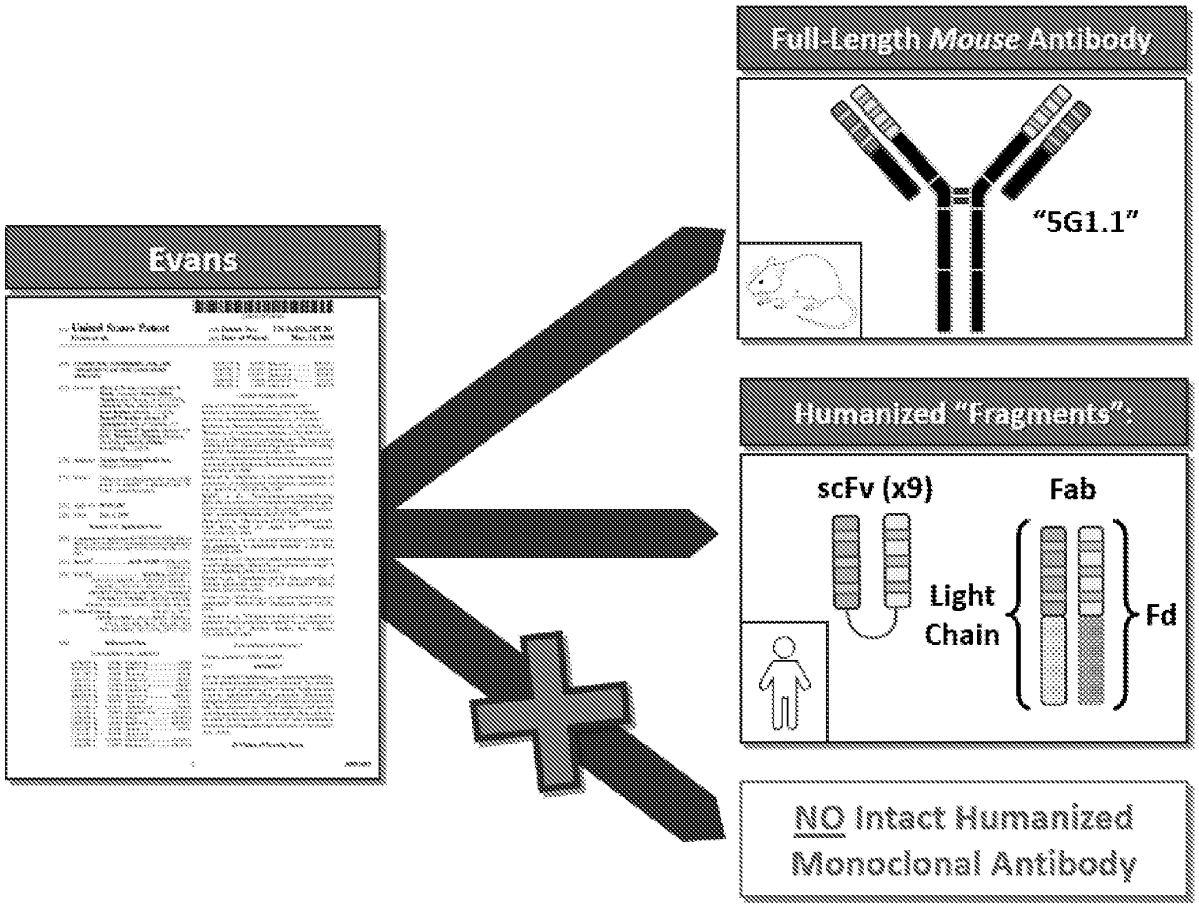
In contrast to Thomas and the literature regarding "eculizumab" that followed Thomas, a POSA would have understood that Evans (AMG1007) did ***not*** disclose "eculizumab." (ALXN2022, ¶¶124-130.) Rather, a POSA would have understood that Evans described an earlier stage of research that predated the design of the intact, full-length humanized antibody "eculizumab" - because Evans did ***not*** disclose any full-length humanized antibodies. (ALXN2022, ¶¶124-128, 216, 222-223; ALXN2032, 163:12-15, 169:13-18.) At most, a POSA would have read Evans as a precursor to the research that resulted in "eculizumab."

As Dr. Balthasar agreed at deposition, the only full-length antibody described in Evans (AMG1007) is the "5G1.1" mouse antibody, which Evans obtained from the "5G1.1" hybridoma. (AMG1007, 19:47-49, Figs. 18-19; ALXN2032, 165:5-21, 169:13-18; ALXN2022, ¶¶125-128.) Evans further describes the researchers' characterization of the "5G1.1" mouse antibody, including its binding affinity, *in vitro* activity blocking complement in hemolytic

assays, and the sequencing and cloning of the variable regions of the "5G1.1 mouse antibody." (AMG1007, Examples 7-10; ALXN2022, ¶125; ALXN2032, 165:5-169:23.) But Evans provides no such information for a full-length ***humanized*** antibody derived from the "5G1.1" mouse antibody – which a POSA would have understood would have a different amino acid sequence and different clinical properties from the mouse antibody. (ALXN2022, ¶126; ALXN2032, 163:12-15, 169:24-170:4.)

To the extent Evans described "humanization" work based on the "5G1.1" mouse antibody, it was the development of recombinant "fragments" – scFv or Fab – that did ***not*** contain an intact heavy chain constant region, let alone the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2 of the '880 patent. (AMG1007, Example 11; ALXN2022, ¶126.) For example, Evans described nine different humanized "scFv" fragments, which are recombinantly-produced molecules containing two variable regions connected by a linker, with no constant region, (AMG1007, 43:6-14, 43:62-45:4), and humanized "Fab" fragments that also lack the "Fc" portion (regions CH2 and CH3) of an intact antibody (AMG1007, 43:21-61). (ALXN2022, ¶126.) Notably, the humanized Fab fragments of Evans have different heavy chain sequences ("Fd," Evans SEQ ID NOs: 11 and 12) from the non-prior art SEQ ID NO: 2 of the '880 patent., including in "CH1" constant region. (ALXN2022, ¶129.) A POSA would have

understood what Evans did disclose – a mouse antibody and humanized "fragments" – and what Evans did not disclose, *i.e.*, an intact humanized monoclonal antibody:



D. The Structure and Sequence of SOLIRIS® Was *Not* Known Prior to March 15, 2007

Today, but ***not*** before the priority date for the '880 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in claims 1-3 of the '880 patent, namely, "a heavy chain consisting of SEQ ID NO: 2 and a light chain

consisting of SEQ ID NO: 4." A POSA prior to the '880 patent, however, would not have known of any antibody consisting of SEQ ID NOs: 2 and 4, and would not have reasonably expected that such an antibody would bind to C5, that it would be useful to treat patients afflicted with PNH or other conditions, or that it could be developed into a pharmaceutical composition suitable for human administration.

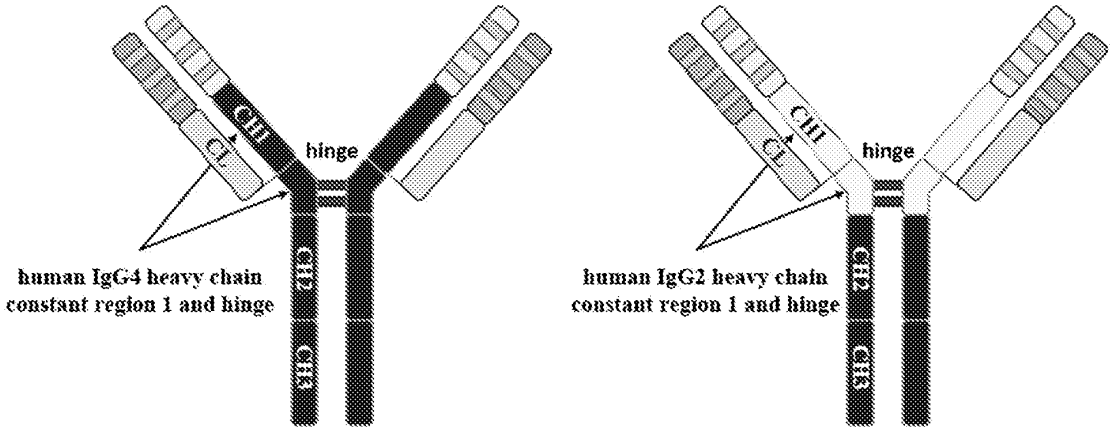
Today, but ***not*** prior to March 15, 2007, it is known that SOLIRIS® is a unique antibody that is ***very different*** from the humanized IgG4 antibody described in Thomas. As understood today, the heavy chain of SOLIRIS® (SEQ ID NO: 2) features a non-naturally occurring, uniquely-engineered constant region – containing sequences from both human IgG2 and IgG4 – that was designed by scientists at Alexion and was tested in human clinical trials. (ALXN2022, ¶¶133-136.)

Notably, SOLIRIS® was the first FDA-approved product containing Alexion's uniquely-engineered heavy chain constant region. A POSA would not have been aware of any published clinical testing showing that an antibody with this uniquely-engineered constant region would be therapeutically useful and suitable for human administration.

The presently-known structure of SOLIRIS® reflected in claims 1-3of the '880 patent is shown below in comparison to the IgG4 isotype antibody described in Thomas, which the literature prior to March 15, 2007 would have taught a

POSA was "eculizumab." The figure depicts how, unlike the IgG4 antibody of Thomas, the claimed antibody uses the CH1 and "hinge" regions of IgG2, thereby providing a meaningfully different antibody than that identified in the literature citing to Thomas.

Left – Structure of the IgG4 isotype antibody referenced to as "eculizumab" in the literature as of March 15, 2007
Right – Structure of SOLIRIS®, having a non-naturally occurring, protein-engineered isotype



Amgen's and Dr. Balthasar's arguments fail because they are based on the erroneous that a POSA would have understood "eculizumab" to contain "a hybrid IgG2/IgG4 constant region." (*See, e.g.*, Petition, 13-14; AMG1002 ¶¶ 44, 47, 56.) That assumption improperly ignores the overwhelming evidence that directed a POSA back then to Thomas for the structure of "eculizumab." (*See* Section II.C above.) Instead, to support its assumption that a POSA would have known that

"eculizumab" contained an IgG2/IgG4 constant region, Amgen relies on a ***single***, ambiguous sentence in just one document – Tacken (AMG1034)[3] – regarding an "isotype control antibody." But a POSA looking for the structure of "eculizumab" would not have considered nor credited Tacken above the consistent, clear statements in earlier and later publications that expressly identified "eculizumab" as the IgG4 antibody of Thomas.

As Dr. Balthasar admitted, Tacken is the ***only*** document on which he relies dated prior to March 15, 2007 that purportedly associated "eculizumab" with a hybrid IgG2/IgG4 constant region. (ALXN2032, 104:14-20.) But unlike the clinical literature discussed in Section II.C above, Tacken did not concern the study of "eculizumab" in binding C5, blocking C5 cleavage or treating conditions such as PNH. (ALXN2022, ¶¶140-150; ALXN2032, 72:23-73:2, 73:12-74:1, 74:16-21.) Rather, Tacken involved the study of an entirely different antibody (the "hD1" antibody) with a wholly different purpose: directing antigens to a dendritic cell receptor for purposes of developing improved vaccinations. (AMG1034, 1278-79, 1283-84.)

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[3] Notably, Amgen does not rely on Tacken (AMG1034) as the basis for any of its Grounds alleging anticipation or obviousness of the '880 patent.

Nothing in Tacken contradicted the consistent teaching of the prior art ***as a whole*** that "eculizumab" had an IgG4 constant region. In a single sentence identifying an "isotype control antibody" for use in studies of the "hD1" antibody directed to dendritic cells, Tacken states the following (including a citation to ***Thomas*** as Ref. No. 19):

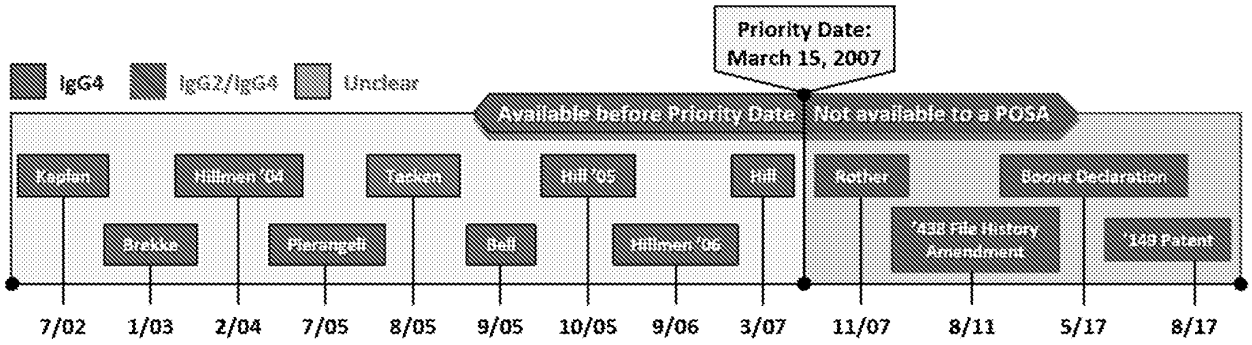
> An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

(AMG1034, 1279.) A POSA reading that isolated statement would not have been dissuaded from the consistent, clear teaching in the literature as of March 15, 2007 (both before and after Tacken's publication) identifying "eculizumab" and "SOLIRIS®" as the ***IgG4*** antibody of Thomas. (*See supra* Table 1; ALXN2022, ¶¶140-150.) A POSA would have seen substantial ambiguity in that statement. Not only does Tacken misspell "eculizumab," but it uses multiple conflicting and undefined terms – including "h5G1.1-mAb," which could refer to a class of various humanized antibodies; and "5G1.1," which can refer to many things, including the original "5G1.1" mouse antibody from the "5G1.1" hybridoma. (ALXN2022, ¶143; ALXN2032, 98:2-99:8, 159:1-10; 202:24-203:14.) Further, a POSA would have seen Tacken's citation to Thomas's IgG4 antibody (Ref. No.

19) for "eculizamab" [sic] as inconsistent with its reference to an IgG2/IgG4 isotype control antibody. On balance, the ambiguous, passing reference in Tacken would not have led a POSA to "understand" that the clinically tested "eculizumab" antibody has an "IgG2/IgG4" constant region.

Amgen's myopic focus on the isotype control antibody of Tacken, to the exclusion of all other prior art information, is also not tenable because at least four prior art documents published ***after*** Tacken confirmed a POSA's belief as of March 15, 2007 that the clinically-tested "eculizumab" antibody was the ***IgG4*** antibody of Thomas. For example, the Hill clinical study was published two months after Tacken in the same journal (Blood), and stated that "[e]culizumab is" the antibody of Thomas. (AMG1047, 2559 (Ref. No. 9); ALXN2032, 113:14-21, 114:19-115:10.) Bell, published a month after Tacken, likewise pointed to Thomas for methods of making "eculizumab," and made no mention of hybrid IgG2/IgG4 antibodies. (AMG1005, ¶[0052]; ALXN2022, ¶¶122, 145; ALXN2032[BalthasarDepTr], 160:18-162:11.) The Hillmen 2006 Phase III study, published more than a year after Tacken in the New England Journal of Medicine, and the Hill 2007 case report, published on March 1, 2007, likewise both stated that "eculizumab is" Thomas's IgG4 isotype antibody. (AMG1012, 1234 (Ref. No. 13); ALXN2028, 31 (Ref. No. 6); ALXN2022, ¶ 145; ALXN2032, 116:16-117:1.)

As the following timeline illustrates, the ***only*** plausible conclusion a POSA could have reached in view of the entire content of the art was that "eculizumab" was the IgG4 antibody of Thomas, and the ambiguous statement in Tacken (a publication having nothing to do with C5 binding) was either supportive of that understanding – as Tacken cites Thomas – or otherwise mistaken. (ALXN2022, ¶¶146, 150.) *See, e.g.*, *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 882-883 (Fed. Cir. 1998) (the "***entire content of the prior art***" must be considered in determining whether the art showed a trend towards the claimed invention).



E. Overview of the '880 Patent

The '880 patent issued on August 1, 2017 from U.S. App. No. 15/148,839, filed on May 6, 2016, and claims priority back to PCT/US2007/006606, filed on March 15, 2007. The patent has three claims, each directed to a pharmaceutical composition:

> **1.** A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> **2.** A pharmaceutical composition comprising an anti-C5 antibody, wherein the anti-C5 antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> **3.** The pharmaceutical composition of **claim 2**, wherein the pharmaceutical composition is a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution.

(AMG1001, 39:1-16.)

The '880 patent claims recite the complete amino acid sequence for SOLIRIS®: the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001, cols. 31-33, 35.) The '880 patent discloses that the claimed antibody binds C5, and provides Phase III clinical data from the "TRIUMPH" study confirming that the claimed antibody is safe and effective for treating PNH, and identifying the safe and effective dosing regimen for that use. (AMG1001, abstract, 3:6-8, 19:41-28:38.) The '880 patent also describes pharmaceutical compositions of eculizumab, including a "300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." (AMG1001, 4:21-24, 5:21-25, 16:19-23.)

F. Prosecution History of the '880 Patent and Related Applications

In prosecution leading to issuance of the '880 patent, as well as prosecution of related U.S. Patent Nos. 9,725,504 ("the '504 patent") and 9,732,149 ("the '149 patent"), the Examiner considered much of the same art that Amgen now asserts. The Examiner made findings undermining Amgen's positions here, including that (1) none of the art recited an antibody comprising SEQ ID NO: 2 and 4, (2) a POSA "would not have been easily guided to mak[e] antibodies with these recited sequences," and (3) SOLIRIS® and its unique sequence was not "accessible to the public" as of March 15, 2007. (AMG1016, 762-763.)

For example, in finding claims 1-3 of the '880 patent to be novel and nonobvious, the Examiner discussed Amgen's asserted references Hillmen (AMG1004) and Evans (AMG1007) as a basis for rejection, before ultimately finding claims 1-3 to be allowable over the art. (*See, e.g.*, AMG1016, 120-121, 179-180, 598-602, 719-724.) The Examiner also considered Amgen's asserted references Hill (AMG1047) and Bell (AMG1005); U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Bowdish (AMG1006); and Mueller II (AMG1031), which is cumulative of Mueller (AMG1008). (*See, e.g.*, AMG1016, 154-155, 158, 625.) Alexion did not mislead the Patent Office or fail to disclose references pertaining to Amgen's arguments here.

Notably, the Examiner confirmed a central fact that Amgen ignores: that Hillmen cites to ***Thomas*** (*i.e.*, "reference number 15" of Hillmen) as "disclosing more information about eculizumab." (AMG1014, 559, 623 (citing AMG1023); *see also* AMG1016, 598 ("Hillmen ... teaches that 'eculizumab' is a recombinant humanized antibody that binds to C5 ... and cites ***Thomas***").) Ultimately, the Examiner agreed that the prior art did not disclose or suggest the specific claimed antibody sequence of the '880 patent. (AMG1016, 762; *see also* AMG1014, 790.)

The Examiner also credited the Declaration of Dr. Laural Boone (AMG1016, 762-763 ("the Boone Declaration")) as showing that Alexion's clinical studies of the claimed antibody did not disclose its sequence or render it

publicly accessible. (AMG1016, 762-763.) The Examiner relied on, among other things, Dr. Boone's showing that "neither doctors nor patients had any knowledge of the ... claimed sequences of the antibody used in the studies." (AMG1016, 762-763; AMG1016, 737-740 ¶¶6-13.) While it is known ***today*** that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4 (AMG1016, 737, ¶ 6), a POSA as of March 15, 2007 would have only been guided by the teachings of the published literature that "eculizumab" had the IgG4 structure of Thomas.

III. PERSON OF ORDINARY SKILL IN THE ART OF THE '880 PATENT

Amgen contends that a POSA would have had "an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with **at least two years of experience in the field**," that a POSA would have had "skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics," and that a POSA could work on a team with others having "specialized skills," including clinicians and formulation chemists. (Petition, 21-22.)

Alexion does not dispute Amgen's POSA definition, except to clarify – as the Board accepted (Paper No. 15, 10-11) – that the POSA would have **at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry**. (ALXN2022, ¶ 26.)

IV. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF CLAIMS 1-3 OF THE '880 PATENT

A. Amgen's Grounds 1 and 2 Fail Because Amgen Cannot Show that Claim 2 Was Anticipated by Hillmen or Hill

Amgen's Grounds 1 and 2 contend that claim 2 of the '880 patent was anticipated by the clinical trial publications Hillmen (AMG1004) or Hill (AMG1047), respectively. As the Board recognized, Amgen's Grounds 1 and 2 fail, because Amgen cannot show how either Hillmen or Hill disclosed the antibody recited in claim 2 of the '880 patent.

1. Hillmen and Hill Did Not Disclose an Antibody "Comprising a Heavy Chain Consisting of SEQ ID NO: 2 and a Light Chain Consisting of SEQ ID NO: 4"

Amgen's Grounds 1 and 2 fail because neither Hillmen nor Hill expressly or inherently discloses all the elements recited in claim 2 of the '880 patent. *See, e.g.*, *Therasense, Inc. v. Becton Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) ("Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim.").

As the Board recognized, both Hillmen and Hill fail to disclose an antibody comprising the specific amino acid sequence recited in claim 2 of the '880 patent. (Paper No. 15, 20, 23-25.) Simply put, there were ***no amino acid sequences*** for "eculizumab" disclosed anywhere within the four corners of the Hillmen and Hill publications. (ALXN2022, ¶¶ 175, 177-180.) And to the extent Hillmen and Hill

provided any guidance about the structure of "eculizumab," they identified "eculizumab" by reference to Thomas (AMG1023) – which in turn described a humanized monoclonal antibody with an "***IgG4***" heavy chain constant region having a very different amino acid sequence from the '880 patent's SEQ ID NO: 2. (*See supra* Section II.C.) Dr. Balthasar conceded that Hillmen's and Hill's statements regarding what "eculizumab is" cited to Thomas; and he was unable to identify ***any*** disclosure within Hillmen, Hill, or their cited references suggesting that "eculizumab" had a hybrid IgG2/IgG4 constant region, rather than the IgG4 constant region of Thomas. (ALXN2032, 123:8-15, 125:13-126:11, 126:19-23, 127:19-128:1, 128:20-129:10, 132:7-12, 134:9-21.)

2. Neither Hillmen nor Hill Inherently Disclosed the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claim 2 of the '880 Patent

To supply the claimed elements of SEQ ID NOs: 2 and 4 that are missing from Hillmen and Hill, Amgen admittedly must go ***outside*** the four corners of the references themselves, and turns to a either patent prosecution document created in 2017 that indisputably was not prior art available to a POSA as of March 15, 2007, or to amino acid sequences that Amgen mixes and matches from extraneous documents (Bowdish, Mueller, and Evans) that were not cited or referenced anywhere in Hillmen and Hill. (Petition, 29-30, 34-35; ALXN2022, ¶181-182.)

For example, Amgen alleges inherent anticipation of claim 2 on the ground that ***today*** – years after the '880 patent's March 15, 2007 priority date – it is known that the clinical studies underlying the Hillmen and Hill publications ***actually*** used an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. (*See, e.g.*, Petition, 29 (citing the May 11, 2017 Declaration of Dr. Laural Boone, AMG1016, 737, 736).) But Amgen is mistaken on the law. The mere naming of an investigational product (*e.g.*, "eculizumab") in a prior art publication does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as of the priority date. *See, e.g.*, *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018). Likewise, post-filing information showing that the later-claimed antibody sequence was actually used in the studies underlying prior art clinical publications is insufficient to give rise to inherent anticipation, when those prior art publications would have guided a POSA to a different, unclaimed antibody sequence. *See, e.g.*, *id.*; *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper No. 15, 3-6 (Apr. 2, 2018).

B. Amgen's Grounds 3 and 4 Fail Because Amgen Cannot Show that Claims 1 and 3 Would Have Been Obvious Over Hillmen or Hill in Combination with Bell and Wang

Amgen's Grounds 3 and 4 contend that claims 1 and 3 (but not claim 2) of the '880 patent would have been obvious in view of Hillmen or Hill, respectively, in combination with Bell (AMG1005) Wang (AMG1028). As Grounds 3 and 4 raise overlapping issues, we address them together here.

1. Hillmen, Hill, Bell, and Wang, In Any Combination, Did Not Teach the Specific Claimed Antibody of Claims 1 and 3

Amgen's Grounds 3 and 4, like its Ground 1, rely upon Hillmen or Hill the sole prior art allegedly disclosing the claimed element of an antibody comprising "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4" in claims 1 and 3 of the '880 patent. (*See* Petition, 36, 44.) But as discussed in Section IV.A above, nothing in Hillmen or Hill expressly or inherently disclosed the claimed antibody sequence. *Par Pharm.*, 773 F.3d at 1195-96. As the Board agreed, Hillmen identified "eculizumab" as the ***IgG4*** isotype antibody of Thomas. (*See supra* Sections II.C, IV.A.) Likewise, Bell (AMG1005) and Wang (AMG1028) were silent on the sequence for "eculizumab." (Petition, 46; ALXN2032[BalthasarDepTr], 146:17-25, 256:15-22.) And Bell, like Hillmen (which corresponds to one of the studies described in Bell), pointed to

Thomas as a reference for "eculizumab."[4] (AMG1005, ¶[0052]; ALXN2022 ¶¶ 187, 195-198.)

Thus, nothing in Hillmen, Bell or Wang would have motivated a POSA to abandon Thomas's IgG4 antibody that they cite as "eculizumab," and instead attempt a method of treating patients with PNH using a different, unknown antibody with the sequence recited in the '880 patent, which was not disclosed anywhere in the four corners of those documents. (ALXN2022, ¶¶186-189 ; ALXN2032, 125:13-126:9, 128:20-129:10, 159:14-160:3, 160:18-162:11, 256:15-22.) Nor would a POSA have reasonably expected success in using such an uncharacterized antibody, as an antibody's therapeutic effects or suitability for human administration could not have been reasonably predicted based on its amino acid sequence alone. (*See supra* Section II.A.)

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[4] While Bell also cited Evans for the disclosure of antibody fragments, a POSA would have understood that Bell's regarding "eculizumab" to refer to Thomas, not Evans, because Evans did not disclose any full-length humanized antibodies. (*See, e.g.*, ALXN2022 ¶¶196-198, ALXN2032, 158:2-8, 159:14-160:3, 160:18-162:11, 163:5-15.)

2. Hillmen, Hill, Bell, and Wang Did Not Teach the Specific Pharmaceutical Compositions of Claims 1 and 3

With nothing in Hillmen and Bell (or Wang) disclosing an antibody with the specific sequence recited in claims 1-3 of the '880 patent, a POSA would not have been motivated to make, or reasonably expected to succeed in making, a "pharmaceutical composition" of such an uncharacterized antibody, as claims 1 and 3 require. (ALXN2024, ¶¶62-89.) As Dr. Trout explains, antibody formulation was an unpredictable field as of that date, and a POSA could not have reasonably expected that any particular uncharacterized antibody would be capable of development into ***any*** pharmaceutical composition suitable for human therapeutic use, or treatment of PNH in particular (as claim 1 requires). (ALXN2024, ¶39-54, 69.) That concern would not be limited to commercial-scale manufacturing, but would extend even to pharmaceutical compositions of antibodies used to treat patients on a smaller, experimental scale, which a POSA would understand still should meet basic stability requirements to avoid harm to patients. (ALXN2024, ¶ 38.) A POSA particularly would have had no motivation, and no reasonable expectation of success, to formulate an uncharacterized antibody having a novel, hybrid "IgG2/IgG4" constant region when nothing in the literature reported the formulation of such an antibody, on a commercial or experimental scale. (ALXN2024, 67-73.)

Even if, for sake of argument, a POSA did associate the "eculizumab" antibody of Hillmen, Hill, Bell and Wang with the claimed antibody sequence, nothing in Bell or Wang would have motivated a POSA to make the specific composition of claims 1 and 3 – "a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution" – or have given a POSA a reasonable expectation of success in doing so. Bell described no specific pharmaceutical compositions, and only suggested that an undefined composition was used for purposes of administering "eculizumab" by intravenous infusion to treat PNH. (ALXN2024, ¶76.) A POSA without the benefit of hindsight would not have been motivated to combine Bell's teachings of an undefined composition for injection with Wang (AMG1028), which broadly concerned administration of a wide range of anti-C5 antibodies and fragments by inhalation through a "nebulizer" device for treating respiratory diseases. (AMG1028, ¶¶[0169]-[0173]; ALXN2024, ¶¶79-81**;** ALXN2032, 257:24-258:15, 259:6-9.) *See, e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013).

Further, nothing in Wang disclosed a pharmaceutical composition containing a "10 mg/ml antibody solution" of "eculizumab" in a "single-use dosage form." (ALXN2024, ¶80.) Even if a POSA had associated Wang's "eculizumab" with the claimed antibody sequence – which Hillmen, Hill, Bell and Wang did ***not*** do – nothing in Wang would have motivated a POSA to make such a composition of

"eculizumab," or given a POSA a reasonable expectation of success in doing so. Wang did not specifically teach "eculizumab formulations of between 1 and 30 mg/ml" as Amgen claims (Petition, 41), but rather disclosed wide ranges including 1-30 mg/ml, 40-200 mg/ml and 1-200 mg/ml that hypothetically might be used for nebulization of various unrelated "anti-C5" antibodies and derivative compounds. (AMG1028, ¶¶[0067], [0130], [0170]-[0172], Fig. 10; ALXN2024, ¶¶82-83.)

Amgen's hindsight-driven combination of Bell and Wang is based on a misunderstanding of what Wang would have taught a POSA. According to Amgen, a POSA would have been motivated to make this combination, and arrive at the claimed 10 mg/ml concentration, because Wang allegedly taught that "eculizumab, formulated at a concentration of 1 to 30 mg/mL, would be ***sufficiently stable and active*** to be used as a drug." (Petition, 41 n.19; *see also* AMG1002 ¶ 105 ("A POSA would have arrived at a concentration of 10 mg/ml because Wang disclosed that eculizumab could be ***stably formulated*** at a concentration between 1 and 30 mg/ml, a range that encompasses 10 mg/ml.") But there is no such disclosure in Wang. Regarding stability, Wang only contained a highly general, hypothetical statement that compositions of undefined anti-C5 antibodies "may be stable" over a wide concentration range of 1-200 mg/ml (AMG1028 ¶ [0067].) – a statement that a POSA would ***not*** have taken as fact with respect to every specific antibody and concentration point. (ALXN2024, ¶84.)

A POSA would have understood that Wang's data, including the "SDS-PAGE" and "HPLC" studies of an unknown concentration of "eculizumab" that Amgen cites (Petition, 41 n.19), did ***not*** teach anything about stability pertinent to a pharmaceutical composition suitable for human administration, including for PNH. A POSA seeking a pharmaceutical composition of "eculizumab" for treatment of PNH (as claim 1 requires) or other conditions would have been motivated to seek a composition with suitable stability under conditions pertinent to storage and transportation (*e.g.*, stability over time, and under different temperatures) to confirm that the product would not degrade prior to human administration to the point where it loses therapeutic effect or becomes dangerous to patients (*e.g.*, potentially immunogenic). (ALXN2024, ¶¶42-54, 82-86; AMG1002, ¶103 ("Developing any given dosage form requires testing, validating, manufacturing, storing, and transporting that dosage form.").) Wang disclosed no such data. Wang disclosed no such data. Instead, Wang's studies of an "eculizumab" solution (at 30 mg/ml or an unspecified concentration) were limited to information irrelevant to the '880 patent, such as the formation of inhalable particles, and the "integrity of the nebulized antibody" when passed through

various nebulizer mouthpieces – with no information on degradation over time or under storage conditions.[5] (AMG1028 ¶¶ [0171]-[0173]; ALXN2024, ¶¶81-86.)

A POSA would also not have found it obvious to make a "300 mg single-usage dosage form" from Bell or Wang. Amgen relies on Bell, which disclosed the administration of 600 mg and 900 mg dosages, but did not describe any particular dosage units or dosage forms. (Petition, 41; ALXN2024, ¶¶74-77.) Amgen's argument that a POSA would have been motivated to make a 300 mg single-use composition disregards the challenges in administering such a composition, which would require healthcare providers to use two or three units at

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[5] Amgen's reliance on other, wholly unrelated antibodies commercially formulated at 10 mg/ml (Petition, 42, citing AMG1029, Table 1; AMG1030, Table 1) is misplaced, because (1) formulations of other antibodies could not reasonably be expected to work for "eculizumab"; (2) of the formulations referenced, only ***one*** was a full-length humanized antibody formulated as a 10 mg/ml solution (as opposed to freeze-dried solid); and (3) many commercial antibodies were not sufficiently stable to be formulated in solution in ***any*** concentration. (ALXN2024, ¶¶39-54, 88; AMG1029, 2-5.)

each dosing, and thus create inconvenience and the greater possibility for provider error. (ALXN2024, ¶89.)

C. Amgen's Ground 5 Fails Because Amgen Cannot Show that Claims 1-3 Would Have Been Obvious Over the Combination of Bell, Wang, Bowdish and Evans

Amgen's Ground 5 contends that claims 1-3 of the '880 patent would have been obvious over a combination of Bell (AMG1005), Wang (AMG1028), Bowdish (AMG1006) and Evans (AMG1007). Amgen's Ground 5 fails because it is founded in an impermissible hindsight-driven premise: that a POSA considering Bell's description of "eculizumab" would have ignored what Bell ***actually*** taught about the structure of "eculizumab" – that it was the full-length IgG4-isotype antibody of Thomas – and would have instead turned to Bowdish (which Bell does not cite) and Evans, both which make no mention of "eculizumab" or any other full-length humanized monoclonal antibodies known to bind C5 or have any therapeutic utility. (Petition, 55-57.)

Without the benefit of hindsight, a POSA as of March 15, 2007 would have had ***no reason*** to select and combine the sequences from Bowdish and Evans that Amgen cherry-picks to recreate the unique claimed sequences of the '880 patent; would have had ***no motivation*** to make such a new, untested antibody with no known or reasonably predictable binding, biological or therapeutic properties; and would have ***no reasonable expectation*** that such a new untested antibody would be

suitable "for use in treating a patient afflicted with [PNH]," as claim 1 requires, or would be an "anti-C5 antibody," as claims 2 and 3 require. (ALXN2022, ¶¶191-233.)

Even if, for sake of argument, Bowdish and Evans in combination disclosed amino acid sequences corresponding to SEQ ID NOs: 2 and 4 – which they did not – the combination of Bell, Wang, Bowdish and Evans did not teach how to make a "pharmaceutical composition" of an uncharacterized antibody having that sequence – particularly with respect to the specific composition of claims 1 and 3. And the combination of Bell, Wang, Bowdish and Evans and certainly did not motivate a POSA to make such a composition "for use in treating a patient afflicted with [PNH]," or provide a POSA with a reasonable expectation of success in doing so, when there was no evidence that an antibody with SEQ ID NOs: 2 and 4 had ***ever*** been tested in people for therapeutic effect and tolerability, or even *in vitro* activity in binding C5 and blocking complement. *See, e.g.*, *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1383 (Fed. Cir. 2019) (finding no reasonable expectation of success for a method of treatment where "the asserted references do not disclose ***any*** data" – regarding the effect of the claimed drug on the claimed disease) (emphasis in original).

The *Helsinn* decision cited by the Board (Paper No. 15, 48-49) confirms Amgen's failure to support Ground 5 with any evidence prior to March 15, 2007

that the claimed antibody would be suitable for use in a pharmaceutical composition to treat PNH (as claim 1 requires), or any other condition. In *Helsinn*, the Court found that claims to pharmaceutical compositions for a clinical use ("reducing the likelihood of emesis") were ready for patenting even though Phase III clinical trials were not complete, because there was "***overwhelming evidence ... the patented invention would work for its intended purpose***," including full Phase II and preliminary Phase III clinical trial results for the claimed composition over a seven year period. *See Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 855 F.3d 1356, 1372-1375 (Fed. Cir. 2017). With respect to the claimed antibody compositions of the '880 patent, however, a POSA would have seen no clinical studies, no formulation studies, no animal studies, no *in vitro* studies of complement-blocking activity, and no C5 binding studies. (*See supra* Section II.D.)

1. Bell and Wang Did Not Disclose the Claimed Sequence, and Would Not Have Motivated a POSA to Make the Claimed Antibody

Amgen relies on Bell (AMG1005) and Wang (AMG1028) for their disclosure of "eculizumab" – which Bell and Wang identify by that name – as allegedly supplying every element of claims 1-3 except the claimed amino acid sequence. (Petition, 46; AMG1002 ¶ 127.) According to Amgen's argument a POSA as of March 15, 2007 would have specifically been motivated to make and

use pharmaceutical compositions of Bell's "eculizumab" antibody, in view of Bell's teaching that "eculizumab" binds C5, blocks its cleavage, and successfully treats PNH. (*See, e.g.*, AMG1002 ¶¶ 129-32; ALXN2032[BalthasarDepTr], 152:13-154: 7; ALXN2022, ¶¶194-95, 199.) For example, Dr. Balthasar admitted that Bell, along with Hillmen and Hill, motivated a POSA to "make and use the eculizumab antibody that they describe" (ALXN2032, 154:1-7.)

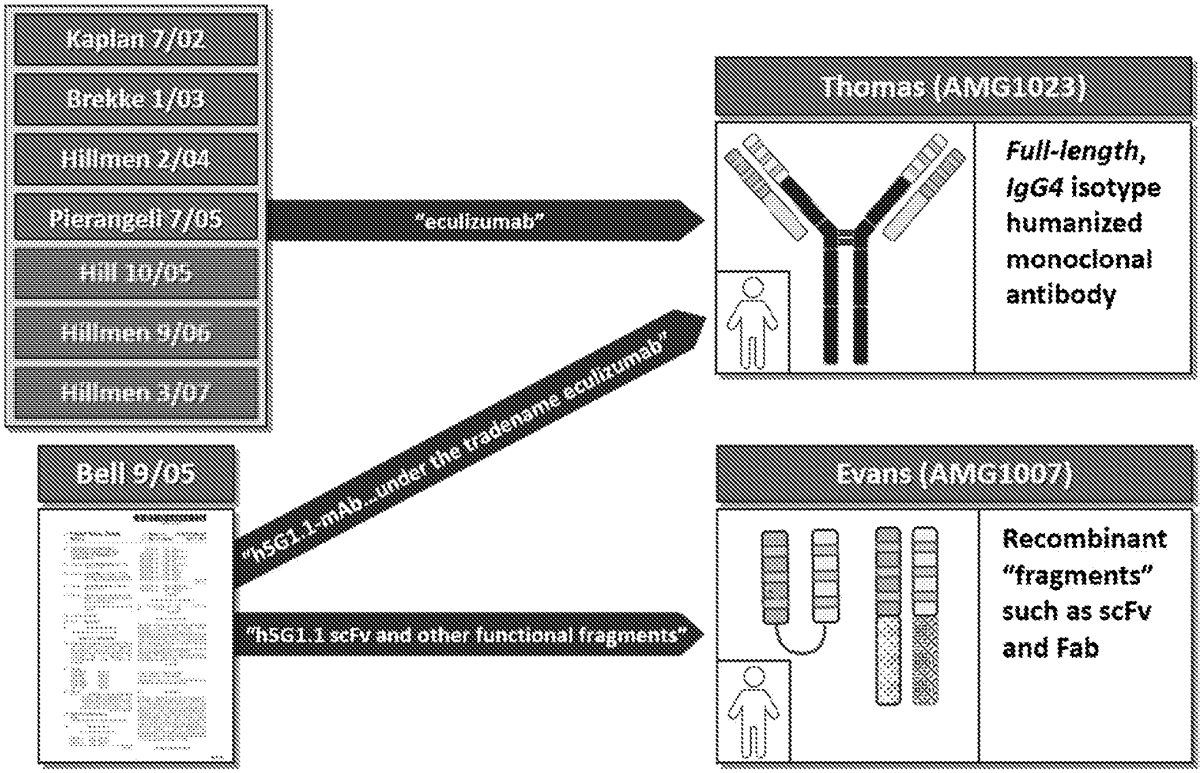
Amgen further concedes that – just like Hillmen and Hillmen 2005 – ***nothing*** in Bell or Wang disclosed the amino acid sequence for "eculizumab," or provided the specific amino acid sequence recited in claims 1-3 of the '880 patent. (Petition, 46; AMG1002 ¶ 140 (admitting that Bell and Wang did not disclose "the requirement that the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4"); ALXN2032, 146:17-25, 257:13-18; ALXN2022, ¶¶193-196.) As Dr. Balthasar admitted, nothing in Bell disclosed or suggested to a POSA that "eculizumab" had a hybrid IgG2/G4 heavy chain constant region. (*See, e.g.*, ALXN2032, 151:4-12, 160:7-9; ALXN2022, ¶¶193-196, 203.)

Rather, as the Board recognized, to the extent Bell disclosed anything about the structure of "eculizumab," it would have directed a POSA towards an antibody with an ***IgG4*** heavy chain constant region – as did Hillmen, Hill, and the many other references prior to March 15, 2007 pointing to Thomas (AMG1023) for

disclosure of "eculizumab". (*See* IPR2019-00741, Paper No. 15, 21 n.14; ALXN2022, ¶¶118-23; *supra* Section II.C.) Accordingly, a POSA reading Bell would have envisioned "eculizumab" to have a different structure and amino acid sequence from an antibody consisting of SEQ ID NOs: 2 and 4 as claimed in the '880 patent. (ALXN2022, ¶¶193-94.)

Specifically, paragraph [0052] of Bell cited two documents – Thomas (AMG1023) and Evans (AMG1007) – for disclosing "[m]ethods for the preparation of h5G1.1-mAb, h5G1.1-scFv, and other functional fragments," and further identified "[t]he antibody h5G1.1-mAb" in this context as "eculizumab." (AMG1005, ¶ [0052]; ALXN2022, ¶¶195-198; ALXN2032, 160:18-162:11.) As Dr. Casadevall's **Figure 8** illustrates, a POSA as of March 15, 2007 reading Bell would have understood that, between Thomas and Evans, only Thomas could have disclosed "eculizumab," because only Thomas disclosed an intact, full-length humanized "h5G1.1" antibody, while Evans disclosed humanized scFvs and other

"fragments." (ALXN2022, ¶¶195-198; ALXN2032, 163:5-15, 163:25-164:5, 164:12-16; 169:13-18; *see supra* 5-6, Section IV.B.1.)



2. A POSA Would Not Have Been Motivated to Combine Bell's Teachings with Bowdish and Evans, or to Make the Specific Claimed Sequence

For the same reason Amgen contends that Bell would have motivated a POSA to make the specific monoclonal antibody "eculizumab" – a C5-binding, clinically-tested antibody that Bell and other clinical literature consistently described as having an ***IgG4*** isotype – a POSA would ***not*** have been motivated to

disregard Bell's teachings, and instead make a different antibody with the uniquely-engineered amino acid sequence recited in claims 1-3 of '880 patent.

A POSA would not have known of an antibody having the specific sequence claimed in the '880 patent – which differs from the IgG4 isotype antibody that Bell identifies as "eculizumab" – and would not have been aware that an antibody with the claimed sequence had ever been tested *in vitro* or clinically. (ALXN2022, ¶¶151-52, 193-94, 206; *see supra* Section II.B.) In view of the unpredictability in the field of therapeutic antibody design, a POSA knowing of the clinically-proven anti-C5 antibody "eculizumab" would not have been motivated to make an antibody with a different, unstudied amino acid sequence – which might neither bind C5, nor be therapeutically useful or suitable for human administration. (ALXN2022, ¶¶224-33.)

Amgen agrees, arguing in Ground 5 that a POSA as of March 15, 2007 reading Bell would have been specifically motivated to make "eculizumab," and not other, different antibodies. (Petition, 46-48, 55; AMG1002 ¶¶124, 149; *see also* ALXN2032, 154:1-7.) But then, Amgen disregards what Bell and other literature ***actually*** taught actually about "eculizumab" – that it was an IgG4 isotype antibody as described in Thomas. There is no reason why a POSA without the benefit of hindsight would have jumped from Bell to Bowdish for an

understanding of "eculizumab," as Amgen contends. *See, e.g.*, *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Amgen's hindsight-driven rationale for combining Bell (regarding the anti-C5 antibody "eculizumab") with Bowdish (regarding a TPO-mimetic fusion compound) falls apart under scrutiny, because it depends on assumptions that lack support or even expressly contradict the art's teachings as of March 15, 2007. For example, Amgen asserts that Bowdish was an "eculizumab teaching[] in the art." (Petition, 55.) But there is no dispute that Bell (and Wang and Evans) did ***not*** cite to Bowdish for "eculizumab" or otherwise, and Bowdish itself made no mention of "eculizumab." (ALXN2022, ¶¶199-202; ALXN2032, 170:5-10, 199:9-12.) Nor did any of the other publications cited by Amgen (*e.g.*, Hill, Hillmen, *etc.*) cite Bowdish for "eculizumab" or otherwise. Bowdish did not concern the development of anti-C5 antibodies, all, but rather focused on generating peptide-mimetic fusion compounds having nothing to do with C5 binding or treatment of PNH. (*See, e.g.*, AMG1006 ¶ [0006]; ALXN2022, ¶¶161, 164, 202-04; ALXN2032, 174:2-12, 175:22-176:6, 180:8-11, 181:5-15.)

Dr. Balthasar's only stated "reason" for a POSA to "look to Bowdish" and "link" Bowdish to Bell (AMG1002, ¶150) further reveals his use of improper hindsight. (ALXN2022, ¶¶199-207.) As Dr. Balthasar contends, a POSA would have connected Bell and Bowdish because (1) Bell's "eculizumab was ... known to

be [a] humanized 5G1.1 with a hybrid IgG2/IgG4 constant region," and (2) "Bowdish ... provides most of the sequence of humanized 5G1.1 with a hybrid IgG2/IgG4 constant region." (AMG1002 ¶ 150; ALXN2032, 196:15-23, 197:15-25; *see also* Petition, 55-57.) That "reason" falls apart under scrutiny.

First, Amgen and Dr. Balthasar are wrong to suggest that Bowdish identified its TPO-mimetic compound as relating to "humanized 5G1.1" or "h5G1.1." (*See, e.g.*, Petition, 56 (claiming that Bowdish "explicitly direct[ed]" a POSA to look to Evans for "information" on the "h5G1.1 antibody" used to generate Bowdish's TPO-mimetic compound).) As Dr. Balthasar admitted, Bowdish used the term "5G1.1," not "h5G1.1" or "humanized 5G1.1"; and nothing in Bowdish said that the "scaffold" antibody used to generate its TPO-mimetic compound was a "humanized antibody." (ALXN2032, 199:19-23, 200:24-200:2; ALXN2022, ¶¶165, 205, 223.) Rather, Bowdish references the '283 application (issued as Evans) for "[c]onstruction of 5G1.1" – a term that, as discussed above, refers to a ***mouse*** antibody when used in Evans. (*See supra* Section IV.B.1.) And even if a POSA did understand Bowdish to be referencing Evans for disclosure of an "h5G1.1 antibody" that was used as Bowdish's "scaffold," they would have found none, because Evans did not disclose ***any*** full length humanized antibodies derived from "5G1.1." (ALXN2032, 163:5-15; ALXN2022, ¶223.)

Second, Bell suggested that "eculizumab" had an ***IgG4*** constant region, and nothing in Bell pointed towards a hybrid IgG2/IgG4 constant region. (*See,* ALXN2032, 146:17-25, 151:3-12, 160:7-9.) Amgen's attempt to associate "eculizumab" with a hybrid IgG2/IgG4 structure ignores Bell entirely, and instead relies on ***non-prior art*** information, and Mueller (AMG1008) which does not mention "eculizumab" at all. (ALXN2032, 55:5-57:1, 58:23-59:3, 59:23-60:6, 60:13-16, 61:13-62:4, 63:5-64:19.) For example, Amgen relies on out-of-context statements made in 2011 from the file history of U.S. App. No. 11/127,438 ("the '438 application") – which is not related to the '880 patent.[6] (*See, e.g.*, Petition, 13-14 (citing AMG1049, 838-39).) These non-prior art statements cite ***nothing*** dated prior to March 15, 2007 identifying "eculizumab" as having a hybrid IgG2/IgG4 constant region. Instead, they cite Mueller II (AMG1031) – a document that makes no mention of "eculizumab," and merely identified "h5G1.1

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[6] Amgen and Dr. Balthasar also rely on a non-prior art publication from November 2007 (AMG1033), and a 2017 submission from an Alexion employee during prosecution of the '880 patent (AMG1016, 733-40). (*See* Petition, 18, 37, n. 16; AMG1002, ¶¶11, 56; ALXN2032, 55:5-20, 56:24-57:1, 58:23-59:3, 64:8-14.)

HuG4" and "h5G1.1 HuG2/G4" as experimental controls – of which ***only*** the "HuG4" antibody was described as an "anti-C5 antibody." (AMG1031, 442-44; *see also* AMG1008, 11:36-12:32; ALXN2022, ¶¶166, 239; ALXN2032, 235:6-19, 237:8-15, 237:25-238:5, 238:13-19.) The prior art must be viewed "***without the benefit of the invention***" – and Amgen failed to do so by disregarding the overwhelming teaching by Bell and the other art prior to March 15, 2007 that "eculizumab" was described as the IgG4 antibody of Thomas. *See Neptune Generics, LLC v. Eli Lilly & Co.*, IPR2016-00237, Paper 84, 74-77 (Oct. 5, 2017), *aff'd*, 921 F.3d 1372 (Fed. Cir. 2019).

Third, Dr. Balthasar admits that nothing in Bowdish referred to its TPO-mimetic compound as having an "IgG2/IgG4" constant region structure. (ALXN2032, 212:22-213:2, 214:2-7.) And Dr. Balthasar fails to prove his contention that a POSA would have identified the hybrid IgG2/IgG4 structure of Bowdish's TPO-mimetic compound using "BLAST or a similar search tool." (ALXN2032, 212:22-213:2, 214:2-7.) Bowdish itself did not guide a POSA to apply such "search tools" to its peptide-mimetic compounds. (ALXN2022[CasadevallDecl], ¶204; ALXN2032, 214:19-24.) Further, Amgen presents ***no evidence*** of "the search results that a POSA would have gotten if, prior to March 15, 2007, they had tried to evaluate the sequences in Bowdish Figures

13A and 13B using 'BLAST or a similar search tool.'" (ALXN2032, 214:25-215:8.)

A POSA also would not have connected Bell and Bowdish simply because Bowdish used the term "5G1.1." (ALXN2022, ¶207.) As Dr. Balthasar testified, a POSA would have understood that the term "5G1.1" alone was ***not*** limited to "eculizumab," and depending on the context, could refer to the original "5G1.1" hybridoma, the "5G1.1" mouse antibody from the hybridoma (as used in Evans), as well as many possible "variants" of that antibody with different structures and sequences. (ALXN2032, 98:22-99:8, 100:16-24, 165:5-21; 169:6-18; 202:24-203:16; ALXN2022, ¶¶95-96.) In contrast, the term "eculizumab" as used in Bell referred to only one humanized monoclonal antibody, having a specific (but unknown) amino acid sequence. (*See supra* Section II.B.) A POSA looking for more information on "eculizumab" thus would have considered the art's pertinent teachings regarding "***eculizumab*** **– *not*** the far broader term ***"5G1.1."*** (ALXN2022, ¶207.) And a POSA certainly would not have focused on Bowdish, which contained no data showing that its TPO-mimetic compound or its "scaffold" antibody would bind C5 or treat complement-mediated conditions such as PNH. (ALXN2022, ¶¶201, 232-33.)

Amgen's Ground 5 improperly uses the '880 patent as a ***reference point*** for reconstructing the amino acid sequence of the claimed antibody, from sequences

selectively combined from Bowdish and Evans. (*See, e.g.*, AMG1002 Figs. 4-7, 13 (hindsight sequence comparisons between the '880 patent and select sequences from Bowdish or Evans), and Figs. 3, 10, 11 and 12 (using green coloration to signify sequences corresponding in hindsight to the '880 patent).) As Dr. Balthasar concedes, a POSA could not have made any of these comparisons, because a POSA would not have had access to the sequence of the '880 patent. (ALXN2032, 222:7-224:24.) Further, Amgen and Dr. Balthasar disclose ***only*** the carefully-selected prior art sequences from Bowdish and Evans that they knew ***in hindsight*** would "align[] perfectly" with the '880 patent sequence that was not available to a POSA prior to March 15, 2007. (*See, e.g.*, AMG1002 ¶¶53, 55.) But "working backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019).

For example, Amgen presented hindsight alignments between the '880 patent and portions of Evans SEQ ID NO:20 – a humanized scFv compound (AMG1002, ¶55) – but withheld from the Board the many other disclosures in Evans that would ***not*** have aligned with the claimed sequence, including:

- Evans Figures 18 and 19 – the variable regions of the mouse antibody that Bowdish references (with respect to the '283 application) for

"[c]onstruction of 5G1.1" (ALXN2022, ¶¶214-15; ALXN2032, 169:19-170:4);

- The "Fd" molecules of Evans SEQ ID NOs: 11, and 12, which a POSA would have understood were more "complete" fragments of a humanized antibody than an scFv, and provide sequences in the constant region (and for SEQ ID NO: 11, the variable region) that do not align with the '880 patent sequence (ALXN2022, ¶¶ 129, 158); and
- The eight other humanized "scFv" molecules of Evans, which Dr. Balthasar admits were different from SEQ ID NO: 20 (*See* AMG1007, 43:6-14, 43:62-45:4; ALXN2022, ¶157; ALXN2032, 222:22-223:9)

Even assuming the disclosures of Bowdish and Evans were fully combined, a POSA without hindsight would not have been directed to the complete amino acid sequence recited in claims 1-3 of the '880 patent. Among other things, a POSA would not have reasonably assumed that "heavy chain CDR3" referenced in Bowdish was the same as the heavy chain CDR3 described in Evans for humanized scFv compounds, which are ***not*** full-length structures like the TPO-mimetic compound of Evans. (ALXN2022, ¶¶216-220.) Even if a POSA reading Bowdish were to consider Evans for its disclosure of heavy chain CDR3 sequences, Evans allows for multiple options, and nothing in Bowdish or Evans indicates which, if any, were used in the "scaffold" antibody used to produce Bowdish's TPO-

mimetic peptide. (AMG1006, [0005]-[0006], [0191]-[0192]; [ALXN2022, ¶¶216-220.)

Amgen further uses improper hindsight by ignoring the disclosure of variable region sequences in ***Thomas*** (AMG1023), which Bell cites alongside Evans. If, prior to March 15, 2007, a POSA reading Bell were to have followed its reference to Thomas for "eculizumab," they would have been directed to variable region sequences that would ***not*** "align perfectly" with the non-prior art '880 patent sequence. (ALXN2022, ¶250.) For example, all of the light chain regions disclosed for "5G1.1" and various mouse and humanized compounds derived from "5G1.1" disclosed in Thomas have an arginine ("R"), light chain position 38, whereas the claimed sequence of the '880 patent has a glutamine ("Gln"). (AMG1023, 1392, 1396; ALXN2022, ¶250.)

3. The Combination of Bell, Wang, Bowdish and Evans Would Not Have Motivated a POSA to Make the Claimed Pharmaceutical Compositions, or Given a POSA a Reasonable Expectation of Success in Doing So

Even if the claimed amino acid sequence of the '880 patent was disclosed by Bowdish and Evans – which Amgen has not shown – Amgen still cannot show that the claimed pharmaceutical compositions of the '880 patent would have been obvious. First, nothing in Bowdish and Evans would have motivated a POSA to formulate the claimed antibody in a composition "for use in treating a patient

afflicted with [PNH]" (claim 1), or taught an "anti-C5" antibody (claims 2 and 3). As discussed above, a POSA would not have understood Bowdish and Evans to disclose "eculizumab" or any full-length humanized anti-C5 antibody. (*See supra* Section IV.C.2.)

Second, nothing in Bowdish, Evans, or any other published literature report that an antibody having the claimed sequence of the '880 patent had been clinically tested. (ALXN2022[CasadevallDecl], ¶¶133-34.) The only antibody identified in the pre-March 15, 2007 literature as having been tested in clinical trials for safety and efficacy in treating PNH, was the ***IgG4*** antibody of Thomas. (*See supra* Section II.C.) With no binding data, *in vitro* or animal testing, or clinical testing of the claimed antibody that Amgen assembles in hindsight from Bowdish and Evans, a POSA would have had no motivation to use that antibody in the claimed pharmaceutical compositions for treatment of PNH. (ALXN2022, ¶¶77-90, 133-136.) *See, e.g.*, *Endo*, 894 F.3d, 1380. Given the unpredictability of humanized monoclonal antibody design and development, a POSA would have had no reasonable expectation of success in making and using the claimed compositions for their intended purpose. (ALXN2022, ¶¶77-90, 133-36, 224-233; *supra* Section II.A.) *See OSI Pharms.*, 939 F.3d, 1383.

A POSA also would not have been motivated to make a "IgG2/IgG4" isotype – which Bowdish and Evans did not disclose – based on references that

Amgen cites regarding the purported benefits of that hybrid (*e.g.*, reduced immunogenicity). A POSA "would not have turned to a [hybrid isotype] approach to solve an undefined problem," when a POSA would have seen the clinical literature pointing Thomas's IgG4 antibody as safe and effective to treat PNH, and understood purported benefits of IgG2/IgG4 hybrids to be speculative and clinically untested. (ALXN2022, ¶¶77-90, 133-36, 226-27, 256-57.) *See, e.g.*, *Amerigen Pharm.*, 913 F.3d, 1087.

Nor would Bowdish, Evans, Bell and Wang have motivated a POSA to make any pharmaceutical composition of the claimed antibody for use in treating PNH or any other condition. A POSA would not have reasonably expected that an uncharacterized antibody would be suitable for formulation at all – particularly if it were thought to have a new hybrid isotype like IgG2/G4. (ALXN2024 ¶¶66-73; *see supra* Section IV.B.2.) Nothing in Bowdish, Evans, Bell or Wang would have motivated a POSA to make the specific claimed composition of claims 1 and 3: a "sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml [anti-C5] antibody solution." (ALXN2024 ¶¶74-89; *see supra* Section IV.B.2.)

D. Amgen's Ground 6 Fails Because Amgen Cannot Show that Claims 1-3 Would Have Been Obvious Over the Combination of Bell, Wang, Evans and Mueller

Amgen's Ground 6 contends that claims 1-3 of the '880 patent would have been obvious over a combination of Bell (AMG1005), Wang (AMG1028), Evans (AMG1007) and Mueller (AMG1008). As the Board found, Amgen's Ground 6 fails, because it relies upon Amgen's present-day knowledge of the antibody sequence recited in claims 1-3 of the '880 patent, which Amgen uses as a guide to pick and combine sequences that it knows in hindsight will align with it. Without the benefit of hindsight, a POSA would have ***no motivation*** to combine Evans with Mueller to obtain the claimed antibody of the '880 patent; would have had ***no reason*** to pick and combine the specific sequences that Amgen selects from Evans and Mueller to reconstruct the claimed antibody of the '880 patent; and would have ***no reasonable expectation*** that such a new untested antibody would be suitable "for use in treating a patient afflicted with [PNH]," as claim 1 requires, or would be an "anti-C5 antibody," as claims 2 and 3 require. (ALXN2022, ¶¶234-260.) As stated above, even if Amgen's combination of Evans and Mueller were made, a POSA would not have been motivated to make, or reasonably expected success in making, the specific claimed pharmaceutical compositions of the '880 patent. (*See supra* Section IV.B.2.)

As with Ground 5, Amgen's Ground 6 relies on Bell (AMG1005) and Wang (AMG1028) for their disclosure of "eculizumab," as allegedly supplying every element of claims 1-3 except the claimed amino acid sequence. (Petition, 58; AMG1002 ¶ 155.) As stated above, Bell and the overwhelming weight of the other art would have directed a POSA towards the IgG4 antibody of Thomas. (*See supra* Section II.C.)

Amgen cannot explain why a POSA would have leapt from Bell to Mueller, which Bell does not cite. Amgen states that a POSA would have been motivated to do so by Mueller's teachings regarding whether its hybrid "G2/G4" constant regions would "activate the complement system." (Petition, 61.) But, a POSA would have understood Thomas's antibody, cited for "eculizumab," to have been proven safe and effective in Phase II and Phase III clinical trials for treatment of PNH. (ALXN2022, ¶¶121-123.) A POSA with the proven clinical evidence pointing towards Thomas's antibody would have had no motivation to change it. *See Amerigen Pharms.*, 913 F.3d, 1087.

Amgen is also wrong that a POSA would have turned from Bell to Mueller because they both reference "h5G1.1." (Petition, 61.) As Dr. Balthasar admitted, "h5G1.1" was a broad term that could potentially refer to a number of different antibody structures (ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14) – and the only full-length "h5G1.1" antibody referenced in Bell is the IgG4 isotype antibody

of Thomas that Bell cites as describing "eculizumab." (ALXN2032, 163:12-15, 163:25-164:5, 164:12-16; 169:13-18.)

Nor would a POSA have been motivated to combine Evans with Mueller. As the Board noted, Mueller did not cite to Evans, and Evans did not cite to Mueller. (Paper No. 15, 54; ALXN2022, ¶239; ALXN2032, 170:21-171:20, 243:16-20.) A POSA also would not have been motivated to consult Evans and Mueller simultaneously, because they addressed very different technological problems. *See, e.g.*, *Broadcom*, 732 F.3d, 1334. While Evans characterized and tested the complement-blocking activity of the anti-C5 mouse "5G1.1" antibody and certain derivative compounds, Mueller studied antibodies to the porcine "VCAM" protein for treating or diagnosing human rejection of transplanted animal tissue, and did not include any experiments or data on C5 binding or blocking C5 cleavage. (AMG1008, 1:4-19, 7:21-28, 8:34-13:16; ALXN2022, ¶¶166, 239.) Insofar as Mueller described two "h5G1.1" antibodies – "h5G1.1 CO12 HuG4" and "h5G1.1 CO12 HuG2/G4" – these were exclusively used as "controls" for Mueller's study of its anti-VCAM antibodies. (AMG1008, 12:27-30; ALXN2022, ¶239; ALXN2032, 232:6-16.)

Amgen is incorrect a POSA "would have readily understood" Mueller's "h5G1.1 CO12 HuG2/G4 mAb" to be "eculizumab." (Petition, 67; *see also* Petition, 63; AMG1002 ¶166.) Neither Evans nor Mueller mentioned

"eculizumab." (ALXN2032, 102:10-14, 199:15-17; ALXN2022, ¶167.) And, contrary to Amgen's assertions, the "overwhelming evidence in the art" was that the C5-binding, clinically proven antibody "eculizumab" antibody was Thomas's ***IgG4*** isotype antibody. (*See supra* Section II.C.) Consistent with that teaching, Mueller identified ***only*** the "h5G1.1 CO12 HuG4" antibody as an "anti-C5" antibody. (AMG1008, 12:1-3; ALXN2022, ¶167; *see supra*, 53-54, 63.)

Further, as the Board recognized, Amgen fails to show how a POSA without hindsight would have been motivated to combine specifically-selected sequences from Evans and Mueller, in the specific manner required to get the specific amino acid sequence of the antibody claimed in the '880 patent. (*See* Paper No. 15, 54-57.) Amgen's figures illustrate its use of improper hindsight. For example, Amgen's Figure 14 mistakenly suggests that a POSA would have understood that Mueller and Evans to have disclosed the same single antibody, with part of the sequence being provided in Evans, and part of the sequence being provided in Mueller. (Petition, 60, Fig. 14; AMG1002 ¶ 156.) But, as Dr. Balthasar admits, Mueller did ***not*** disclose the amino acid sequence of any full-length "h5G1.1" antibody. (ALXN2032, 232:17-21; ALXN2022, ¶168.) Nor did Evans provide a partial sequence for a full-length humanized antibody, as Amgen's Figure 14 suggests. Rather, a POSA would have seen that Evans disclosed only a full-length "mouse" antibody, and truncated compounds like scFvs and Fabs that were ***not***

fragmented off a full-length antibody, but rather were produced from scratch using recombinant DNA technology. (ALXN2022, ¶243; *see supra*, 20-22.)

Neither Mueller nor Evans provided any ***guidance*** on how to combine their various sequences. As with Ground 5, Amgen's Ground 6 uses its present-day knowledge of the '880 patent to justify its selection and combination of sequences, by showing carefully curated sequence alignments that Amgen knows in hindsight will match with the claimed sequence. (AMG1002 Figs. 10, 14-16; ALXN2022 ¶¶245-253.)

And, as stated above for Ground 5: Even if a POSA were to have combined sequences from Evans and Mueller in the exact way that Amgen does in hindsight to reconstruct the claimed antibody, a POSA would not have (1) reasonably expected that the claimed antibody would be suitable "for use in treating a patient afflicted with [PNH]" (claim 1) or would even be "anti-C5" (claims 2-3); (2) been motivated to make, or reasonably expected to succeed in making, a "pharmaceutical composition" of the claimed antibody for use in treating PNH (claim 1) or suitable for any other complement-mediated condition (claims 2-3); or (3) been motivated to make, or reasonably expected to succeed in making, a "sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml [anti-C5] antibody solution" using the claimed antibody (claims 1-3). (*See supra* Section IV.B.2.)

As Dr. Balthasar conceded, nothing in Mueller disclosed that its "h5G1.1 CO12 HuG2/G4" antibody binds to C5; and nothing in Evans disclosed the binding properties of any full-length humanized antibodies, let alone one with a hybrid "IgG2/IgG4" constant region (which Evans also does not disclose). (ALXN2032, 247:13-18, 163:12-15; 163:25-164:5; 169:6-170:4; (ALXN2022, ¶¶155-156.) With such an uncharacterized antibody, a POSA would have had no motivation or reasonable expectation of success in using it to treat PNH patients, or to include it in any pharmaceutical formulation suitable for human administration. (*See supra* Section IV.C.3; ALXN2022 ¶¶254-260.)

And, nothing in Bell or Wang would have motivated a POSA to make the specific claimed composition of claims 1 and 3: a "sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml [anti-C5] antibody solution." (*See supra* Section IV.B.2.)

E. The Objective Indicia of Nonobviousness Support Validity

Objective indicia of nonobviousness, including commercial success, long-felt but unmet need, and industry praise, further support the validity of the claims 1-3 of the '880 patent. *See, e.g., LEO Pharm. Prods., Ltd. v. Rea,* 726 F.3d 1346, 1358 (Fed. Cir. 2013).

There is no question that SOLIRIS® (eculizumab) is the commercial embodiment of the '880 patent, and that the objective evidence regarding

SOLIRIS® and its commercial and therapeutic success has a direct nexus to the '880 patent. The '880 patent claims pharmaceutical compositions of the sole active ingredient in SOLIRIS®: the uniquely-engineered, non-naturally occurring antibody comprising SEQ ID NOs: 2 and 4, which is responsible for the remarkable clinical properties of SOLIRIS®, and consequently, its commercial success as a treatment for PNH, as well as the complement-mediated hemolytic condition aHUS, and the neurologic conditions myasthenia gravis and NMOSD. (ALXN2022, ¶¶263-66; ALXN2032, 262:2-19.) *See, e.g., Henny Penny,* 938 F.3d, 1332; *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392-93 (Fed. Cir. 1988). Claims 1 and 3 more specifically claim the pharmaceutical composition of SOLIRIS®, which is supplied as a 300 mg single-dose vial containing 30 mg of a 10 mg/ml solution of the claimed antibody, and has an indication for "[t]he treatment of patients with [PNH] to reduce hemolysis." (ALXN2053, 1; ALXN2022, ¶278.)

SOLIRIS® is unquestionably a huge commercial success. The annual net product sales for SOLIRIS® have grown consistently since launch, including total U.S. sales of $1 billion over the past three years, continuing to grow to over $1.588 billion in 2018 (a 28.6% increase from 2017). (ALXN2056; ALXN2059-ALXN2073.)

The invention of the '880 patent, in its commercial embodiment of SOLIRIS®, also fulfilled a long-felt, unmet need for a safe and effective treatment for PNH, a rare and potentially fatal blood disease. (ALXN2022, ¶¶268-77.) *See, e.g., Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994, 997-998 (Fed. Cir. 2009). Before SOLIRIS®, PNH patients had to suffer with debilitating symptoms and life-threatening thrombosis, and were often dependent on frequent blood transfusions for survival. (AMG1047, 2559; AMG1012, 1234; ALXN2022[, ¶¶271-72.) SOLIRIS® was the ***first*** FDA-approved treatment to reduce hemolysis in patients with PNH – transforming patients' quality of life and reducing their transfusion dependency. (ALXN2022, ¶¶270-75.) While other researchers were interested in developing anti-C5 antibodies for treating PNH and other untreated complement-mediated conditions, only the inventors of SOLIRIS® succeeded in doing so. (ALXN2022, ¶¶276-77; ALXN2032, 262:23-263:3, 263:23-264:13; AMG1039.)

SOLIRIS® has also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade for pharmaceutical research and development), including the Prix Galien USA 2008 Award for Best Biotechnology Product, and the Prix Galien France 2009 Award for Most Innovative Drug for Rare Disease. (ALXN2020; ALXN2021; ALXN2022, ¶¶281-82.)

The substantial efforts by Amgen and other companies to copy SOLIRIS® with its their proposed biosimilar eculizumab products – which would necessarily include the claimed antibody of the '880 patent – is further strong evidence of the nonobviousness of the '880 patent. (ALXN2088; ALXN2090; ALXN2089; ALXN2022 ¶¶283-84.) That Amgen and at least three others have chosen to copy the specific amino acid sequence of the '880 patent, rather than make a different anti-C5 antibody with a different amino acid sequence, evidences the significant impact of the '880 patent's invention. *See Liqwd, Inc. v. L'Oreal USA, Inc.*, --- F.3d ---, 2019 WL 5587047,*2 (Fed. Cir. Oct. 17, 2019).

V. CONCLUSION[7]

Alexion respectfully submits that the Board confirm the patentability of claims 1-3.

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[7] Alexion provides this Patent Owner Response without prejudice to its right to raise a further constitutional challenge on appeal, including but not limited to challenges to the Board's institution decision and final written decision, based on the Federal Circuit's resolution of pending challenges. *Arthrex, Inc. v. Smith & Nephew, Inc.*, 2019 WL 5616010, at *11 (Fed. Cir. Oct. 31, 2019).

Respectfully submitted,

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The undersigned hereby certifies that the portions of the above-captioned **PATENT OWNER RESPONSE** specified in 37 C.F.R. § 42.24 has 13,682 words, in compliance with the 14,000 word limit set forth in 37 C.F.R. § 42.24.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00741
Patent: 9,732,149

PATENT OWNER RESPONSE PURSUANT TO 37 C.F.R. § 42.120

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TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 8

A. Design of Humanized Monoclonal Antibodies for Human Therapeutic Use Was a Complex, Unpredictable Art 8

B. Naming of Humanized Monoclonal Antibodies 12

C. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" to be the IgG4 Monoclonal Antibody of Thomas 13

D. The Structure and Sequence of SOLIRIS® Was *Not* Known Prior to March 15, 2007 20

E. Overview of the '149 Patent 27

F. Prosecution History of the '149 Patent and Related Applications 28

III. PERSON OF ORDINARY SKILL IN THE ART OF THE '149 PATENT 29

IV. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF CLAIM 1 OF THE '149 PATENT 30

A. Amgen's Grounds 1 and 2 Fail Because Amgen Cannot Show that Claim 1 Was Anticipated by Hillmen or Hill 30

1. Hillmen and Hill Did Not Disclose an Antibody "Comprising a Heavy Chain Consisting of SEQ ID NO: 2 and a Light Chain Consisting of SEQ ID NO: 4" 30

2. Neither Hillmen nor Hill Inherently Disclosed the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claim 1 of the '149 Patent 32

B. Amgen's Ground 3 Fails Because Amgen Cannot Show that Claim 1 Was Anticipated by Bowdish 33

1. Bowdish Did Not Disclose or Incorporate by Reference an Antibody Comprising SEQ ID NO: 2 and SEQ ID NO: 4 35

Table of Contents
(continued)

Page

2. Bowdish, Even if Combined with Evans in its Entirety – Did Not Disclose, Either Expressly or Inherently, an Antibody with the Specific Sequences Recited in Claim 1 of the '149 Patent 44

3. Bowdish Did Not Disclose "[A]n Antibody that Binds C5" Having the Sequence Claimed in the '149 Patent 48

C. Amgen's Ground 4 Fails Because Amgen Cannot Show that Claim 1 Would Have Been Obvious Over the Combination of Bell, Bowdish and Evans 50

1. Bell Did Not Disclose the Claimed Sequence, and Would Not Have Motivated a POSA to Make the Claimed Antibody 51

2. A POSA Would Not Have Been Motivated to Combine Bell's Teachings with Bowdish and Evans, or to Make the Specific Claimed Sequence 54

3. A POSA Without Hindsight Would Not Have Reasonably Expected Success with the Combination of Bell, Bowdish and Evans 62

D. Amgen's Ground 5 Fails Because Amgen Cannot Show that Claim 1 Would Have Been Obvious Over the Combination of Evans and Mueller 63

E. The Objective Indicia of Nonobviousness Support Validity 67

V. CONCLUSION 70

Samsung Bioepis Exhibit No. 1002
Page 12722

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212 F.3d 1272 (Fed. Cir. 2000) 38

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2064	Alexion Form 10-K for FY 2012 (Excerpts)
2065	Alexion Form 10-K for FY 2013 (Excerpts)
2066	Alexion Form 10-K for FY 2014 (Excerpts)
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I. INTRODUCTION

Claim 1 of the U.S. Patent No. 9,732,149 ("the '149 patent") recites the novel, uniquely-engineered amino acid sequence of SOLIRIS®, the groundbreaking, commercially successful anti-C5 monoclonal antibody developed by Alexion. SOLIRIS®, also referred to today by its non-proprietary name "eculizumab," is a first-in-class treatment for patients with the rare, potentially fatal blood disease paroxysmal nocturnal hemoglobinuria ("PNH"), caused by red blood cells losing their normal protection against the "complement" immune pathway. SOLIRIS® works by binding to component 5 ("C5") of the complement pathway and preventing its cleavage into components "C5a" and "C5b," which mediate downstream effects of the complement pathway, including hemolysis in patients with PNH.

Prior to March 15, 2007, the priority date of the '149 patent, the unique amino acid sequence of SOLIRIS® recited in claim 1 of the '149 patent was ***not*** publicly known or disclosed in the prior art. While a person of ordinary skill in the art ("POSA") as of that date would have known that Alexion had designed and clinically tested an antibody named "eculizumab," the POSA would not have known that "eculizumab" had the uniquely-engineered amino acid sequence claimed in the '149 patent. That is because the literature as of March 15, 2007 consistently identified "eculizumab" as the antibody described in the "Thomas"

publication (AMG1023), which has a naturally-occurring "***IgG4***" heavy chain constant region. In contrast, the novel antibody of the '149 patent has a very different, uniquely-engineered, non-naturally occurring constant region. A POSA would not have known of any antibody with the specific sequence recited in claim 1 of the '149 patent, and would have had no basis to reasonably expect that such an antibody would bind C5 or have the therapeutic utility that the literature on "eculizumab" attributed to Thomas's IgG4 antibody.

Amgen has not shown how any of the prior art of its Grounds disclosed or would have led a POSA to the uniquely-engineered amino acid sequence of SOLIRIS® recited in claim 1 of the '149 patent. Instead, Amgen disregards the perspective of a POSA as of March 15, 2007, and impermissibly uses its ***hindsight knowledge*** of the '149 patent's novel, previously-undisclosed claimed sequence to misstate the disclosures of the prior art, pick and choose from those misstated disclosures, and reconstruct the claimed invention using the '149 patent's teachings as a guide. When the art is viewed from the proper perspective of a POSA, each of Amgen's Grounds fails.

Amgen's Grounds 1 and 2 fail because Amgen incorrectly presumes that a POSA would have understood that the clinical publications Hillmen (AMG1004) and Hill (AMG1047) somehow disclosed the claimed sequence of the '149 patent by using the name "eculizumab." But nothing within the four corners of the

Hillmen and Hill publications disclosed the present-day knowledge that eculizumab has the uniquely-engineered amino acid sequence described and claimed in the '149 patent. Rather, as the Board correctly recognized, both Hillmen and Hill identified "eculizumab" as the ***IgG4 antibody of Thomas***. (*See, e.g.*, Paper No. 15, 20-21 & n.14, 24-25, 27.)

Amgen's Ground 3, styled as anticipation by Bowdish (AMG1006), fails because a POSA would not have seen ***any*** disclosure in Bowdish of the uniquely-engineered C5-binding antibody consisting of SEQ ID NOs: 2 and 4 claimed in the '149 patent. Bowdish disclosed neither "eculizumab" nor any other antibody that binds C5. Rather, Bowdish described a very different compound – a "peptide-mimetic" compound designed solely for presenting the peptide hormone "TPO" on a neutral "scaffold" to enhance the peptide's stability and half-life.

Recognizing Bowdish's deficiencies, Amgen's Ground 3 instead culls and recombines sequences from ***two*** documents: Bowdish, and Evans (AMG1007) – a patent that did not describe ***any*** full-length humanized antibodies for binding C5, let alone the antibody of the '149 patent. Ground 3 first fails for lack of proof, because Amgen and its declarant admittedly neglected to consider and introduce in the record the ***actual*** document that Bowdish cites – the "'283 application," which is ***not*** AMG1007, the Evans patent itself. Even using the Evans patent as a stand-in for the '283 application (which it is not), Amgen overreads Bowdish's single

reference to Evans for "[c]onstruction of 5G1.1" – a mouse antibody whose sequence is nowhere close to the uniquely-engineered humanized antibody claimed in the '149 patent. Amgen cannot rewrite Bowdish's limited reference to construction of Evans's "5G1.1" mouse antibody as an open-ended incorporation of Evans's entire 93-page disclosure, including sequences for humanized fragments that are ***not*** the "5G1.1" antibody.

Even if Amgen were correct to read Bowdish as incorporating Evans in its entirety (which it does not) Amgen still cannot show how Bowdish anticipates the '149 patent, when the presently claimed antibody is not disclosed ***anywhere*** in the two references, alone or combined. Instead, Amgen attempts to recreate the '149 patent's novel, unique claimed sequence by mixing and matching bits and pieces of sequences plucked from Bowdish's full-length TPO-mimetic compound, and structurally distinct "scFv" compounds from Evans. That cannot be anticipation, which requires that "the prior art reference...show[s] the claimed invention ***arranged or combined in the same way*** as recited in the claim." *Net MoneyIN v. Verasign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008).[1]

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[1] Unless otherwise noted, all emphasis is added, and all internal citations and internal quotation marks are omitted.

Amgen's Grounds 4 and 5, alleging obviousness, fail because they rely on post-hoc knowledge of the '149 patent's unique claimed sequence to reconstruct that invention from bits and pieces of structurally and functionally distinct compounds in unrelated art. *See Merck Sharpe & Dohme B.V. v. Warner Chilcott Co.*, 711 Fed. App'x 633, 637 (Fed. Cir. 2017) ("[U]sing the [patent-in-suit] as a roadmap to piece together various elements of [the prior art] . . . represents an improper reliance on hindsight."). As Dr. Balthasar conceded at deposition, he was handed his cited prior art by counsel; he read only the portions of his references that he contends showed obviousness of the claimed invention; he could not testify with any "confidence" as to whether his references did or did not disclose key aspects of the claimed invention; and he assembled his figures based on the claimed sequence of the '149 patent that was not available to a POSA prior to March 15, 2007. (ALXN2032, 64:23-65:14, 74:16-75:5, 77:7-78:2, 85:10-17, 108:17-109:10, 148:24-149:10, 180:8-11, 244:17-245:9, 267:17-268:11.)

For example, Amgen's Ground 4 contends that a POSA would have started with Bell (AMG1005) – which identified "eculizumab" as a clinically studied anti-C5 antibody – and then surmises that a POSA would have turned to Bowdish and Evans for the sequence of "eculizumab." But as the Board recognized, Bell – like Hillmen, Hill, and the other pertinent art – informed a POSA as of March 15, 2007 that "eculizumab" was Thomas's ***IgG4*** antibody. (Paper No. 15, 21 n.14.)

Amgen cannot explain why a POSA would have ignored the clear and unequivocal direction toward Thomas' IgG4 antibody and instead looked to Bowdish, which was not even cited by Bell.

Nothing in Bowdish or Evans remotely indicated to a POSA that either reference, alone or in combination, disclosed the specific full-length antibody "eculizumab." A POSA would have had no reason to jump from Bell to the combination of Bowdish and Evans to learn anything about the structure or sequence of "eculizumab." It is undisputed that Evans did not disclose ***any*** full-length humanized antibody, let alone "eculizumab."

Likewise, nothing would have guided a POSA to turn from Bell to Bowdish for the structure of "eculizumab." Amgen assumes that a POSA considering the structure and sequence of Bell's "eculizumab" would have (1) selected Bowdish, rather than Thomas, as a starting point – despite that Bowdish never mentions "eculizumab," is not cited by Bell or any other prior art references defining "eculizumab," and does not even contain any C5-binding or clinical data suggesting that it might be associated with "eculizumab"; (2) identified Bowdish's TPO-mimetic compound as relating to a humanized antibody with a hybrid IgG2/IgG4 constant region – even though nothing in Bowdish contains such a statement; and (3) associated the purported IgG2/IgG4 structure of Bowdish's TPO-mimetic compound with "eculizumab" – despite the teaching in Bell itself,

and the consistent teaching throughout the prior art, that a POSA would have understood "eculizumab" to be an ***IgG4*** isotype antibody, which would not match with the sequence of a hybrid IgG2/IgG4 antibody.

Amgen's Ground 5 uses improper hindsight to recreate the claimed sequence of the '149 patent from sequences plucked from Mueller (AMG1008) and Evans. Mueller concerned antibodies directed at "VCAM" – a very different target from C5 – and used the antibody "h5G1.1 CO12 HuG2/G4 mAb" only as an "isotype control" for experiments involving VCAM. As the Board noted, Mueller identified only an ***IgG4*** isotype antibody (*i.e.*, the isotype of Thomas) as an "anti-C5 antibody," and taught nothing about the C5 binding or clinical properties of "h5G1.1 CO12 HuG2/G4 mAb."

Nor would a POSA would have been motivated to combine the sequences in Evans and Mueller – neither of which cites to the other – in the exact manner to get the specific claimed antibody sequence of the '149 patent. As the Board correctly recognized, nothing in Evans or Mueller instructs whether or how such a combination should be done, including "precisely the portions of Evans's and Mueller's disclosed amino acid sequences to use and which to discard so as to arrive at a final antibody that perfectly matched the claimed antibody." (Paper No. 15, 53-54.)

II. BACKGROUND

A. Design of Humanized Monoclonal Antibodies for Human Therapeutic Use Was a Complex, Unpredictable Art

There is no dispute that as of March 15, 2007, a POSA would have understood a "monoclonal" antibody (including a "humanized monoclonal antibody" such as "eculizumab") to be a single, unique antibody with one defined structure, and critically, ***one unique primary amino acid sequence*** for the entire antibody. (ALXN2022, ¶70; ALXN2032, 10:9-22, 11:10-17.) A humanized monoclonal antibody, in turn, was understood to be a unique antibody with a unique sequence, designed by grafting mouse monoclonal antibody sequences associated with antigen binding into a human monoclonal antibody. (ALXN2022, ¶¶76, 78.) And a POSA would have understood that a humanized monoclonal antibody for therapeutic use – the subject matter of the invention described and claimed in the '149 patent – was a humanized monoclonal antibody intended to bind its target and achieve a desired biological and therapeutic activity when administered to patients, while maintaining sufficient safety to be suitable for human administration. (*See* ALXN2022, ¶¶76-82, 86-90; ALXN2032, 43:15-22, 46:20-48:2.)

Critically, a POSA would have understood that development of a "humanized" antibody intended for human therapeutic use was a complex and

unpredictable art. (ALXN2022, ¶¶76-90.) A particular new humanized monoclonal antibody could not simply be assumed to retain the original mouse antibody's binding affinity and biological activity against its target antigen. Accordingly, a new humanized monoclonal antibody would need to be tested *in vitro* to establish its binding properties and its biological activity. (ALXN2022, ¶82.) Further, to determine the suitability of a new humanized antibody as a therapeutic agent, additional extensive testing would need to be performed, including "pre-clinical" toxicology testing in animal species; clinical testing of efficacy, immunogenicity, and overall safety; and pharmaceutical formulation work to confirm that a suitably stable composition could be safely and efficaciously administered to people. (ALXN2022, ¶¶77-90; ALXN2032, 46:20-48:2.)

Further, a POSA as March 15, 2007 could not reasonably extrapolate the *in vitro* or clinical properties of one monoclonal antibody with a unique amino acid sequence to a different antibody with a different sequence. A POSA would have understood that antibodies were complex three-dimensional structures, and that a monoclonal antibody's specific amino acid sequence was essential to its structure and function. (ALXN2022, ¶¶62-63, 70, 116.) In particular, it was known that even small changes in an antibody's sequence could affect its critical properties. (ALXN2022, ¶¶104-117.)

For example, a POSA would have understood that sequences ***beyond*** a monoclonal antibody's "CDRs" could substantially influence its antigen-binding properties, including its "affinity" (tightness of binding) for the target antigen, "specificity" for binding the target antigen versus non-targets, and "fine specificity" for binding the target antigen in the particular region ("epitope") needed to provide the desired therapeutic activity. (ALXN2022, ¶¶104-117.) It was well-known that non-CDR amino acids within an antibody's "variable" region (*i.e.*, "framework" residues) could impact antigen binding, either by direct involvement in binding or indirect effects on three-dimensional antibody structure. (ALXN2022, ¶106.) A POSA also would have known that the ***constant regions*** of monoclonal antibodies play an indirect role in antigen binding, and that switching between different constant regions ("isotype switching") could significantly impact antigen binding, even while leaving the variable region unchanged. (ALXN2022, ¶107-114.) In particular, the art described how changes to the "CH1" and "hinge" portions of the heavy chain constant region impact antigen affinity and specificity. (ALXN2022, ¶113; ALXN2012, 3388, 3391-92; ALXN2009, 13917-18, 13924.)

Once a suitable humanized monoclonal antibody was designed and tested to show it has its desired *in vitro* activity, it would need to be further studied with clinical tests in humans. (ALXN2022, ¶¶86-88.) A POSA would have been particularly concerned about the unpredictability of a humanized monoclonal

antibody for therapeutic use if, in addition to the mouse sequences of the variable region, it contained a non-naturally occurring constant region that was not known to have been clinically tested and shown to be suitable for human administration (*e.g.*, a hybrid constant region fusing sequences from different isotypes). (ALXN2022, ¶86.)

A POSA would have also understood that truncated antibody-like molecules could be made, containing amino acid sequences that include less than a full-length, intact humanized monoclonal antibody. (ALXN2022, ¶¶91-93.) While commonly called "fragments," these compounds were typically made by recombinant DNA means, rather than "broken off" from a full-length, pre-existing antibody. (ALXN2022, ¶91; ALXN2032, 143:18-22.) For example, a humanized single-chain Fv or "scFv" compound could be made, containing only the variable light and heavy chain regions connected by a linker; or an "Fab" compound could be made, containing a complete light chain but only the variable and CH1 constant region of the heavy chain ("Fd"), with no intact "Fc" region (the stem of the Y-shaped antibody structure). (ALXN2022, ¶¶67, 92; ALXN2032, 143:8-25.) A POSA would have understood that these "fragments" were very different from a full-length humanized antibody, and have different properties (*e.g.*, shorter half-life but greater tissue penetration). (ALXN2022, ¶93.) A POSA would have further understood that because the constant regions of a full-length, intact antibody could

impact its antigen-binding properties as well as its immunogenicity, the properties of a "fragment" lacking a full heavy chain constant region could not reliably be extrapolated to a new, untested full-length humanized monoclonal antibody. (ALXN2022, ¶¶93, 105-117.)

B. Naming of Humanized Monoclonal Antibodies

A POSA as of March 15, 2007 would have understood that different naming conventions were used for humanized monoclonal antibodies at different stages of development. (ALXN2022, ¶94.) Depending on the convention used and the stage of development, a POSA might understand that a particular name refers to a group of several related antibodies, or in other cases, that a specific non-proprietary name (*e.g.*, "eculizumab") or a brand name (*e.g.*, "SOLIRIS®") refers to a single, unique monoclonal antibody with one defined structure and one primary amino acid sequence. (ALXN2022, ¶¶ 94-103; ALXN2032, 10:9-11:17, 98:2-99:8, 100:3-24, 202:24-203:14.)

At early stages of development of a humanized monoclonal antibody, a POSA would have understood that informal research code names were commonly used, and typically referenced the original source mouse antibody from which the humanized antibody was generated (*e.g.*, "5G1.1"). (ALXN2022, ¶95; ALXN2032, 98:2-99:8, 202:24-203:14.) A POSA would have understood that, depending on the context, these code names could potentially refer to a number of

different structures or sequences. (ALXN2022, ¶95; ALXN2032, 98:2-99:8, 159:1-10, 202:24-203:14.)

In contrast, after a specific humanized monoclonal antibody with a single, unique sequence has progressed into clinical development, it may be assigned a "non-proprietary" name (*e.g.*, "eculizumab") by authorities including INN and USAN. (ALXN2022, ¶97.) A POSA would have understood that these non-proprietary names with respect to humanized monoclonal antibodies would refer to one – and only one – specific antibody as defined by its unique amino acid sequence. (ALXN2022, ¶¶100-101, 120; ALXN2032, 10:9-11:17, 98:19-99:8, 100:3-10; ALXN2046, 1; ALXN2045, 1210.) The same would be true when, as the product neared FDA submission, the research sponsor would propose a unique branded trade name (*e.g.*, "SOLIRIS®"). (ALXN2022, ¶102.)

C. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" to be the IgG4 Monoclonal Antibody of Thomas

As of March 15, 2007, a POSA would have understood that a unique humanized monoclonal antibody named "eculizumab," that specifically targets human C5 and prevents its cleavage, had been developed. (ALXN2022, ¶¶118-123; AMG1047, 2559 (citing Thomas, AMG1023).)

But the POSA as of March 15, 2007 would ***not*** have known that "eculizumab" had the sequence claimed in the '149 patent, including the uniquely-

engineered heavy chain constant region reflected in SEQ ID NO: 2. Rather, a POSA at that time would have believed that "eculizumab" contained an "***IgG4***" constant region – which is very different from the uniquely-engineered heavy-chain constant region recited in claim 1 of the '149 patent. (ALXN2022, ¶¶120-123; ALXN2032, 97:7-21.) Specifically, the literature regarding the development of "eculizumab" consistently described "eculizumab" by referencing Thomas (AMG1023). (ALXN2022, ¶¶120-123, 139, 205-208; ALXN2032, 125:13-126:9, 128:20-129:10, 192:13-22, 160:18-162:12.) Thomas, in turn, detailed the design and testing of a full-length, ***IgG4***-isotype humanized antibody ("humanized 5G1.1") with anti-C5 affinity, specificity, and complement-blocking activity comparable to the original mouse "5G1.1" antibody. (AMG1023, 1396-99; ALXN2022, ¶123; ALXN2032, 242:21-243:4.)

As the following table illustrates, a POSA would have had no doubt that "eculizumab" was Thomas's IgG4-isotype humanized antibody, because the pertinent literature consistently and unambiguously said so:

Table 1: References to "Eculizumab" as Thomas's Humanized IgG4 Antibody

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hillmen (AMG1004) at 553 – Phase II clinical trial for treatment of PNH	"***Eculizumab is*** a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components." (Citing ***Thomas***, Ref. No. 15)
Hill (AMG1047) at 2559 – 52-week extension of Hillmen Phase II clinical trial	"***Eculizumab is*** a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage." (Citing ***Thomas***, Ref. No. 9)
Hillmen 2006 (AMG1012) at 1234 – pivotal Phase III clinical trial for treatment of PNH,	"***Eculizumab (Soliris, Alexion Pharmaceuticals) is*** a humanized monoclonal antibody directed against the terminal complement protein C5." (Citing ***Thomas***, Ref. No. 13)
Hill 2007 (ALXN2028) – post-Phase III case report for PNH patient	"***Eculizumab is*** a novel humanized monoclonal antibody directed against the complement protein C5." (Citing ***Thomas***, Ref. No. 6)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Bell (AMG1005) at [0052] – Phase II clinical studies described in Hillmen and Hill	States that "[m]ethods for the preparation of h5G1.1-mAb" are described in ***Thomas***, and that "[t]he antibody h5G1.1-mAb is currently undergoing clinical trials under the name ***eculizumab***."
Kaplan (AMG1021) at 1018	States that "***Eculizumab*** (5G1.1), under development by Alexion Pharmaceuticals Inc. is a humanized C5 inhibitory monoclonal antibody (mAb)," and cites ***Thomas*** for the synthesis and complement-blocking activity of "intact humanized 5G1.1 antibody" or "humanized 5G1.1"
Brekke (AMG1019) at 56	"***Eculizumab*** (5G1.1; Alexion Pharmaceuticals) ***is*** a humanized monoclonal antibody that prevents the cleavage of human complement component C5" (citing ***Kaplan***, Ref. No. 31, which in turn cites to ***Thomas***)
Pierangeli (AMG1020) at 2123	Stating that "***eculizumab*** has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH]" (citing to ***Hillmen***, Ref No. 18, which in turn cites to ***Thomas***)

Looking at this literature, a POSA would have believed that Thomas's IgG4 antibody was the ***only*** full-length humanized antibody shown to bind C5 and prevent its cleavage, tested for safety and efficacy in treating PNH, and submitted to the FDA for marketing approval.[2] In Thomas, a POSA would have seen the extensive work in rationally designing an "intact" humanized monoclonal antibody preserving the anti-C5 activity of the "5G1.1" mouse antibody, using an IgG4 isotype. (AMG1023, 1393-99; ALXN2022, ¶123; ALXN2032, 242:21-243:4.) And, prior to March 15, 2007, a POSA would have seen that "eculizumab" – consistently identified as Thomas's IgG4 antibody – was shown to be safe and effective in treating PNH, and was submitted for FDA and European approval under the trade name SOLIRIS®. (*See, e.g.*, AMG1004, AMG1047, AMG1012, ALXN2028; AMG1005, ¶¶[0052], [0081-0096]; ALXN2022, ¶¶121-123.)

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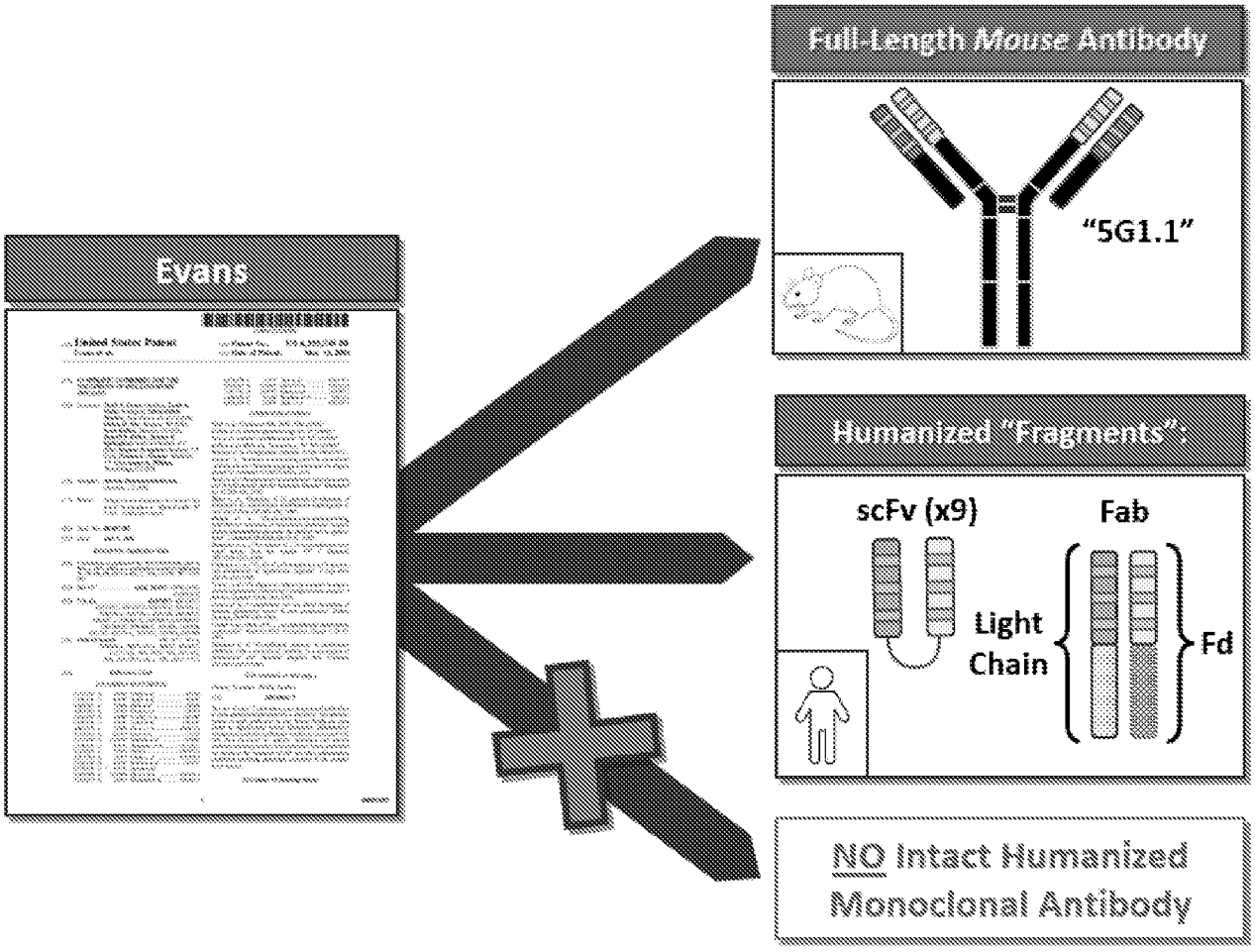
[2] Thomas also does not disclose the specific light chain amino acid sequence recited in SEQ ID NO: 4 of the '149 patent. In particular, the light chain variable region sequence provided by Thomas differs from SEQ ID NO: 4 of the '149 patent at amino acid position 38, flanking light chain CDR1. (*Compare* AMG1023 at 1392, 1396 (identifying position 38 as "R" (arginine)) *with* AMG1001 at col. 35, SEQ ID NO 4 (identifying position 38 as "Gln" (glutamine).)

In contrast to Thomas and the literature regarding "eculizumab" that followed Thomas, a POSA would have understood that Evans (AMG1007) did ***not*** disclose "eculizumab." (ALXN2022, ¶¶124-130.) Rather, a POSA would have understood that Evans described an earlier stage of research that predated the design of the intact, full-length humanized antibody "eculizumab" – because Evans did ***not*** disclose any full-length humanized antibodies. (ALXN2022, ¶¶124-128, 191, 198-199; ALXN2032, 163:12-15, 169:13-18.) At most, a POSA would have read Evans as a precursor to the research that resulted in "eculizumab."

As Dr. Balthasar agreed at deposition, the only full-length antibody described in Evans (AMG1007) is the "5G1.1" mouse antibody, which Evans obtained from the "5G1.1" hybridoma. (AMG1007, 19:47-49, Figs. 18-19; ALXN2032, 165:5-21, 169:13-18; ALXN2022 ¶¶125-128.) Evans further describes the researchers' characterization of the "5G1.1" mouse antibody, including its binding affinity, *in vitro* activity blocking complement in hemolytic assays, and the sequencing and cloning of the variable regions of the "5G1.1 mouse antibody." (AMG1007, Examples 7-10; ALXN2022 ¶125; ALXN2032, 165:5-169:23.) But Evans provides no such information for a full-length ***humanized*** antibody derived from the "5G1.1" mouse antibody – which a POSA would have understood would have a different amino acid sequence and different

clinical properties from the mouse antibody. (ALXN2022 ¶126; ALXN2032, 163:12-15, 169:24-170:4.)

To the extent Evans described "humanization" work based on the "5G1.1" mouse antibody, it was the development of recombinant "fragments" – scFv or Fab – that did ***not*** contain an intact heavy chain constant region, let alone the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2 of the '149 patent. (AMG1007, Example 11; ALXN2022 ¶126.) For example, Evans described nine different humanized "scFv" fragments, which are recombinantly-produced molecules containing two variable regions connected by a linker, with no constant region (AMG1007, 43:6-14, 43:62-45:4), and humanized "Fab" fragments that also lack the "Fc" portion (regions CH2 and CH3) of an intact antibody (AMG1007, 43:21-61). (ALXN2022 ¶126.) Notably, the humanized Fab fragments of Evans have ***different*** heavy chain sequences ("Fd," Evans SEQ ID NOs: 11 and 12) from the non-prior art SEQ ID NO: 2 of the '149 patent, including in "CH1" constant region. (ALXN2022 ¶129.) The following figure illustrates how a POSA would have understood what Evans did disclose – a mouse antibody and humanized "fragments" – and what Evans did not disclose, *i.e.*, an intact humanized monoclonal antibody:



D. The Structure and Sequence of SOLIRIS® Was *Not* Known Prior to March 15, 2007

Today, but ***not*** before the priority date for the '149 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in claim 1 of the '149 patent, namely, "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." A POSA prior to the '149 patent, however, would not have known of any antibody consisting of SEQ ID NOs: 2 and 4, and would

not have reasonably expected that such an antibody would bind to C5 or would have any therapeutic application in humans.

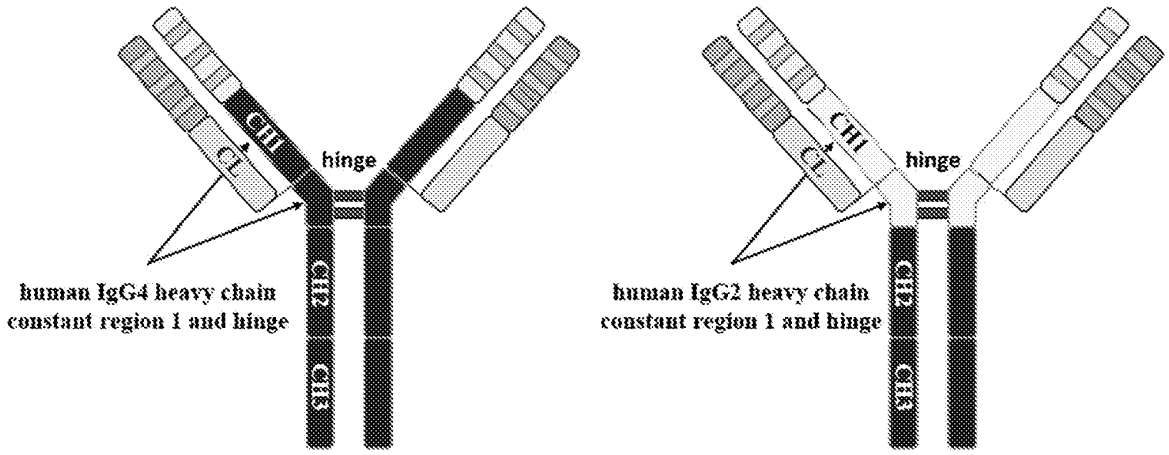
Today, but ***not*** prior to March 15, 2007, it is known that SOLIRIS® is a unique antibody that is ***very different*** from the humanized IgG4 antibody described in Thomas. As understood today, the heavy chain of SOLIRIS® (SEQ ID NO: 2) features a non-naturally occurring, uniquely-engineered constant region – containing sequences from both human IgG2 and IgG4 – that was designed by scientists at Alexion and was thoroughly tested in human clinical trials. (ALXN2022 ¶¶133-136.)

Notably, SOLIRIS® was the first FDA-approved product containing Alexion's uniquely-engineered heavy chain constant region. A POSA would not have been aware of any published clinical testing showing that an antibody with this uniquely-engineered constant region would be therapeutically useful and suitable for human administration.

The presently-known structure of SOLIRIS® reflected in claim 1 of the '149 patent is shown below in comparison to the IgG4 isotype antibody described in Thomas, which the literature prior to March 15, 2007 would have taught a POSA was "eculizumab." The figure depicts how, unlike the IgG4 antibody of Thomas, the claimed antibody uses the CH1 and "hinge" regions of IgG2, thereby providing

a meaningfully different antibody than that identified in the literature citing to Thomas.

Figure 2: **Left** – Structure of the IgG4 isotype antibody referenced to as "eculizumab" in the literature as of March 15, 2007
Right – Structure of SOLIRIS®, having a non-naturally occurring, protein-engineered isotype



Amgen's and Dr. Balthasar's arguments fail because they are based on the erroneous assumption that a POSA would have understood "eculizumab" to contain "a hybrid IgG2/IgG4 constant region." (*See, e.g.*, Petition, 15-16, 56; AMG1002 ¶¶ 42, 45, 54.) That assumption improperly ignores the overwhelming evidence that directed a POSA back then to look to Thomas for the structure of "eculizumab." (*See* Section II.C above.) Instead, to support its assumption that a POSA would have known that "eculizumab" contained an IgG2/IgG4 constant region, Amgen relies on a ***single***, ambiguous sentence in just one document –

Tacken (AMG1034)[3] – regarding an "isotype control antibody." But a POSA looking for the structure of "eculizumab" would not have considered, and certainly would not have credited, Tacken above the consistent, clear statements in earlier and later publications that expressly identified "eculizumab" as the IgG4 antibody of Thomas.

As Dr. Balthasar admitted, Tacken is the ***only*** document on which he relies dated prior to March 15, 2007 that purportedly associated "eculizumab" with a hybrid IgG2/IgG4 constant region. (ALXN2032, 104:14-20.) But unlike the clinical literature discussed in Section II.C above, Tacken did not concern the study of "eculizumab" in binding C5, blocking C5 cleavage or treating conditions such as PNH. (ALXN2022, ¶¶140-150; ALXN2032, 72:23-73:2, 73:12-74:1, 74:16-21.) Rather, Tacken involved the study of an entirely different antibody (the "hD1" antibody) with a wholly different purpose: directing antigens to a dendritic cell receptor for purposes of developing improved vaccinations. (AMG1034, 1278-79, 1283-84.)

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[3] Notably, Amgen does not rely on Tacken (AMG1034) as the basis for any of its five Grounds alleging anticipation or obviousness of the '149 patent.

Nothing in Tacken contradicted the consistent teaching of the prior art ***as a whole*** that "eculizumab" had an IgG4 constant region. In a single sentence identifying an "isotype control antibody" for use in studies of the "hD1" antibody directed to dendritic cells, Tacken states the following (including a citation to ***Thomas*** as Ref. No. 19):

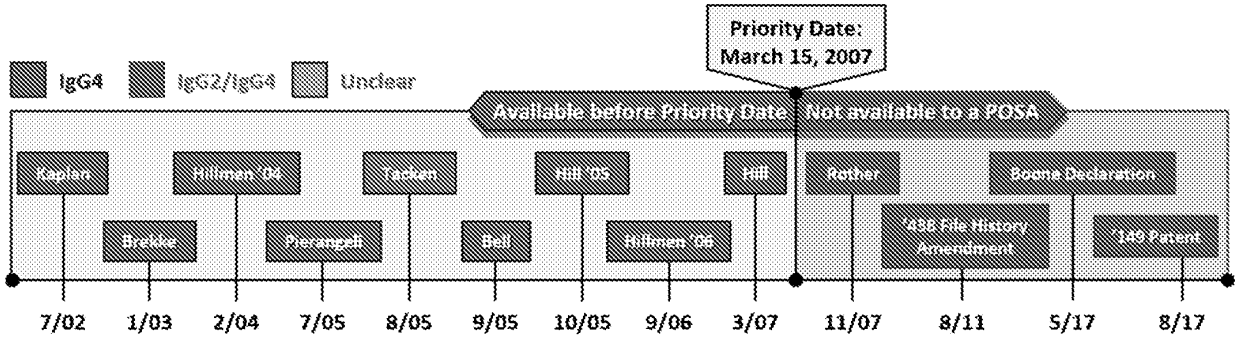
> An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

(AMG1034, 1279.) A POSA reading that isolated, unclear statement would not have been dissuaded from the consistent, clear teaching in the literature as of March 15, 2007 (both before and after Tacken's publication) identifying "eculizumab" and "SOLIRIS®" as the ***IgG4*** antibody of Thomas. (*See supra* Table 1; ALXN2022, ¶¶140-150.) A POSA would have seen substantial ambiguity in that statement. Not only does Tacken misspell "eculizumab," but it uses multiple conflicting and undefined terms – including "h5G1.1-mAb," which could refer to a class of various humanized antibodies; and "5G1.1," which can refer to many things, including the original "5G1.1" mouse antibody from the "5G1.1" hybridoma. (ALXN2022, ¶143; ALXN2032, 98:2-99:8, 159:1-10; 202:24-203:14.) Further, a POSA would have seen Tacken's citation to Thomas's IgG4

antibody (Ref. No. 19) for "eculizamab" [sic] as inconsistent with its reference to an IgG2/IgG4 isotype control antibody. On balance, the ambiguous, passing reference in Tacken would not have led a POSA to "understand" that the clinically tested "eculizumab" antibody has an "IgG2/IgG4" constant region.

Amgen's myopic focus on the isotype control antibody of Tacken, to the exclusion of all other prior art information, is also not tenable because at least four prior art documents published ***after*** Tacken confirmed a POSA's belief as of March 15, 2007 that the clinically-tested "eculizumab" antibody was the ***IgG4*** antibody of Thomas. (ALXN2022, ¶¶145, 150.) For example, the Hill clinical study was published two months after Tacken in the same journal (Blood), and stated that "[e]culizumab is" the antibody of Thomas. (AMG1047, 2559 (Ref. No. 9); ALXN2032, 113:14-21, 114:19-115:10.) Bell, published a month after Tacken, likewise pointed to Thomas for methods of making "eculizumab," and made no mention of hybrid IgG2/IgG4 antibodies. (AMG1005, ¶[0052]; ALXN2032, 160:18-162:11.) The Hillmen 2006 Phase III study, published more than a year after Tacken in the New England Journal of Medicine, and the Hill 2007 case report, published on March 1, 2007, likewise both stated that "eculizumab is" Thomas's IgG4 isotype antibody. (AMG1012, 1234 (Ref. No. 13); ALXN2028, 31 (Ref. No. 6); ALXN2032, 116:16-117:1.)

As the following timeline figure illustrates, the ***only*** plausible conclusion a POSA could have reached in view of the entire contents of the art was that "eculizumab" was the IgG4 antibody of Thomas, and the ambiguous statement in Tacken (a publication having nothing to do with C5 binding) was either supportive of that understanding – as Tacken cites Thomas – or otherwise mistaken. (ALXN2022, ¶¶146, 150.) *See, e.g.*, *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 882-883 (Fed. Cir. 1998) (the "***entire contents of the prior art***" must be considered in determining whether the art showed a trend towards the claimed invention).



E. Overview of the '149 Patent

The '149 patent issued on August 15, 2017 from U.S. App. No. 15/284,015, filed on October 3, 2016, and claims priority to PCT/US2007/006606, filed on March 15, 2007. The patent has one claim:

> **1.** An antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

(AMG1001, 39:1-4.).

Claim 1 of the '149 patent recites the complete amino acid sequence for SOLIRIS® (eculizumab): the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001, cols. 31-33, 35.) Claim 1 of the '149 patent further requires that the claimed antibody is "[a]n antibody that binds C5."

The '149 patent discloses that the claimed antibody binds C5, and provides Phase III clinical data from the "TRIUMPH" study confirming that the claimed antibody is safe and effective for treating PNH, and identifying the safe and effective dosing regimen for that use. (AMG1001, abstract, 3:4:63-67, 19:50-28:35.)

F. Prosecution History of the '149 Patent and Related Applications

In prosecution leading to issuance of the '149 patent, as well as prosecution of related U.S. Patent Nos. 9,725,504 ("the '504 patent") and 9,719,880 ("the '880 patent"), the Examiner considered much of the same art that Amgen now asserts. The Examiner made findings undermining Amgen's positions here, including that (1) none of the art recited an antibody comprising SEQ ID NOs: 2 and 4, (2) a POSA "would not have been easily guided to mak[e] antibodies with these recited sequences," and (3) SOLIRIS® and its unique sequence was not "accessible to the public" as of March 15, 2007. (AMG1015, 772.)

For example, in finding claim 1 of the '149 patent to be novel and nonobvious, the Examiner expressly discussed Amgen's asserted references Hillmen 2004 (AMG1004) and Evans (AMG1007) as a basis for rejection, before ultimately finding claim 1 to be allowable over the art. (*See, e.g.*, AMG1015, 486-487, 596-598). The Examiner also considered Amgen's asserted references Hill (AMG1047) and Bell (AMG1005); U.S. Patent No. 7,482,435 (ALXN2016) (the parent to, and cumulative of, Bowdish (AMG1006)); and "Mueller II" (AMG1031), which is cumulative of Mueller (AMG1008). (*See, e.g.*, AMG1015, 489-490, 497, 504, 506.) Alexion did not "mislead" the Patent Office or fail to disclose references pertaining to Amgen's arguments here.

Notably, the Examiner confirmed a central fact that Amgen ignores: Hillmen cites to ***Thomas*** (*i.e.*, "reference number 15" of Hillmen) as "disclosing more information about eculizumab." (AMG1014, 559, 623 (citing AMG1023); *see also* AMG1015, 596 ("Hillmen ... teaches that 'eculizumab' is a recombinant humanized antibody that binds to C5 ... and cites ***Thomas***."). Ultimately, the Examiner agreed that the prior art did not disclose or suggest the specific claimed antibody sequence of the '149 patent. (AMG1015, 772; *see also* AMG1014, 790.)

The Examiner also credited the Declaration of Dr. Laural Boone (AMG1015, 734-741 ("the Boone Declaration") as showing that Alexion's clinical studies of the claimed antibody did not disclose its sequence or render it publicly accessible. (AMG1015, 772-73.) The Examiner relied on, among other things, Dr. Boone's showing that "neither doctors nor patients had any knowledge of the ... claimed sequences of the antibody used in the studies." (AMG1015, 738-741 ¶¶ 6-13, 772-773.) While it is known ***today*** that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4 (AMG1015, 738 ¶ 6), a POSA as of March 15, 2007 would have only been guided by the teachings of the published literature that "eculizumab" had the IgG4 structure of Thomas.

III. PERSON OF ORDINARY SKILL IN THE ART OF THE '149 PATENT

Amgen contends that a POSA would have had "an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a

related discipline, with **at least two years of experience in the field**," and that a POSA would have had "skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics." (Petition, 20-21.)

Alexion does not dispute Amgen's POSA definition, except to clarify – as the Board accepted (Paper No. 15, 10-11) – that the POSA would have **at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry**. (ALXN2022, ¶¶25-26.)

IV. AMGEN'S PETITION FAILS TO SHOW UNPATENTABILITY OF CLAIM 1 OF THE '149 PATENT

A. Amgen's Grounds 1 and 2 Fail Because Amgen Cannot Show that Claim 1 Was Anticipated by Hillmen or Hill

Amgen's Grounds 1 and 2 contend that claim 1 of the '149 patent was anticipated by the clinical trial publications Hillmen (AMG1004) or Hill (AMG1047), respectively. As the Board recognized, Amgen's Grounds 1 and 2 fail, because Amgen cannot show how either Hillmen or Hill disclosed the claimed antibody of the '149 patent.

1. Hillmen and Hill Did Not Disclose an Antibody "Comprising a Heavy Chain Consisting of SEQ ID NO: 2 and a Light Chain Consisting of SEQ ID NO: 4"

Amgen's Grounds 1 and 2 fail because neither Hillmen nor Hill expressly or inherently discloses all the elements recited in claim 1 of the '149 patent. *See, e.g.*,

Therasense, Inc. v. Becton Dickinson & Co., 593 F.3d 1325, 1332 (Fed. Cir. 2010) ("Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim.").

In particular, as the Board recognized, both Hillmen and Hill fail to disclose an antibody comprising the specific amino acid sequence recited in claim 1 of the '149 patent. (Paper No. 15, 24-27.) Simply put, there were ***no amino acid sequences*** for "eculizumab" disclosed anywhere within the four corners of the Hillmen and Hill publications. (ALXN2022, ¶¶172-181.) To the extent Hillmen and Hill provided any guidance about the structure of "eculizumab," they identified "eculizumab" by reference to Thomas (AMG1023) – which in turn described a humanized monoclonal antibody with an "***IgG4***" heavy chain constant region having a very different amino acid sequence from the '149 patent's SEQ ID NO: 2. (*See supra* Section II.C.) At deposition, Dr. Balthasar conceded that Hillmen's and Hill's statements regarding what "eculizumab is" cited to Thomas; and he was unable to identify ***any*** disclosure within Hillmen, Hill, or their cited references suggesting that "eculizumab" had a hybrid IgG2/IgG4 constant region, rather than the IgG4 constant region of the cited Thomas reference. (ALXN2032, 123:8-15, 125:13-126:11, 126:19-23, 127:19-128:1, 128:20-129:10, 132:7-12, 134:9-21.)

Accordingly, neither Hillmen nor Hill, including their references to "eculizumab," disclosed each and every element of claim 1 of the '149 patent.

2. Neither Hillmen nor Hill Inherently Disclosed the Unique, Non-Public Amino Acid Sequence of SOLIRIS® Recited in Claim 1 of the '149 Patent

To supply the claimed elements of SEQ ID NOs: 2 and 4 that are plainly missing from Hillmen and Hill, Amgen admittedly must go ***outside*** the four corners of the references themselves, and turns to a either patent prosecution document created in 2017 that indisputably was not prior art available to a POSA as of March 15, 2007, or to amino acid sequences that Amgen mixes and matches from extraneous documents (Bowdish, Mueller, and Evans) that were not cited or referenced anywhere in Hillmen and Hill. (Petition, 25-26, 32-34; (ALXN2022, ¶¶179-180.)

For example, Amgen alleges inherent anticipation of claim 1 on the ground that ***today*** – years after the '149 patent's March 15, 2007 priority date – it is known that the clinical studies underlying the Hillmen and Hill publications ***actually*** used an antibody with a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. (*See, e.g.*, Petition, 25 (citing the May 11, 2017 Declaration of Dr. Laural Boone, AMG1015, 734-741).) But Amgen is mistaken on the law. The mere naming of an investigational product (*e.g.*, "eculizumab") in a prior art publication does ***not*** inherently anticipate later-filed patent claims

detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as of the priority date. *See, e.g.*, *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-83 (Fed. Cir. 2018). Likewise, post-filing information showing that the later-claimed antibody sequence was actually used in the studies underlying prior art clinical publications is insufficient to give rise to inherent anticipation, when those prior art publications would have guided a POSA to a different, unclaimed antibody sequence. *See, e.g.*, *id.*; *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018).

B. Amgen's Ground 3 Fails Because Amgen Cannot Show that Claim 1 Was Anticipated by Bowdish

Amgen's Ground 3 contends that claim 1 of the '149 patent was anticipated by Bowdish (AMG1006). But Amgen cannot show how Bowdish disclosed all of the elements of claim 1 of the '149 patent, including "[a]n antibody that binds C5" having the specific, uniquely-engineered amino acid sequence recited in the claim. *See, e.g.*, *Therasense*, 593 F.3d at 1325. There is simply no disclosure in Bowdish – even if fully combined with Evans (AMG1007) – of an antibody having the full sequence claimed in the '149 patent. Amgen fails to show why Evans should be considered at all, when Bowdish incorporated not Evans but a different document

(the "'283 application") that Amgen neglected to consider or introduce in this proceeding.

Even if Evans is considered in the '283 application's place, Amgen overreads Bowdish's limited incorporation by reference for "[c]onstruction of 5G1.1," a mouse antibody with a very different sequence and structure from the claimed antibody of the '149 patent. Even if the entirety of Evans was improperly considered to be incorporated by reference, Amgen exceeds the bounds of anticipation by culling and recombining bits and pieces from Bowdish and Evans to reconstruct the claimed sequence of the '149 patent. This cannot meet the requirement "for an anticipatory reference to show all of the limitations of the claims ***arranged or combined in the same way*** as recited in the claims…." *Net MoneyIN, Inc. v. Verisign, Inc.*, 545 F.3d 1359, 1369-70 (Fed. Cir. 2008); *see also id.* at 1371 ("[I]t is not enough that the prior art reference … includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention.").

Further, Amgen fails to show how Bowdish disclosed or enabled the element of "[a]n antibody that binds C5" as required by claim 1 of the '149 patent. In particular, Amgen has pointed to nothing in Bowdish or Evans, even in full combination, that disclosed anything about the C5 binding properties of an antibody comprised of SEQ ID NO: 2 and SEQ ID NO: 4 as recited in claim 1.

1. Bowdish Did Not Disclose or Incorporate by Reference an Antibody Comprising SEQ ID NO: 2 and SEQ ID NO: 4

Amgen concedes that Bowdish alone does not disclose an antibody "comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4" as recited in claim 1. As Dr. Balthasar admitted, Bowdish does not disclose the entire amino acid sequence recited in claim 1 of the '149 patent; and the compound consisting of the amino acid sequences listed in Bowdish Figures 13A and 13B is not the claimed antibody of the '149 patent. (ALXN2032, 181:17-23, 182:21-183:1; (ALXN2022, ¶185.)

Amgen also does not contend that Bowdish alone expressly discloses "[a]n antibody that binds C5" as recited in claim 1 of the '149 patent. Bowdish concerned using an antibody – ***any*** antibody – as a "scaffold" to house a peptide (*e.g.*, the hormone TPO), thereby providing greater stability and longer half-life for the peptide *in vivo*. (AMG1006, ¶¶[0005]-[0006]; ALXN2022, 159-161, 200; AMG1002, ¶50.) The assays reported in Bowdish had nothing to do with C5 binding or blocking complement-mediated lysis. Rather, Example 4 of Bowdish assessed the binding of TPO-mimetic peptide (presented on an antibody scaffold) with a TPO receptor (the "cMpl receptor") – a biological interaction that is not part of the complement pathway and has nothing to do with cleavage of C5.

(AMG1006., ¶[0192]; ALXN2022, ¶¶159-161, 200.) Those two facts should end the inquiry on anticipation.

Conceding that Bowdish alone does not disclose the invention recited in claim 1 of the '149 patent, Amgen's Ground 3 depends wholly on Bowdish's "incorporation by reference" of limited subject matter from "U.S. Application Ser. No. 08/487,283" ("the '283 application") for "[c]onstruction of 5G1.1." (Petition, 37-40 (citing AMG1006, ¶[0191]).) But that limited incorporation by reference does not save Amgen's Ground 3. First, Amgen's anticipation arguments based on Bowdish fail for lack of proof, because – as Dr. Balthasar conceded at deposition – Amgen did not consider or introduce into the record the "'283 application" that Bowdish purports to incorporate. (AMG1006 ¶ [0191]; ALXN2032, 191:2-11, 192:7-11, 208:3-8.) Instead, Amgen combines Bowdish with a different document that Bowdish did ***not*** incorporate by reference – the Evans patent (AMG1007). (Petition, i, 37-40; ALXN2032, 191:12-25, 192:7-13, 207:19-208:8.) While Evans (AMG1007) issued from the '283 application, it is not the '283 application itself, and Amgen's failure to even ***consider*** the contents of the actual '283 application referenced by Bowdish is fatal to its anticipation position in Ground 3.

Even using Evans (AMG1007) as a stand-in for the '283 application – which Amgen cannot do – Amgen cannot show that Bowdish anticipates claim 1 of the '149 patent. Amgen misreads Bowdish's narrow reference to the '283 application,

which does ***not*** support treating the two documents as merged in their entirety. Amgen further ignores the requirement that an anticipating reference "must ***clearly and unequivocally*** disclose the claimed invention or direct those skilled in the art to the invention without ***any*** need for picking, choosing, and combining various disclosures not directly related to each other." *Net MoneyIN*, 545 F.3d at 1371 (emphasis in original). In particular, Amgen disregards the ambiguity in Bowdish and its reference to the '283 application, and uses improper hindsight analysis to recombine select parts of Bowdish and Evans – which is not permitted in assessing anticipation. *See In re Ruschig*, 353 F.2d 965, 974 (C.C.P.A. 1965) (forbidding "the mechanistic dissection and recombination" of the prior art "to create hindsight anticipations with the guidance of an applicant's disclosures").

The only reference in Bowdish to the '283 application states: "Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated by reference herein." (AMG1006, ¶[0191].) Amgen fails to show how that one reference could magically convert Bowdish into an anticipatory disclosure of claim 1 of the '149 patent. First, Bowdish's vague statement referencing the '283 application for "[c]onstruction of 5G1.1," without further explanation, is not effective to incorporate any specific material from Evans into Bowdish, because it fails the requirement that "the host document . . . identify with ***detailed particularity*** what specific material it incorporates and ***clearly indicate*** where that

material is found in various documents." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000).

Even if a POSA had attempted to make sense of Bowdish's reference to "[c]onstruction of 5G1.1 as described in [the '283 application]," it would not have led them to a clear and unequivocal disclosure of the invention claimed in the '149 patent. A POSA reading Bowdish would have understood that its incorporation was ***limited*** to the portion of the Evans[4] describing the "[c]onstruction of 5G1.1." (ALXN2022 ¶¶162-163, 187-190.) In turn, a POSA looking to Evans for "[c]onstruction of 5G1.1" would have been directed to Evans's description of a ***mouse*** antibody – "the 5G1.1 antibody" or "the 5G1.1 mAb", obtained from the original "5G1.1" hybridoma. (*See supra* 19; ALXN2022 ¶¶189-190.) For example, Evans explains that "[a] particularly preferred antibody of the invention is ***the 5G1.1 antibody*** (5G1.1, ***produced by the 5G1.1 hybridoma***, ATCC designation HB-11625)," and identifies Figs. 18 and 19 as disclosing the light

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[4] For ease of reference, we refer herein to "Evans" rather than the "'283 application," without any waiver of Alexion's position that Bowdish incorporates by reference only limited portions of the '283 application (not in evidence in this proceeding), and does not at all incorporate or reference Evans (AMG1007).

chain and heavy chain variable regions of "***the antibody 5G1.1***." (AMG1007, 19:47-49, Figs. 18-19; ALXN2032, 165:5-21.)

This combination of Bowdish with Evans's description of the "5G1.1" mouse antibody cannot anticipate claim 1 of the '149 patent, because it fails to "describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art." *Wasica Finance GmbH v. Continental Automotive Sys., Inc.*, 853 F.3d 1272, 1284 (Fed. Cir. 2017). As the following figures illustrate, a comparison of the sequences for Evans's "5G1.1" mouse antibody variable regions (AMG1007, Figs. 18-19) or the whole "5G1.1" mouse antibody (ALXN2026; ALXN2087) with the sequences for Bowdish's TPO-mimetic compound (AMG1006, Figs. 13A and 13B) would have revealed a mismatch in amino acids ***beyond*** those that Bowdish identified as the TPO-mimetic peptide insert (ALXN2022 ¶¶214-215):

```
Bowdish13A:  QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGE
             |||| |||||  |||||||| |||| ||||||||||   | || |||| ||
   Evans19:  QVQLQQSGAELMKPGASVKMSCKATGYIFSNYWIQWIKQRPGHGLEWIGE

Bowdish13A:  ILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLP
             |||||||||||||||||    | |||  | || |||| ||| |||||||||
   Evans19:  ILPGSGSTEYTENFKDKAAFTADTSSNTAYMQLSSLTSEDSAVYYCAR--

Bowdish13A:  IEGPTLRQWLAARAP-----VWGQGTLVTVSS
             ||||||||      |||||||| || |||||
   Evans19:  ---------YFFGSSPNWYFDVWGAGTTVTVSS
```

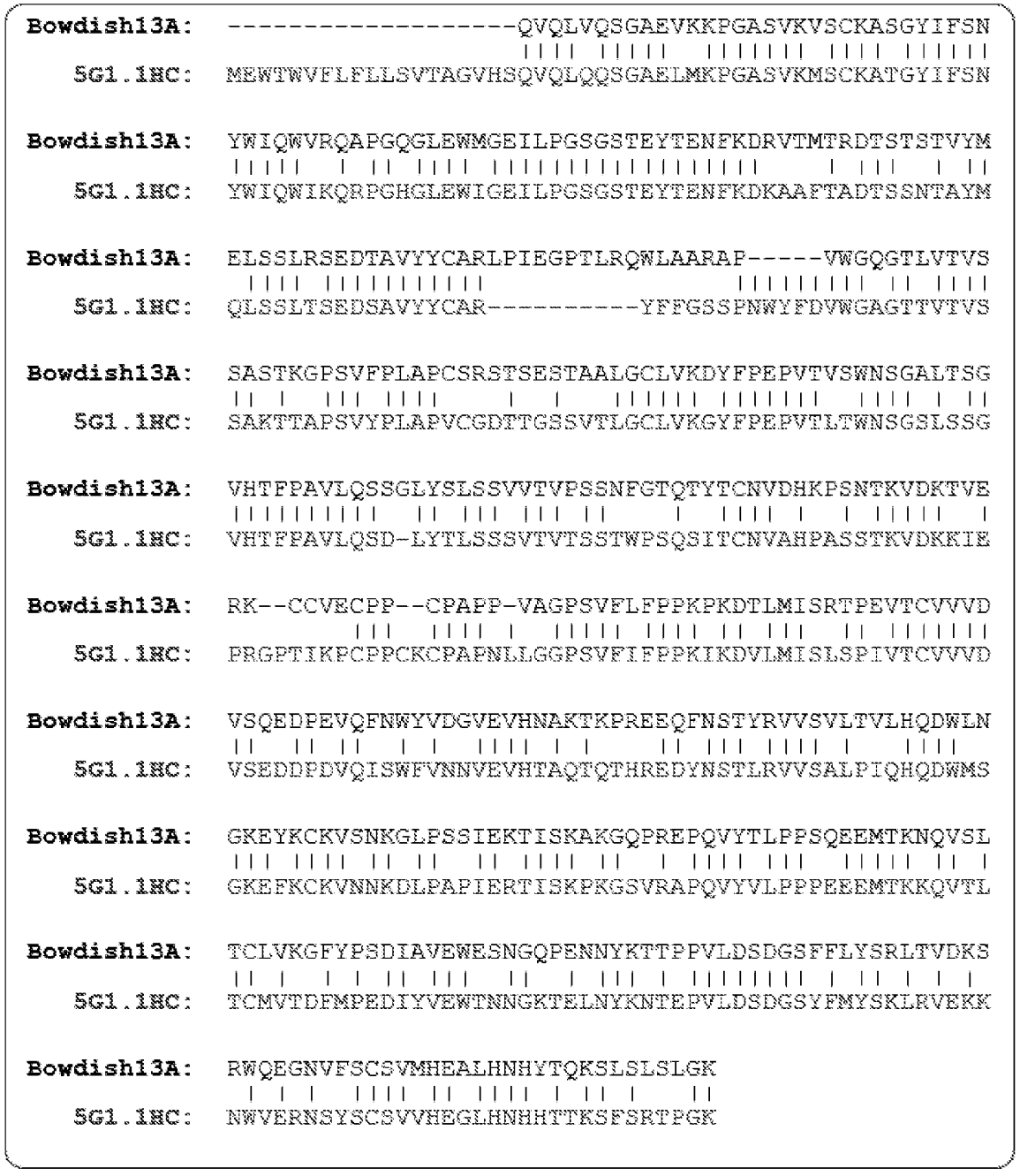
```
Bowdish13B:  DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYG
             |||||||| |||||||  |||||||||||||||||| | || | |||||
   Evans18:  DIQMTQSPASLSASVGETVTITCGASENIYGALNWYQRKQGKSPQLLIYG

Bowdish13B:  ATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQ
             |||||||  |||||||||    | |||| | | ||||||||||||||||
   Evans18:  ATNLADGMSSRFSGSGSGRQYYLKISSLHPDDVATYYCQNVLNTPLTFGA

Bowdish13B:  GTKVEIK
             ||| | |
   Evans18:  GTKLELK
```

Top: Bowdish Figure 13A (SEQ ID NO: 67) compared to Evans Fig. 19

Bottom: Bowdish Fig. 13B compared to Evans Fig. 18



Bowdish Figure 13A (SEQ ID NO: 67) compared to heavy chain of 5G1.1 antibody from HB-11625

In view of the mismatch between the sequences of Bowdish and the incorporated sequences of Evans, a POSA as of March 15, 2007 would have found Bowdish's reference to Evans to be at most, ambiguous, and certainly would not have understood Bowdish to clearly and unequivocally disclose an antibody consisting of SEQ ID NOS: 2 and 4 recited in claim 1 of the '149 patent. In particular, nothing in Bowdish's reference to the "5G1.1" mouse antibody of Evans would have indicated to a POSA that the "scaffold" antibody (whose sequence was not disclosed in Bowdish) used to generate Bowdish's TPO-mimetic compound was the specific antibody consisting of SEQ ID NOs: 2 and 4 of the '149 patent. ALXN2022, ¶¶162-163, 190.) Claim 1 of the '149 patent cannot be anticipated by such an ambiguous disclosure. *See, e.g.*, *Wasica Finance*, 853 F.3d at 1284 ("[A]mbiguous references do not, as a matter of law, anticipate a claim.").

Rather than acknowledge the limitations and ambiguity of Bowdish's reference to the '283 application, Amgen misconstrues the scope of that cross-reference, and disregards its limitations entirely. For example, Amgen attempts to rewrite the statement regarding "[c]onstruction of 5G1.1" to refer to "[c]onstruction of ***eculizumab***" (Petition, 6-7, 17), or construction of the antibody used as the "***scaffold***" for Bowdish's TPO-mimetic compound (Petition, 38; AMG1002, ¶ 94). There is no dispute that neither Bowdish nor Evans mention "eculizumab." ALXN2022 ¶¶124, 131, 185; ALXN2032, 199:9-17.) And reading

Bowdish as referencing Evans for "construction of eculizumab" or "construction of the scaffold antibody" would have made no sense, because Evans did not disclose the construction of ***any*** full-length, intact humanized monoclonal antibodies, let alone "eculizumab." (*See supra* 18-19.) As Dr. Balthasar admitted, "the 5G1.1 antibody" disclosed in Evans was a ***mouse*** antibody – and was the only full-length antibody that Evans disclosed. (ALXN2032, 165:5-169:23; *see supra* 19.)

Amgen's Ground 3 further fails because it relies on material from Evans that Bowdish did ***not*** clearly incorporate by reference. In particular, Amgen's Ground 3 depends upon the mixing and matching of Bowdish's sequences with sequences from Evans's "***scFvs***" – which are ***not*** the "5G1.1 antibody" of Evans, but rather are "fragments" produced by recombinant DNA technology containing only variable regions connected by a linker sequence.

Amgen is simply mistaken to the extent it contends that Bowdish may be combined with Evans ***in its entirety*** for purposes of assessing anticipation by Bowdish – as Dr. Balthasar admitted he was instructed by counsel. (ALXN2032, 189:23-191:1.) *See, e.g.*, *Schwarz Pharma, Inc. v. Warner-Lambert Co.*, 95 F. App'x 994, 998 (Fed. Cir. 2004) (an incorporation by reference referring to the "disclosure" of drug compounds did not also incorporate the drug compounds' synthesis or pharmaceutical compositions). Notably, when Bowdish intended to

incorporate other documents "in their entirety," it did so expressly (AMG1006, ¶ [0001]). Bowdish did not do so for Evans.

2. Bowdish, Even if Combined with Evans in its Entirety – Did Not Disclose, Either Expressly or Inherently, an Antibody with the Specific Sequences Recited in Claim 1 of the '149 Patent

Even if a POSA reading Bowdish were to consider the disclosures of Evans beyond those pertaining to construction of Evans's "5G1.1" mouse antibody – which the law does not allow – they still would not find a clear and unequivocal disclosure of the specific antibody recited in claim 1 of the '149 patent. *See Net MoneyIN*, 545 F.3d at 1371. Nor would it have been apparent to a POSA, as Amgen posits, that the "scaffold" antibody used to generate Bowdish's TPO-mimetic compound "***necessarily*** possessed the claimed sequences" of the '149 patent. (Petition, 35.) To the contrary, Amgen's anticipation argument fails here because it cannot show that the specific claimed antibody consisting of SEQ ID NOs: 2 and 4 was "***necessarily present,***" or, frankly, present at all, in the disclosure of Bowdish and its reference to the '283 application. *See, e.g.*, *Endo*, 894 F.3d at 1383; *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991).

Unlike a POSA, who would have had no clear picture of the structure and sequence of Bowdish's "scaffold" antibody, Amgen uses the benefit of its

hindsight knowledge of the '149 patent to reconstruct that sequence from bits and pieces of Bowdish and Evans. Such selective mixing and matching from unconnected disclosures in hindsight is forbidden in anticipation analysis. (*See supra* 37-38.) In particular, Amgen attempts to prove its anticipation case by illustrating sequence alignments between, on the one hand, carefully selected sequences from Bowdish and Evans, and on the other hand, the sequences claimed in the '149 patent. (Petition, 19, 36, 39, 43; AMG1002 Figs. 3-7, 10, 10-14.) But a POSA as of March 15, 2007 could not have done that analysis, because ***the '149 patent was not available*** for a POSA to use as a point of comparison. (ALXN2032, 222:7-224:24; ALXN2022, ¶196.)

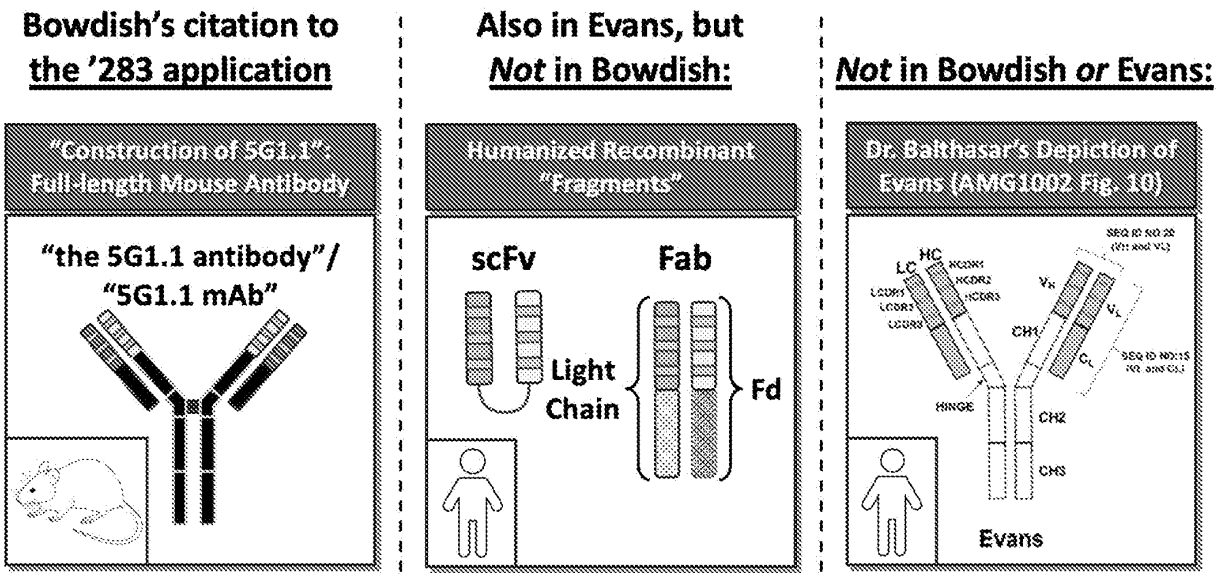
To the contrary, a POSA as of March 15, 2007 reading Bowdish and Evans together would have been left without knowing the precise structure of Bowdish's "scaffold" antibody, and certainly would not have had a clear and unambiguous picture of the specific, unique sequence recited in claim 1 of the '149 patent. Even if Amgen were correct that Bowdish guided a POSA to look to Evans for construction of the "scaffold" used to produce Bowdish's TPO-mimetic compound (*e.g.*, Petition, 38; AMG1002 ¶ 94), the POSA would have come up empty-handed, because nothing in Evans disclosed ***any*** full-length antibodies, aside than the "5G1.1" mouse antibody. (ALXN2022, ¶191; *supra* 18-19.)

Further, if a POSA were to look elsewhere in Evans for "heavy chain CDR3" sequences not associated with the (undisclosed) Bowdish "scaffold" antibody, they still would not have ***necessarily*** arrived at the specific claimed sequence recited in claim 1 of the '149 patent. Rather, a POSA have seen that Evans provided for ***multiple*** possible definitions for that CDR sequence, and did not specify which, if any, would have been the "heavy chain CDR3" of the "scaffold" antibody referenced in Bowdish. (ALXN2022, ¶195.) For example, Evans described "minimal" and "maximal" definitions for the CDRs it disclosed, and also expressly allowed for CDRs comprising overlapping ranges of those minimal and maximal sequences. (AMG1007, 5:15-36.) Nothing in Bowdish or Evans would have clearly and unambiguously identified which, if any, of those sequences was the "heavy chain CDR3" featured in the "scaffold" antibody used to make Bowdish's TPO-mimetic compound – a full-length structure that is found nowhere in Evans. (ALXN2022, ¶195.)

Instead, Amgen incorrectly assumes that a POSA would have determined Bowdish's "scaffold" to have the presently-claimed sequence by combining sequences from Bowdish's TPO-mimetic compound with a CDR sequence for Evans's recombinant "***scFv***" fragments. (Petition, 38-40; AMG1002, ¶¶95-96.) Nothing in Bowdish referred to Evans for disclosure of scFv compounds, or would have guided a POSA to look to such recombinant fragments to understand the

sequence of the structurally distinct full-length "scaffold" antibody used to generate Bowdish's TPO-mimetic compound. (ALXN2022, ¶¶192-194, 198.) As discussed above, there is no dispute that a POSA would have understood scFvs to be very different structures from the full-length antibody from which Bowdish's TPO-mimetic compound was derived. (*See supra* 11-12.)

Accordingly, Amgen's "Figure 12," which purports to construct the claimed antibody of the '149 patent from sequences recombined from Bowdish and Evans, is misleading, because it improperly depicts Evans's "scFvs" as if Evans disclosed them as the variable regions of an intact, full-length antibody "Y" structure. As Dr. Casadevall's **Figure 8** demonstrates, a POSA would not have understood Evans's disclosures to be as Amgen depicted them in hindsight, but rather would have understood Evans to disclose (1) a full-length mouse antibody that differed in sequence and structure from Bowdish's "scaffold" antibody, and (2) recombinantly-generated humanized scFvs that were not associated with, or even derived from, Bowdish's "scaffold" antibody or any other full-length human or humanized antibody.



3. Bowdish Did Not Disclose "[A]n Antibody that Binds C5" Having the Sequence Claimed in the '149 Patent

Amgen further fails to show how Bowdish and Evans, even if combined in their entirety, would have disclosed or enabled the element of "[a]n antibody that binds C5" comprising the specific, uniquely-engineered amino acid sequence of claim 1 of the '149 patent. The element of "an antibody that binds C5" is a fundamental characteristic required by claim 1 of the '149 patent. (*E.g.*, AMG1002, ¶107 ("'[A]n antibody that binds C5' [is] required by claim 1 ….") *See In re Jasinski*, 508 Fed. App'x 950, 952 (Fed. Cir. 2013). But Bowdish, on its face, says nothing about C5 binding of either its TPO-mimetic compound or the "scaffold" used to generate it, and contains no discussion or data concerning C5

binding. (ALXN2022, ¶¶158-161, 211; ALXN2032, 174:2-176:6, 180:8-11, 181:5-15, 188:4-10.)

The required element of "[a]n antibody that binds C5" also was not disclosed or enabled by Bowdish's reference to the '283 application. The only antibody that Bowdish referenced from Evans, and that Evans further described as binding C5, was the ***mouse*** "5G1.1" antibody, which has a very different sequence and structure from the claimed antibody of the '149 patent. (*See supra* 18-19.) And even considering Evans in its entirety (which Bowdish did not instruct a POSA to do), nothing in Evans disclosed the structure or C5 binding properties Bowdish's "scaffold" antibody or ***any*** full-length antibody other than the mouse antibody. (*See supra* 18-21.)

Accordingly, even if the sequence of Bowdish's "scaffold" antibody were fully known, a POSA would still not have known that antibody to be "[a]n antibody that binds C5." As Dr. Casadevall explains, a POSA would not have been able to infer the C5 binding properties of a new, untested antibody structure from its amino acid sequence alone. (ALXN2022, ¶¶224-229.)

Bowdish's reference to the "5G1.1" antibody of Evans – a mouse antibody – would have taught a POSA nothing about whether Bowdish's structurally distinct "scaffold" antibody bound C5. (ALXN2022, ¶¶159-163, 214-215.) Likewise, Amgen's assertion that Evans "disclosed preparing different humanized C5-

binding antibodies referred to as '5G1.1' antibodies" (Petition, 38) is incorrect, because it is undisputed that Evans disclosed ***no*** full-length "humanized C5-binding antibodies," and the only full-length "5G1.1" antibody set forth in Evans was a mouse antibody – which would have taught a POSA nothing about the binding properties of the very different "scaffold" antibody of Bowdish. (ALXN2022, ¶¶214-215.)

Amgen also cannot show how Bowdish, even if fully combined with Evans, was enabling for "[a]n antibody that binds C5" with the specific amino acid sequence recited in claim 1 of the '149 patent. *See, e.g.*, *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. and Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003). Even if the entire claimed sequence could have been determined from Bowdish (which Amgen fails to show), a POSA would not have been able to reasonably predict whether that sequence – which was not characterized for C5 binding in Bowdish or Evans – would constitute an anti-C5 antibody. (ALXN2022, ¶200.)

C. Amgen's Ground 4 Fails Because Amgen Cannot Show that Claim 1 Would Have Been Obvious Over the Combination of Bell, Bowdish and Evans

Amgen's Ground 4 contends that claim 1 of the '149 patent would have been obvious over a combination of Bell (AMG1005), Bowdish (AMG1006) and Evans (AMG1007). Amgen's Ground 4 fails because it is founded in an incredible, impermissible hindsight-driven premise: that a POSA considering Bell's

description of "eculizumab" would have ignored what Bell ***actually*** taught about the structure of "eculizumab" – that it was the full-length IgG4-isotype antibody of Thomas – and would have instead turned to Bowdish (which Bell does not cite) and Evans, both which make no mention of "eculizumab" or any other full-length humanized monoclonal antibodies known to bind C5 or have any therapeutic utility. (Petition, 41-47.)

Without the benefit of hindsight, a POSA as of March 15, 2007 would have had ***no reason*** to select and combine the sequences from Bowdish and Evans that Amgen picks and chooses to recreate the claimed sequences of the '149 patent; would have had ***no motivation*** to make such a new, untested antibody with no known or reasonably predictable binding, biological or therapeutic properties; and would have ***no reasonable expectation*** that such a new untested antibody would be "[a]n antibody that binds C5," as claim 1 requires. (ALXN2022, ¶¶202-229.)

1. Bell Did Not Disclose the Claimed Sequence, and Would Not Have Motivated a POSA to Make the Claimed Antibody

To supply the claim element "[a]n antibody that binds C5," Amgen relies upon Bell for its disclosure of "eculizumab," which Bell identifies by that name. (Petition, 41-42; AMG1002, ¶105; ALXN2032, 145:9-14, 152:19-25.) According to Amgen's argument – which we do not dispute in this respect – a POSA as of March 15, 2007 would have specifically been motivated to make and use Bell's

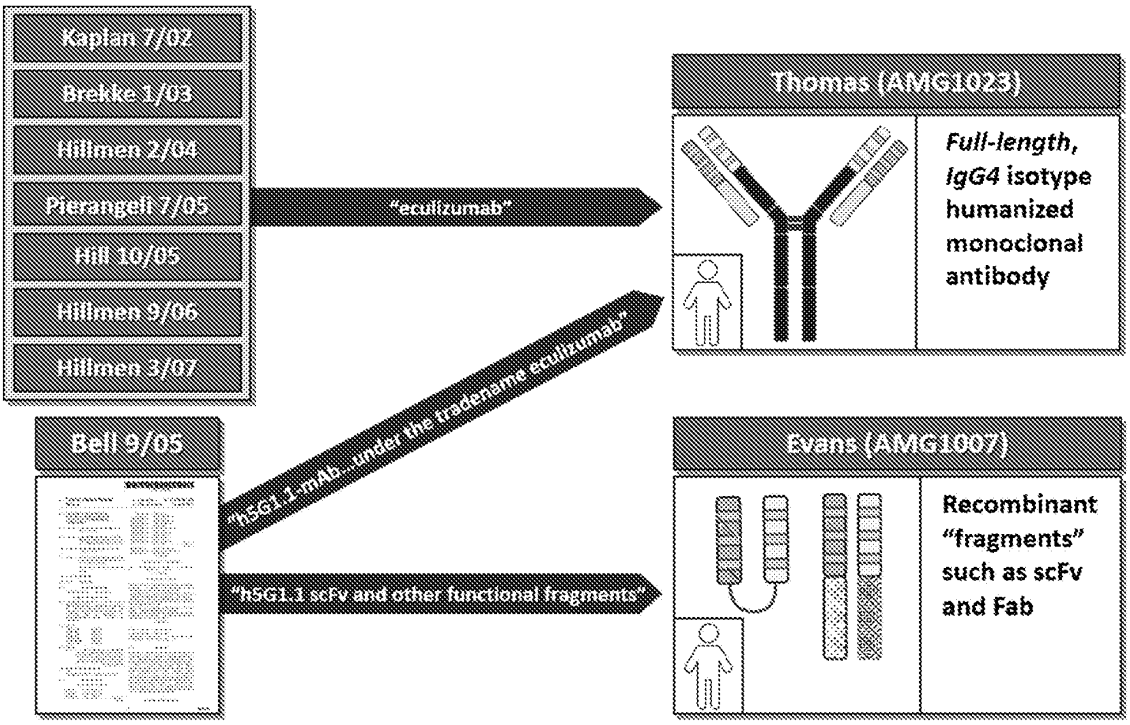
"eculizumab" antibody, in view of Bell's teaching that "eculizumab" binds C5, blocks its cleavage, and successfully treats PNH. (*See, e.g.*, AMG1002, ¶107; ALXN2032, 152:14-18, 153:1-11; 154:1-17; ALXN2022, ¶¶204-208.) For example, Dr. Balthasar admitted that Bell, along with Hillmen and Hill, motivated a POSA as of March 15, 2007 to "make and use the eculizumab antibody that they describe." (ALXN2032, 154:1-7.)

Amgen further concedes that – just like Hillmen and Hill – ***nothing*** in Bell disclosed the amino acid sequence for "eculizumab," or provided the specific amino acid sequence recited in claim 1 of the '149 patent. (Petition, 42; AMG1002, ¶105 (admitting that Bell does not disclose "the requirement that the anti-C5 antibody 'comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4"); ALXN2032, 146:17-25; ALXN2022 ¶204.) As Dr. Balthasar admitted, nothing in Bell disclosed or suggested to a POSA that "eculizumab" had a hybrid IgG2/G4 heavy chain constant region. (*See, e.g.*, ALXN2032, 151:4-12, 160:7-9; ALXN2022, ¶206.)

Rather, as the Board recognized, to the extent Bell disclosed anything about the structure of "eculizumab," it would have directed a POSA towards an antibody with an ***IgG4*** heavy chain constant region – as did Hillmen, Hill, and the many other references pointing to Thomas (AMG1023) for disclosure of "eculizumab". (*See* Paper No. 15, 21 n.14; ALXN2022, ¶¶204-207; *supra* Section II.C.)

Accordingly, a POSA reading Bell would have envisioned "eculizumab" to have a different structure and amino acid sequence from an antibody consisting of SEQ ID NOs: 2 and 4 as claimed in the '149 patent – which again, Amgen concedes was not disclosed anywhere in Bell. (ALXN2032, 146:17-25, 151:4-12.)

Specifically, Bell cited two documents – Thomas (AMG1023) and Evans (AMG1007) – for disclosing "[m]ethods for the preparation of h5G1.1-mAb, h5G1.1-scFv, and other functional fragments," and further identified "[t]he antibody h5G1.1-mAb" in this context as "eculizumab." (AMG1005 ¶[0052]; ALXN2032, 160:18-162:11.) As Dr. Casadevall's **Figure 9** illustrates, a POSA as of March 15, 2007 reading Bell would have understood that, between Thomas and Evans, only Thomas could have disclosed "eculizumab," because only Thomas disclosed an intact, full-length humanized "h5G1.1" antibody, while Evans disclosed humanized scFvs and other "fragments." (ALXN2022 ¶¶204-207; ALXN2032, 163:12-15, 163:25-164:5, 164:12-16; 169:13-18; *see supra* 44-47.)



2. A POSA Would Not Have Been Motivated to Combine Bell's Teachings with Bowdish and Evans, or to Make the Specific Claimed Sequence

For the same reason Amgen contends that Bell would have motivated a POSA to make the specific monoclonal antibody "eculizumab" – a C5-binding, clinically-tested antibody that Bell and other clinical literature consistently described as having an ***IgG4*** isotype – a POSA would ***not*** have been motivated to disregard Bell's teachings, and instead make a different antibody with the uniquely-engineered amino acid sequence recited in claim 1 of '149 patent.

A POSA would not have known of an antibody having the specific sequence claimed in the '149 patent – which differs from the IgG4 isotype antibody that Bell

identifies as "eculizumab" – and would not have been aware that an antibody with the claimed sequence had ever been tested *in vitro* or clinically. (ALXN2022, ¶¶135; *see supra* Section II.B.) In view of the unpredictability in the field of therapeutic antibody design, a POSA knowing of the clinically-proven anti-C5 antibody "eculizumab" would not have been motivated to make an antibody with a different, unstudied amino acid sequence – which might neither bind C5, nor be therapeutically useful or suitable for human administration. (ALXN2022, ¶¶209, 221-229.)

Amgen agrees, arguing in Ground 4 that a POSA as of March 15, 2007 reading Bell would have been specifically motivated to make "eculizumab," and not other, different antibodies. (Petition, 41, 45.) But then, Amgen disregards what Bell and other literature ***actually*** taught actually about "eculizumab" – that it was an IgG4 isotype antibody as described in Thomas. Instead, Amgen implausibly contends that a POSA seeking the sequence of "eculizumab" would have turned to ***Bowdish*** – a document that a POSA would have had no reason to associate with "eculizumab." (Petition, 45-47; AMG1002, ¶¶114-115; (ALXN2022, ¶¶209-213.) There is no reason why a POSA without the benefit of hindsight would have jumped from Bell to Bowdish for an understanding of "eculizumab," as Amgen contends. *See, e.g.*, *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019).

Amgen's hindsight-driven rationale for combining Bell (regarding the anti-C5 antibody "eculizumab") with Bowdish (regarding a TPO-mimetic fusion compound) falls apart under scrutiny, because it depends on assumptions that lack support or even expressly contradict the art's teachings. For example, Amgen asserts that Bowdish was a "known teaching[] in the art pertaining to eculizumab (5G1.1)." (Petition, 45.) But there is no dispute that Bell did ***not*** cite to Bowdish (for "eculizumab" or otherwise), and Bowdish itself made no mention of "eculizumab." (ALXN2022, ¶¶211-212; ALXN2032, 199:9-17.) Nor did any of the other publications cited by Amgen (*e.g.*, Hill, Hillmen, *etc.*) cite Bowdish for "eculizumab" or otherwise. Bowdish did not concern the development of anti-C5 antibodies at all, but rather focused on generating peptide-mimetic fusion compounds having nothing to do with C5 binding or treatment of PNH. (*See, e.g.*, AMG1006 ¶ [0006]; ALXN2022, ¶¶159-160, 211; ALXN2032, 174:2-12, 175:22-176:6, 180:8-11, 181:5-15.)

Dr. Balthasar's only stated "reason" for a POSA to "look to Bowdish" and "link" Bowdish to Bell further reveals his use of improper hindsight. (ALXN2022 ¶¶221-229.) Dr. Balthasar contends, a POSA would have connected Bell and Bowdish because (1) Bell's "eculizumab was . . . known to [*sic*] a humanized 5G1.1 with a hybrid IgG2/IgG4 constant region," and (2) "Bowdish . . . provides most of the sequence of humanized 5G1.1 with a hybrid IgG2/IgG4 constant

region." (AMG1002, ¶115; ALXN2032, 196:15-23, 197:15-25; Petition, 45.) That "reason" falls apart under scrutiny.

First, Amgen and Dr. Balthasar are wrong to suggest that Bowdish identified its TPO-mimetic compound as relating to "humanized 5G1.1" or "h5G1.1." (*See, e.g.*, Petition, 46 (claiming that Bowdish "explicitly direct[ed]" a POSA to look to Evans for "information" on the "h5G1.1 antibody" used to generate Bowdish's TPO-mimetic compound).) As Dr. Balthasar admitted, Bowdish used the term "5G1.1," not "h5G1.1" or "humanized 5G1.1"; and nothing in Bowdish said that the "scaffold" antibody used to generate its TPO-mimetic compound was a "humanized antibody." (ALXN2032, 199:19-23, 200:24-200:2; ALXN2022, ¶¶162, 164, 197-199, 216-217.) Rather, Bowdish references the '283 application (issued as Evans) for "[c]onstruction of 5G1.1" – a term that, , as discussed above, refers a ***mouse*** antibody when used in Evans. (*See supra* Section IV.B.1.) Even if a POSA did understand Bowdish to be referencing Evans for disclosure of an "h5G1.1 antibody" that was used as Bowdish's "scaffold," they would have found none, because Evans did not disclose ***any*** full length humanized antibodies derived from "5G1.1." (*See supra* 18-21.)

Second, Bell suggested that "eculizumab" had an ***IgG4*** constant region, and nothing in Bell pointed towards a hybrid IgG2/IgG4 constant region. (*See, e.g.*, AMG1002, ¶105; ALXN2032, 146:17-25, 151:4-12, 160:7-9.) Amgen's attempt

to associate "eculizumab" with a hybrid IgG2/IgG4 structure ignores Bell entirely, and instead relies on ***non-prior art*** information, and Mueller (AMG1008), which does not mention "eculizumab" at all. (ALXN2032, 55:5-57:1, 58:23-59:3, 59:23-60:6, 60:13-16, 61:13-62:4, 63:5-64:19.) For example, Amgen relies on out-of-context statements made in 2011 from the file history of U.S. App. No. 11/127,438 ("the '438 application") – which is not related to the '149 patent.[5] (*See, e.g.*, Petition, 12 (citing AMG1049, 838-39, 855).) These non-prior art statements cite ***nothing*** dated prior to March 15, 2007 identifying "eculizumab" as having a hybrid IgG2/IgG4 constant region. Instead, they cite Mueller II (AMG1031) – a document that makes no mention of "eculizumab," and merely identified "h5G1.1 HuG4" and "h5G1.1 HuG2/G4" as experimental controls – of which ***only*** the "HuG4" antibody was described as an "anti-C5 antibody." (AMG1031, 446; AMG1008, 12:1-2; ALXN2022, ¶166; ALXN2032, 242:21-243:14.) The prior art must be viewed "***without the benefit of the invention***" – and Amgen failed to do

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[5] Amgen and Dr. Balthasar also rely on a non-prior art publication from November 2007 (AMG1033), and a 2017 submission from an Alexion employee during prosecution of the '149 patent (AMG1015 at 734-741.) (AMG1002 ¶¶11, 54; ALXN2032, 55:5-57:1, 58:23-59:3, 63:5-64:1, 64:8-19.)

so by disregarding the overwhelming teaching by Bell and the other art that "eculizumab" was described as the IgG4 antibody of Thomas. *See Neptune Generics, LLC v. Eli Lilly & Co.*, IPR2016-00237, Paper 84 at 74-77 (Oct. 5, 2017), *aff'd*, 921 F.3d 1372 (Fed. Cir. 2019).

Third, Dr. Balthasar admits that nothing in Bowdish referred to its TPO-mimetic compound as having an "IgG2/IgG4" constant region structure. (ALXN2032, 212:22-213:2, 214:2-7.) Dr. Balthasar fails to prove his contention that a POSA would have identified the hybrid IgG2/IgG4 structure of Bowdish's TPO-mimetic compound using "BLAST or a similar search tool." (ALXN2032, 212:22-213:2, 214:2-7.) Bowdish itself did not guide a POSA to apply such "search tools" to its peptide-mimetic compounds. ([ALXN2022, ¶216; ALXN2032, 214:19-24.) Further, Amgen presents ***no evidence*** of "the search results that a POSA would have gotten if, prior to March 15, 2007, they had tried to evaluate the sequences in Bowdish Figures 13A and 13B using 'BLAST or a similar search tool.'" (ALXN2032, 214:25-215:8.)

A POSA also would not have connected Bell and Bowdish simply because Bowdish used the term "5G1.1." (ALXN2022, ¶219.) As Dr. Balthasar testified, a POSA would have understood that the term "5G1.1" alone was ***not*** limited to "eculizumab," and depending on the context, could refer to the original "5G1.1" hybridoma, the "5G1.1" mouse antibody from the hybridoma (as used in Evans), as

well as many possible "variants" of that antibody with different structures and sequences. (ALXN2032, 98:22-99:8, 100:16-24, 165:5-21; 169:6-18; 202:24-203:16; ALXN2022, ¶¶95-96.) In contrast, the term "eculizumab" as used in Bell referred to only one humanized monoclonal antibody, having a specific (but unknown) amino acid sequence. (*See supra* Section II.B.) A POSA looking for more information on "eculizumab" thus would have considered the art's pertinent teachings regarding "***eculizumab*" – *not*** the far broader term ***"5G1.1."*** (ALXN2022, ¶219.) And a POSA certainly would not have focused on Bowdish, which contained no data showing that its TPO-mimetic compound or its "scaffold" antibody would bind C5 or treat complement-mediated conditions such as PNH. (ALXN2022, ¶¶211, 228-229.)

Amgen's Ground 4 improperly uses the '149 patent as a ***reference point*** for reconstructing the amino acid sequence of the claimed antibody, from sequences selectively plucked and combined from Bowdish and Evans. (*See, e.g.*, AMG1002 Figs. 4-7, 13 (hindsight sequence comparisons between the '149 patent and select sequences from Bowdish or Evans), and Figs. 3, 10, 11 and 12 (using green coloration to signify sequences corresponding in hindsight to the '149 patent).) As Dr. Balthasar concedes, a POSA could not have made any of these comparisons, because a POSA would not have had access to the sequence of the '149 patent. (ALXN2032, 222:7-224:24.) Further, Amgen and Dr. Balthasar disclose ***only*** the

carefully-selected prior art sequences from Bowdish and Evans that they knew ***in hindsight*** would "align[] perfectly" with the '149 patent sequence that was not available to a POSA prior to March 15, 2007. (*See, e.g.*, AMG1002 ¶¶ 51, 53, 102.) But "working backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019).

For example, Amgen presented hindsight alignments between the '149 patent and portions of Evans SEQ ID NO: 20 – a humanized scFv compound (AMG1002, Figs. 6-7) – but withheld from the Board the many other disclosures in Evans that would ***not*** have aligned with the claimed sequence, including:

- Evans Figures 18 and 19 – the variable regions of the mouse antibody that Bowdish references (with respect to the '283 application) for "[c]onstruction of 5G1.1" (ALXN2022, ¶¶ 214-215; ALXN2032, 169:19-170:4);
- The "Fd" molecules of Evans SEQ ID NOs: 11, and 12, which a POSA would have understood were more "complete" fragments of a humanized antibody than an scFv, and provide sequences in the constant region (and for SEQ ID NO: 11, the variable region) that do not align with the '149 patent sequence (ALXN2022, ¶129); and

- The eight other humanized "scFv" molecules of Evans, which Dr. Balthasar admits were different from SEQ ID NO: 20 (*See* AMG1007, 43:6-14, 43:62-45:4; ALXN2022, ¶156; ALXN2032, 222:22-223:9.)

Even assuming the disclosures of Bowdish and Evans were fully combined, a POSA without hindsight would not have been directed to the complete amino acid sequence recited in claim 1 of the '149 patent. (*See supra* Section IV.B.2.)

Amgen further uses improper hindsight by ignoring the disclosure of variable region sequences in ***Thomas*** (AMG1023), which Bell cites alongside Evans. If, prior to March 15, 2007, a POSA reading Bell were to have followed its reference to Thomas for "eculizumab," they would have been directed to variable region sequences that would ***not*** "align perfectly" with the non-prior art '149 patent sequence. For example, all of the light chain regions disclosed for "5G1.1" and various mouse and humanized compounds derived from "5G1.1" disclosed in Thomas have an arginine ("R") at light chain position 38, whereas the claimed sequence of the '149 patent has a glutamine ("Gln"). (AMG1023, 1392, 1396; ALXN2022, ¶244.)

3. A POSA Without Hindsight Would Not Have Reasonably Expected Success with the Combination of Bell, Bowdish and Evans

Amgen's Ground 4 also fails to show that a POSA would have reasonably expected that the antibody it constructs in hindsight from Bowdish and Evans

would be an "[a]n antibody that binds C5," as claim 1 of the '149 patent requires. *See, e.g.*, *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1383 (Fed. Cir. 2019). Amgen relies exclusively on Bell for the teaching of this element. (Petition, 41-42; AMG1002, ¶114.) But Bell only identified "eculizumab" (citing to Thomas's IgG4 antibody) as an anti-C5 antibody, and taught nothing about the C5 binding, if any, of a different antibody with the specific amino acid sequence recited in claim 1 of the '149 patent. (*See supra* Sections IV.B.3, IV.C.1.) Likewise, as discussed above, Bowdish stated nothing regarding the C5 binding, if any, of its TPO-mimetic compound or the "scaffold" antibody it was made from. (*See supra* Section IV.B.2-3.) And as discussed above in Section IV.B.2-3, Evans did not disclose any C5 binding data for the claimed antibody of the '149 patent, or for any other full-length humanized antibody.

In the absence of any disclosure that the antibody with the sequence claimed in the '149 patent was "[a]n antibody that binds C5," a POSA would not have reasonably expected that antibody to bind C5. (ALXN2022, ¶¶ 221-229.)

D. Amgen's Ground 5 Fails Because Amgen Cannot Show that Claim 1 Would Have Been Obvious Over the Combination of Evans and Mueller

Amgen's Ground 5 contends that claim 1 of the '149 patent would have been obvious over a combination of Evans (AMG1007) and Mueller (AMG1008). As the Board correctly found, Amgen's Ground 5 fails, because it relies upon

Amgen's present-day knowledge of the antibody sequence recited in claim 1, which Amgen uses as a guide to pick and combine sequences that it knows in hindsight will align with it. Without the benefit of hindsight, a POSA as of March 15, 2007 would have ***no motivation*** to combine Evans with Mueller to obtain the claimed antibody of the '149 patent; would have had ***no reason*** to pick and combine the specific sequences that Amgen selects from Evans and Mueller to reconstruct the claimed antibody of the '149 patent; and would have ***no reasonable expectation*** that such a new untested antibody would be "[a]n antibody that binds C5," as claim 1 requires. . (ALXN2022, ¶¶ 230-252.)

Nothing in Evans, Mueller, or elsewhere in the art would have motivated a POSA prior to March 15, 2007 to combine the two documents to obtain the specific amino acid sequence claimed in the '149 patent. Mueller did not cite to Evans, and Evans did not cite to Mueller. (ALXN2022, ¶233; ALXN2032, 170:21-171:20, 243:16-20.) A POSA also would not have been motivated to consult Evans and Mueller simultaneously, because they addressed very different technological problems. *See, e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013). While Evans characterized and tested the complement-blocking activity of the anti-C5 mouse "5G1.1" antibody and certain derivative compounds, Mueller studied antibodies to the porcine "VCAM" protein for treating or diagnosing human rejection of transplanted animal tissue, and did

not include any experiments or data on C5 binding or blocking C5 cleavage. (AMG1008, 1:4-19, 7:21-28, 8:34-13:16; ALXN2022, ¶¶165, 233, 242.) Insofar as Mueller described two "h5G1.1" antibodies – "h5G1.1 CO12 HuG4" and "h5G1.1 CO12 HuG2/G4" – these were exclusively used as "controls" for Mueller's study of its anti-VCAM antibodies. (AMG1008, 12:27-30 ALXN2022, ¶ 233; ALXN2032, 232:6-16.)

Amgen is incorrect a POSA "would have readily understood" Mueller's "h5G1.1 CO12 HuG2/G4 mAb" to be "eculizumab." (Petition, 56; *see also* Petition, 52; AMG1002, ¶136.) Neither Evans nor Mueller mentioned "eculizumab." (ALXN2032, 102:10-14, 199:15-17; ALXN2022 ¶166.) And, contrary to Amgen's assertions, the "overwhelming evidence in the art" was that the C5-binding, clinically proven antibody "eculizumab" antibody was Thomas's ***IgG4*** isotype antibody. (*See supra* Section II.C.) Consistent with that teaching, Mueller identified ***only*** the "h5G1.1 CO12 HuG4" antibody as an "anti-C5" antibody. (AMG1008, 12:1-3; ALXN2022, ¶166; *see supra* 57-58.)

Further, as the Board recognized, Amgen fails to show how a POSA without hindsight would have been motivated to combine specifically-selected sequences from Evans and Mueller, in the specific manner required to get the specific amino acid sequence of the antibody claimed in the '149 patent. (*See* Paper No. 15, 52-54.)

Again, Amgen's figures illustrate its use of improper hindsight. For example, Amgen's Figure 16 mistakenly suggests that a POSA would have understood Mueller and Evans to have disclosed the same single antibody, with part of the sequence being provided in Evans, and part of the sequence being provided in Mueller. (Petition, 49, Fig. 16; AMG1002 ¶ 133.) But, as Dr. Balthasar admits, Mueller did ***not*** disclose the amino acid sequence of any full-length "h5G1.1" antibody. (ALXN2032, 232:17-21; ALXN2022, ¶167.) Nor did Evans provide a partial sequence for a full-length humanized antibody, as Amgen's Figure 16 suggests. Rather, a POSA would have seen that Evans disclosed only a full-length "mouse" antibody, and truncated compounds like scFvs and Fabs that were ***not*** fragmented off a full-length antibody, but rather were produced from the ground up using recombinant DNA technology. (ALXN2022, ¶237; *see supra* 18-21.)

Neither Mueller nor Evans provided any ***guidance*** on how to combine their various sequences. As with Ground 4, Amgen's Ground 5 uses its present-day knowledge of the '149 patent to justify its selection and combination of sequences, by showing carefully curated sequence alignments that Amgen knows in hindsight will match with claimed sequence. (AMG1002 Figs. 10, 15-16, 18; ALXN2022, ¶¶239-247.)

E. The Objective Indicia of Nonobviousness Support Validity

Objective indicia of nonobviousness, including commercial success, long-felt but unmet need, and industry praise, further support the validity of the claim 1 of the '149 patent. *See, e.g., LEO Pharm. Prods., Ltd. v. Rea,* 726 F.3d 1346, 1358 (Fed. Cir. 2013).

There is no question that SOLIRIS® (eculizumab) is the commercial embodiment of the '149 patent, and that the objective evidence regarding SOLIRIS® and its commercial and therapeutic success has a direct nexus to the '149 patent. The '149 patent claims the sole active ingredient in SOLIRIS®: the uniquely-engineered, non-naturally occurring antibody comprising SEQ ID NOs: 2 and 4, which is responsible for the remarkable clinical properties of SOLIRIS®, and consequently, its commercial success as a treatment for PNH, as well as the complement-mediated hemolytic condition aHUS, and the neurologic conditions myasthenia gravis and NMOSD. (ALXN2022, ¶¶255-258; ALXN2032, 262:2-19.) *See, e.g., Henny Penny,* 938 F.3d at 1332; *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392-93 (Fed. Cir. 1988).

SOLIRIS® is unquestionably a commercial success, having generated substantial sales in the relevant market. The annual net product sales for SOLIRIS® have grown consistently since launch, including total U.S. sales of

$1 billion over the past three years, continuing to grow to over $1.588 billion in 2018 (a 28.6% increase from 2017). (ALXN2056; ALXN2059-ALXN2073.)

The invention of the '149 patent, in its commercial embodiment of SOLIRIS®, also fulfilled a long-felt, unmet need for a safe and effective treatment for PNH, a rare and potentially fatal blood disease. (ALXN2022, ¶¶260-269.) *See, e.g., Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994, 997-998 (Fed. Cir. 2009). Before SOLIRIS®, PNH patients had to suffer with debilitating symptoms and life-threatening thrombosis, and were often dependent on frequent blood transfusions for survival. (AMG1047, 2559; AMG1012, 1234; ALXN2022, ¶¶263-264.) SOLIRIS® was the ***first*** FDA-approved treatment to reduce hemolysis in patients with PNH – improving patients' quality of life and reducing their transfusion dependency. (ALXN2022, ¶¶262-267.) While other researchers before March 15, 2007 were interested in developing anti-C5 antibodies for treating PNH and other untreated complement-mediated conditions, only the inventors of SOLIRIS® succeeded in doing so. (ALXN2022, ¶¶268-269**;** ALXN2032, 262:23-263:3, 263:23-264:13; AMG1039.)

SOLIRIS® has also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade for pharmaceutical research and development), including the Prix Galien USA 2008 Award for Best Biotechnology Product, and the Prix Galien France 2009 Award for Most Innovative Drug for Rare Disease. (ALXN2020; ALXN2021; ALXN2022, ¶¶273-274.)

The substantial efforts by Amgen and others to copy SOLIRIS® with their own proposed biosimilar eculizumab products – which would necessarily include the claimed antibody of the '149 patent – is further strong evidence of the nonobviousness of the '149 patent. (ALXN2088; ALXN2090; ALXN2089; (ALXN2022, ¶¶275-276.) That Amgen has chosen to copy the specific amino acid sequence of the '149 patent, rather than make different anti-C5 antibody with a different amino acid sequence, evidences the significant impact of the '149 patent's invention. *See Liqwd, Inc. v. L'Oreal USA, Inc.*, --- F.3d ---, 2019 WL 5587047, at *2 (Fed. Cir. Oct. 17, 2019).

V. CONCLUSION

Alexion respectfully submits that the Board confirm the patentability of claim 1.[6]

[6] Alexion provides this Patent Owner Response without prejudice to its right to raise a further constitutional challenge on appeal, including but not limited to challenges to the Board's institution decision and final written decision, based on the Federal Circuit's resolution of pending challenges. *Arthrex, Inc. v. Smith & Nephew, Inc.*, 2019 WL 5616010, at *11 (Fed. Cir. Oct. 31, 2019).

Respectfully submitted,

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Production technologies for monoclonal antibodies and their fragments

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In recent years, monoclonal antibodies have emerged as an increasingly important class of human therapeutics. A variety of forms of antibodies, including fragments such as Fabs, Fab'_2s and single-chain Fvs, are also being evaluated for a range of different purposes. A variety of expression systems and improvements within these systems have been developed to address these growing and diverse needs.

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Abbreviations

ADCC	antibody-dependent cellular cytotoxicity
CHO	Chinese hamster ovary
DHFR	dihydrofolate reductase
IgG	immunoglobulin G
PEG	polyethylene glycol

Introduction

Several recent successful clinical results have led to an increased interest in approaches for expressing various forms of monoclonal antibodies. Large doses are often required for therapeutic purposes, in some cases exceeding a gram per patient per year. This need has driven the development of a variety of production systems to make these molecules efficiently and cost-effectively. Truncated forms of antibodies, including Fab, Fab'_2 and single-chain Fv forms, have also been used for a variety of clinical applications. Depending on the specific use, different forms and different production hosts might be desirable and several recent reviews have specifically addressed issues surrounding production in microbial systems [1,2•] and transgenic plants [3], as well as general production issues [4]. Given the rapid pace of progress and large amount of active work in this field, this review will necessarily be incomplete and will focus on a subset of the most recently reported advances and developments in expression technologies for antibodies and antibody fragments.

Antibody fragments and microbial production

Antibody fragments such as Fabs or Fab'_2s can be the therapeutic of choice for some applications where Fc-mediated effector functions are either not required or are deleterious. The smaller antibody fragments exhibit a shorter circulating half-life than full-length immunoglobulin G (IgG) molecules, but their smaller size can also make them more suitable for applications such as tumor penetration and imaging [4].

These antibody fragments can be generated from mammalian-produced full-length antibodies by treating the IgGs with pepsin or papain. However, *Escherichia coli* remains the production system of choice for antibody fragments used in therapeutic applications for several reasons. Firstly, *E. coli* production can offer a rapid means to progress from antibody selection to good manufacturing practice (GMP) production of antibodies, due to the ease and speed of making productive cell lines compared to eukaryotic cell lines [1]. Secondly, as will be discussed below, high production levels of antibody fragments are usually attainable when *E. coli* is used as the production organism. Currently, there are several Fabs or Fab's in clinical trials (Genentech http://www.gene.com and Celltech http://www.celltech.com) produced using *E. coli*.

A variety of approaches have been adopted by different groups to improve the production levels of antibody fragments using the *E. coli* system. Expression levels of up to 2 g/L have been reported [5]. The approaches taken include optimizing the expression of light and heavy chains to obtain increased titers of a Fab′ [6], host-cell engineering to prevent proteolysis of the light chain [5], and co-expressing chaperones to improve protein folding [7] or disulfide bond formation [8].

Although the short circulating half-life of antibody fragments is suitable for some applications such as tumor imaging, it can also be a limitation for a wider range of therapeutic uses. Chapman showed that site-specific attachment of either a single or a double 25 kDa or a single 40 kDa polyethylene glycol (PEG) moiety to an Fab′ could increase the circulating half-life by up to 80% of that seen for the IgG without a loss in antigen binding [9]. Leong *et al.* showed that the circulating half-life of an Fab′ could be modulated by the choice of size and

Samsung Bioepis Exhibit No. 1002
Page 12803

structure of the PEG moiety attached [10]. A recent review by Chapman further discusses the increases in circulating half-life that can be obtained by attaching PEG moieties to antibodies [11]. Dennis *et al.* describe an albumin-binding peptide that they fused to the C terminus of a Fab light chain. Using this peptide they were able to demonstrate a 26- to 37-fold increase in circulating half-life in either mice or rabbits [12••]. The development of such techniques to increase the circulating half-life can extend the therapeutic usefulness of antibody fragments and allows for less frequent patient dosing.

There has also been a recent report of producing full-length antibodies in *E. coli* [13••]. Up until this report, the dogma had been that it was too difficult to make Fc-containing antibodies in *E. coli*. The full-length antibodies produced in *E. coli* are aglycosylated and lack the ability to bind to the various Fc_γ receptors, but they do retain binding to the neonatal Fc receptor (FcRn) and, thus, have a long circulating half-life. Although many therapeutic uses of antibodies are thought to require the effector functions mediated through Fc_γ receptors, there are also therapeutic indications such as the binding of a soluble antigen that do not require effector functions. Aglycosylated antibodies can be a suitable choice for these types of indications.

Fungal production

There have been recent reports describing the use of *Aspergillus niger* for the production of monoclonal antibodies or antibody fragments. Fungal production of antibodies could offer potential advantages over *E. coli*, if production titers can be boosted in the fungal systems. Antibodies and fragments produced in the *E. coli* system are usually retained in the *E. coli* periplasm, necessitating some type of cell lysis and recovery of the antibody of interest from a complex protein milieu. Proteins made in fungal systems are generally secreted to the culture supernatant, a potential advantage for product purification. Filamentous fungi such as *Aspergillus* are capable of secreting high levels of homologous proteins, but these high levels have yet to be obtained with heterologous proteins [14].

Ward *et al.* expressed full-length IgGs in *A. niger* using an N-terminal fusion to glucoamylase for both light and heavy chains. They relied on the endogenous KexB protease in *A. niger* to cleave off the fusion during the secretion of the antibody [15•]. The authors found inefficient cleavage of glucoamylase from the antibody, but were able to partially remedy the problem with the addition of glycine residues between the glucoamylase and either the light chain or heavy chain sequence. The resulting antibody was found to have glycine residues at the N terminus of the two chains. Expression levels of up to 900 mg/L are reported.

An outstanding question concerning antibody production in fungal systems is whether the differences in glycosylation compared with mammalian systems will cause immune responses or lead to a lack of effector functions in therapeutic uses. The antibodies made in *A. niger* were found to contain a mixture of glycosylated and aglycosylated heavy chains, but did demonstrate a long circulating half-life and antibody-dependent cellular cytotoxicity (ADCC).

An interesting new approach to modifying the glycans attached to recombinant proteins made in fungal systems was recently described by Hamilton *et al.* [16••]. They used a combinatorial library to optimize the cloning of various glycotransferases to humanize the glycosylation pathway of *Pichia pastoris*. If this approach can be combined with high-level expression of antibodies (up to 1.2 g/L has been reported [17]), it could compete with existing mammalian culture systems for the production of antibodies that retain effector functions and have human-like glycosylation. In another recent study, monomeric scFv production in *P. pastoris* was also demonstrated and optimized [18].

Plant production

Research has continued into using plants as a production platform for antibodies and other therapeutic proteins. A recent review [3] discusses the current state of progress and the outstanding issues that need to be resolved in order for a plant-derived antibody for parental delivery to be approved for marketing. The potential advantages for the plant system that are often cited are capital cost savings, the ability to either increase or decrease production output depending on market needs, and the lack of mammalian pathogens in plants. Some of the current hurdles include a long initial lead time for production, regulatory uncertainties, and questions about the suitability of plant glycans for human therapeutics. One approach has been to mutate the N-linked glycosylation site found in the Fc of monoclonal antibodies and to thereby produce an aglycosylated antibody. Another approach taken has been to try and modify the glycosylation enzymes in plants to more closely resemble those in humans. Bakker *et al.* co-expressed human β1,4-galactosyltranferase and an antibody in tobacco plants and obtained a galactosylation profile resembling that found in mammalian antibodies [19].

Mammalian cell production

While specific types of antibodies and antibody fragments are amenable to production in microbial or other systems, mammalian cells remain the dominant system for the production of the majority of full-length therapeutic antibodies. Recombinant Chinese hamster ovary (CHO) and NS0 cells remain the most prominent cell lines of choice, although numerous other cell lines have been explored as well. For example, the human cell line

Samsung Bioepis Exhibit No. 1002
Page 12804

PER.C6 has recently been demonstrated to produce significant levels of recombinant products including antibodies in serum-free, suspension cultures [20,21].

Cell line development

The generation of stable cell lines that produce high levels of product is certainly one of the most critical elements required for the development of an efficient cell culture process. The use of dihydrofolate reductase (DHFR) as a marker for selection and amplification using methotrexate represents the most common system for generating cells with high expression in CHO cells. In a recent modification of this standard approach, Bianchi and McGrew divided DHFR into two fragments that could re-associate, aided by a leucine zipper, into an active molecule [22•]. The two pieces could then be inserted into the expression vector adjacent to light and heavy chains, respectively, to increase the probability that only amplification events that amplified both the heavy and light chain segments would be selected. Several groups have also identified flanking elements to include in vectors for the purpose of increasing the development of stable, high-producing clones, such as the recently reported example of expression augmenting sequence elements (EASE) [23] (reviewed in [24–26]).

The most commonly used approaches for transfection with random integration also lead to a wide diversity of expression levels (e.g. see [27]). Recent approaches to screen through this diversity in a high-throughput manner include approaches based on fluorescence-activated cell sorting (FACS) using a labeled anti-Fc antibody [28], a metallothionein green fluorescent protein (GFP) fusion [29] or a surface affinity matrix [30].

Cellular engineering

A recent trend has been the development of additional genetic manipulations to antibody-producing cell lines to confer properties enabling improved bioreactor performance. Specifically, manipulations have been directed primarily at controlling cell growth, preventing cell death or influencing folding and glycosylation.

Over the past decade, a variety of approaches have been developed and evaluated to enable growth control with the goal of decoupling growth and recombinant protein production (reviewed in [25]). A recent example is the use of inducible expression of p27 to induce growth arrest in a serum-free recombinant CHO culture [31]. Another study correlated the increased productivity observed in p27-arrested CHO cultures with increased cell energy usage [32]. Bi *et al.* also recently reported that specific antibody expression was increased approximately fourfold in an NS0 culture arrested using p21 overexpression [33]. Non-genetic approaches for growth control with sustained protein production, which hold the potential advantage of being easier to implement for existing cell culture processes, have also been reported in CHO systems through the use of galactose in place of glucose as a carbon source [34] or the use of nucleosides such as adenosine [35]. Finally, an approach using FACS-sorting of GFP-expressing cells was used to isolate protein-producing CHO cells in a growth-arrested state [36].

Apoptosis can be the major mechanism for cellular death in fed-batch cell culture. Consequently, several different approaches have been recently evaluated to prolong culture viability and, potentially, increase product titers. Members of the Bcl family, specifically *bcl-2* and *bcl-x_L*, have represented the most common elements for engineering apoptosis resistance (see [37]), although recent studies have also demonstrated effects using Aven [38], XIAP and CrmA [39] and approaches targeting Caspase-3 at the RNA level have been reported [40]. Another study showed a modest benefit of hsp70 overexpression on NS0 apoptosis-resistance and on the productivity of hybridoma cells generated from these hosts [41]. Following earlier work in which Bcl-2 expression was shown to improve antibody and recombinant protein expression in the presence of butyrate in CHO cultures, an apotosis-resistant, DHFR- and Bcl-2 overexpressing host was recently created by Lee and Lee [42]. In one recent study, the relative merits of Bcl-2 and Bcl-x_L were evaluated using a serum-free CHO-DG44 line producing a soluble intercellular adhesion molecule. In this analysis, Bcl-x_L was observed to have more potent apoptosis-resistance effects, although benefits on total recombinant protein expression were only observed after amplifying the Bcl-x_L expression to relatively high levels [43]. In response to potential concerns about the long-term effects of Bcl-x_L overexpression, another group recently developed an inducible system, using the metallothionein promoter, for Bcl-x_L expression and apoptosis-resistance during the production phase of hybridoma cultures [44]. Finally, the combination of growth control and anti-apoptosis effects via genetic engineering was recently evaluated in perfusion NS0 cultures using combined p21 and Bcl-2 overexpression and enabled antibody specific productivities approaching 50 pg/cell/day [45•].

In addition to growth control and apoptosis, limitations in the secretory pathway represent a third target for cellular engineering approaches. For example, one recent study evaluated the levels of three potentially important secretory pathway proteins, heavy chain binding protein (BiP), glucose regulated protein 94 (GRP94) and protein disulfide isomerase (PDI), in hybridomas grown in serum-containing and serum-free medium and found a correlation between GRP94 and PDI levels and monoclonal antibody production rates [46]. In another study, calnexin and calreticulin overexpression were found to nearly double the specific productivity of thrombopoietin in recombinant CHO cultures [47].

Samsung Bioepis Exhibit No. 1002
Page 12805

A variety of approaches have been demonstrated for engineering the glycosylation pathway to manipulate the characteristics of antibodies mediated by oligosaccharides (reviewed by [24,48,49]). Recent studies have demonstrated that the absence of fucose can dramatically increase ADCC [50•,51]. As previously described for plant cultures, an alternative approach is to engineer the antibody sequence to manipulate effector functions (reviewed by [52]). In another recent study, Fc sequence changes were identified to increase serum half-life as well [53].

Process conditions

As monoclonal antibody production processes are increasingly scaled to larger fermentor volumes to meet increasing commercial demands, traditional scale-up issues may present new challenges. For example, a recent study using NS0 cultures explored the effects of pH perturbations, which can occur in large fermentors as a consequence of base addition for pH control [54]. Depending on the fermentor configuration, elevated carbon dioxide levels can also become an issue at larger scales. Carbon dioxide could have direct effects on cell metabolism or could affect culture performance by more general mechanisms related to the increased osmolality resulting from increased carbon dioxide levels. To distinguish between these potential mechanisms, carbon dioxide and osmolality were independently manipulated in hybridoma cultures and revealed an increase in productivity with increased osmolality, while carbon dioxide alone inhibited productivity [55]. Additionally, galactosylation of a hybridoma-produced IgG2a decreased with elevated osmolality, while it increased with elevated carbon dioxide levels (and controlled osmolality) [56]. Certain amino acids were also shown to restore the hybridoma growth rate, although only glycine betaine was found to restore specific productivity at high carbon dioxide levels [57]. In a separate study, antibody productivity was observed to increase by 50% with increased osmolality, which was attributed to improved antibody processing and assembly in the secretory pathway [58]. In another hybridoma example, an IgG3 was observed to have increased galactosylation at higher pH (pH 7.4 versus 7.2 and 6.9) and an increased ratio of *N*-acetylneuraminic acid to *N*-glycolylneuraminic acid [59].

A series of four antibody-producing CHO lines, differing in gene copy number, were also evaluated under hyperosmotic conditions. Antibody productivity was observed to increase most significantly in the lines with the lowest gene dosages (and corresponding mRNA levels) [60]. A proteomics approach was used to investigate the mechanism underlying the beneficial aspects of hyperosmolality on antibody specific productivity in CHO culture. The study identified an upregulation of certain glycolytic enzymes that could lead to increased metabolic energy in these cultures [61].

The effects of temperature have also been evaluated in recent studies. One recent analysis of antibody production in a CHO cell line showed no change in specific productivity at reduced temperature, which contrasts with other reports including a study using the same CHO host and a cytomegalovirus promoter with a different protein [62,63]. In another system, specific Fab production by a CHO line was seen to increase at reduced temperatures [64]. These results demonstrate that the effects of temperature might be cell-line specific. Given that the optimal temperature for growth and productivity can differ for a given cell line, a modeling approach was recently reported to aid identification of the optimal profile for a given process [65].

Complex raw materials such as hydrolysates are still commonly used in cell-culture processes, although the mechanisms for the benefits of these additives are not well understood and may vary between cell lines. A recent study in which certain di- to pentapeptides were added to the medium showed increased monoclonal antibody production in hybridoma cultures using specific peptides, supporting at least one possible type of beneficial component in the hydrolysates [66]. In another recent study, a hollow-fiber microbioreactor was used to distinguish between the effects of fresh medium on hybridoma specific productivity and conditioned medium in increasing cell density [67].

Conclusions

As the clinical applications and needs for recombinant antibodies and antibody fragments have increased in recent years, the need for improvements in expression technologies to support these demands has correspondingly increased. Much recent work has led to significant improvements in the development of multiple expression platforms across the range of microbial, fungal, plant and mammalian systems. Improvements in the microbial production of antibodies and fragments have resulted from host-cell engineering to give increased productivity. There is also a trend towards producing antibodies or fragments with increased circulating half-life. This can be done either post-translationally, by adding PEG moieties, or during translation by adding an albumin-binding peptide or by expressing full-length IgG. There is a growing interest with both fungal and plant systems to address the issues surrounding non-mammalian glycosylation, either through glycosylation engineering or through the mutagenesis of glycosylation sites. For the case of mammalian systems, a growing trend has been towards manipulation of specific cellular pathways to improve performance, both regarding protein titers and antibody characteristics. The development of these approaches has also led to an increased understanding of the fundamental cellular phenomena controlling cell growth, death and productivity in these systems.

Samsung Bioepis Exhibit No. 1002
Page 12806

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Samsung Bioepis Exhibit No. 1002
Page 12807

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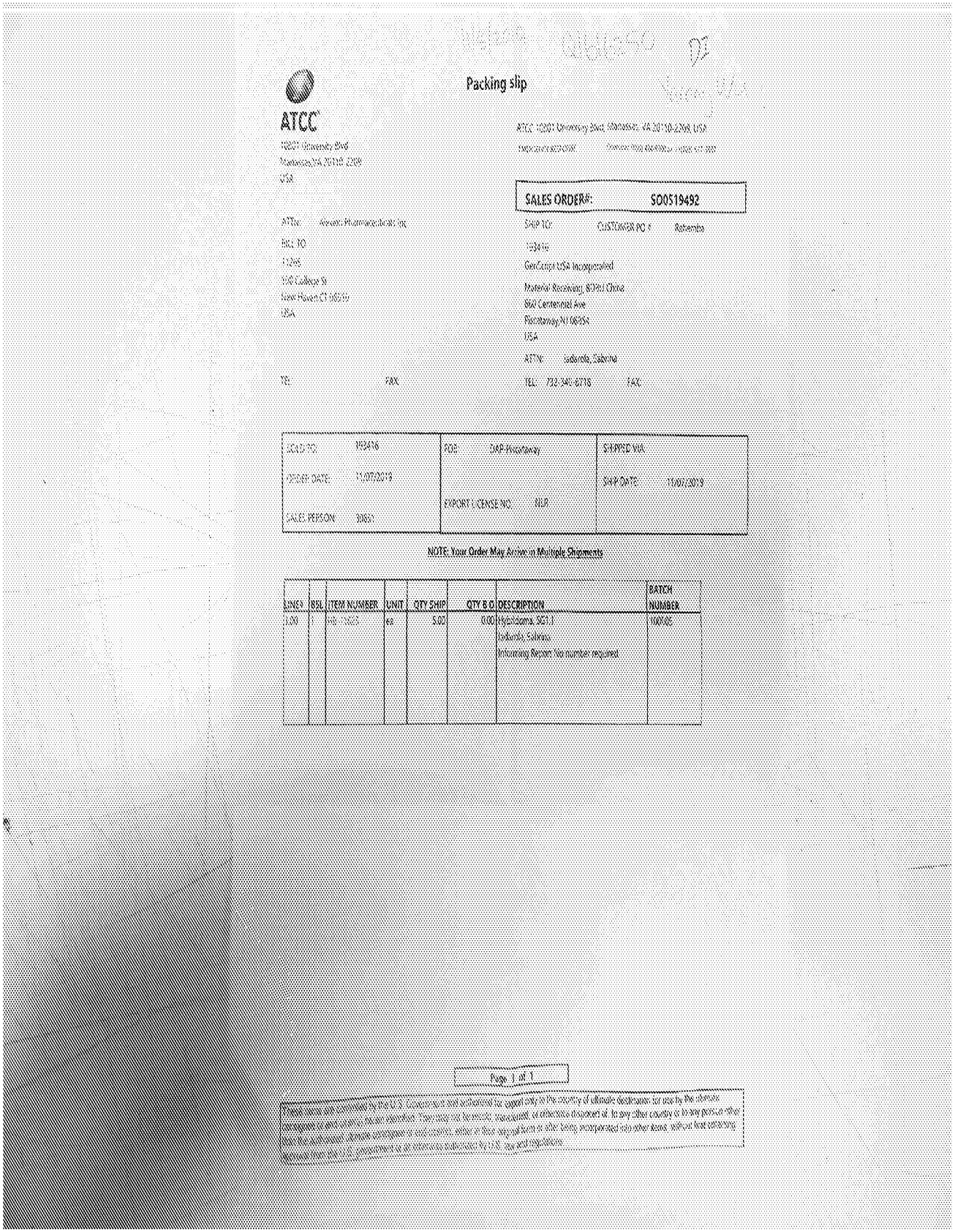
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Propagation

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Page 12811

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Hybridoma: 5G1.1

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Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease

June 10, 2009 01:00 PM Eastern Daylight Time

CHESHIRE, Conn. & PARIS--(BUSINESS WIRE)--Alexion Pharma France and Alexion Pharmaceuticals, Inc. (NASDAQ: ALXN) today received the 2009 Prix Galien France for Soliris® (eculizumab) in the category of medicines for rare diseases. The award recognizes the scientific innovation represented by the complement-inhibition technology of Soliris, and the impact the drug is having on the lives of patients with paroxysmal nocturnal hemoglobinuria (PNH), an ultra-rare, debilitating and life-threatening blood disorder.

Soliris is a first-in-class terminal complement inhibitor that selectively blocks the formation of terminal complement, a component of the normal immune system. Patients with PNH lack naturally occurring proteins that ordinarily prevent terminal complement from causing the red blood cell destruction (hemolysis) that is central to the serious morbidities and mortality associated with PNH. The French award follows receipt last year by Alexion of the 2008 Prix Galien USA Award for Soliris as the Best Biotechnology Product with broad implications for future biomedical research.

“Alexion’s employees in France and throughout Europe are gratified by this award and by the opportunity we have to improve the lives of patients with PNH,” said Patrice Coissac, Senior Vice President of Alexion Pharmaceuticals, Inc. and President of Alexion International Sàrl. “Alexion is committed to the objective that every patient with PNH who can benefit from Soliris will have access to Soliris, and each day, we are working with physicians and national healthcare authorities in Europe toward this goal.”

About the Prix Galien

The Prix Galien (http://www.prixgalien.com/) was established in France in 1970 by French pharmacist Roland Mehl to recognize and promote significant advances in pharmaceutical research. The award is among the industry’s highest accolades. The French award committee includes 17 eminent members from the scientific, medical, and academic communities of France.

Since its debut in France, the Prix Galien has been introduced in other countries of Europe, as well as in the U.S. and Canada. As in France, a prominent and independent panel of judges selects the winner, based on the innovative aspects and therapeutic advantages of the recipients. In addition, an International Prix Galien is selected from winners of the country awards every two years.

"We deeply appreciate this honor, which recognizes more than 15 years of basic and clinical research in the field of complement inhibition," said Leonard Bell, M.D., Chief Executive Officer of Alexion. "We are building on the success of Soliris by increasing our understanding of PNH and by evaluating the promise of complement inhibition for the treatment of patients with other ultra-rare and life-threatening disorders."

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Page 12813

About PNH

Patients with PNH suffer from hemolysis (red blood cell destruction) which leads to thromboses (blood clots), disabling fatigue, anemia, impaired quality of life, pulmonary hypertension, shortness of breath, recurrent pain, kidney disease and intermittent episodes of dark-colored urine (hemoglobinuria). (1,2) PNH is an ultra-rare blood disorder that strikes people of all ages, with an average age of onset in the early 30s. (3) Approximately 10 percent of all patients first develop symptoms at 21 years of age or younger. (1) PNH develops without warning and can occur in men and women of all races, backgrounds and ages. PNH often goes unrecognized, with delays in diagnosis ranging from one to more than 10 years. (4) It is estimated that approximately one-third of patients with PNH do not survive more than five years from the time of diagnosis. (4) PNH has been identified more commonly among patients with disorders of the bone marrow, including aplastic anemia (AA) and myelodysplastic syndromes (MDS). (5,6,7) In patients with thrombosis of unknown origin, PNH may be an underlying cause. (1) More information on PNH is available at www.pnhsource.com.

About Soliris

Soliris has been approved by the U.S. Food and Drug Administration (March 2007), the European Commission (June 2007), Health Canada (January 2009) and Australia's Therapeutic Goods Administration (February 2009) as the first treatment for all patients with paroxysmal nocturnal hemoglobinuria (PNH), an ultra-rare, debilitating and life-threatening blood disorder defined by hemolysis, or the destruction of red blood cells. All four jurisdictions reviewed and approved their respective marketing applications for Soliris under their priority review or accelerated assessment procedures, and all four have designated Soliris as an orphan drug. Soliris is not approved for the treatment of transplant rejection. More information on Soliris is available at www.soliris.net.

Important Safety Information

Soliris is generally well tolerated. The most frequent adverse events observed in clinical studies were headache, nasopharyngitis (a runny nose), back pain and nausea. Treatment with Soliris should not alter anticoagulant management because the effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established. The U.S. product label for Soliris also includes a boxed warning: "Soliris increases the risk of meningococcal infections. Vaccinate patients with a meningococcal vaccine at least two weeks prior to receiving the first dose of Soliris; revaccinate according to current medical guidelines for vaccine use. Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary." During clinical studies, two out of 196 vaccinated PNH patients treated with Soliris experienced a serious meningococcal infection. Prior to beginning Soliris therapy, all patients and their prescribing physicians are encouraged to enroll in the PNH Registry, which is part of a special risk-management program that involves initial and continuing education and long-term monitoring for detection of new safety findings.

About Alexion

Alexion Pharmaceuticals, Inc. is a biopharmaceutical company working to develop and deliver life-changing drug therapies for patients with serious and life-threatening medical conditions. Alexion is engaged in the discovery, development and commercialization of therapeutic products aimed at treating patients with a wide array of severe disease states, including hematologic and kidney diseases, transplant, cancer, and autoimmune disorders. Soliris is Alexion's first marketed product, approved in the U.S. and Europe in 2007, and Canada and Australia in 2009. Alexion is evaluating other potential indications for Soliris as well as other formulations of eculizumab for additional clinical indications, and is pursuing development of other antibody product candidates in early stages of development. This press release and further information about Alexion Pharmaceuticals, Inc. can be found at www.alexionpharma.com.

[ALXN-G]

This news release contains forward-looking statements, including statements related to potential health and medical benefits from Soliris. Forward-looking statements are subject to factors that may cause Alexion's results and plans to differ from those expected, including for example, decisions of regulatory authorities regarding marketing approval or material limitations on the marketing of Soliris, the possibility that results of clinical trials are not predictive of safety and efficacy results of Soliris in broader patient populations, the possibility that third party payers will decide not to reimburse for use of Soliris at acceptable levels or at all, and a variety of other risks set forth from time to time in Alexion's filings with the

Samsung Bioepis Exhibit No. 1002
Page 12814

Securities and Exchange Commission, including but not limited to the risks discussed in Alexion's Quarterly Report on Form 10-Q for the period ended March 31, 2009. Alexion does not intend to update any of these forward-looking statements to reflect events or circumstances after the date hereof, except when a duty arises under law.

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Therapeutic antibody expression technology

Helen E Chadd* and Steven M Chamow†

With the technological advances made during the past decade, antibodies now represent an important and growing class of biotherapeutics. With the potential new targets resulting from genomics and with methods now in place to make fully human antibodies, the potential of antibodies as valuable therapeutics in oncology, inflammation and cardiovascular disease can be fully realised. Systems to produce these antibodies as full-length molecules and as fragments include expression in both mammalian and bacterial cells grown in bioreactors and in transgenic organisms. Factors including molecular fidelity and the cost of goods are critical in evaluating expression systems. Mammalian cell culture and transgenic organisms show the greatest promise for the expression of full-length, recombinant human antibodies, and bacterial fermentation seems most favorable for the expression of antibody fragments.

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Abbreviations
cGMP current good manufacturing practice
CHO Chinese hamster ovary
GlcNAc *N*-acetylglucosamine
scFv single-chain Fv fragment

Introduction

Antibody therapeutics can potentially treat diseases ranging from autoimmune disorders to cancer and viral or bacterial infections. The number of monoclonal antibodies currently in development is higher than in any other therapeutic category, except for vaccines [1]. The emergence of antibodies as an attractive therapy is the result of the evolution of monoclonal antibody technology over the past 25 years from 100% mouse protein through chimeric and humanised proteins to fully human antibodies (Figure 1).

Recombinant expression technology in mammalian cell culture is the principal means for the commercial production of therapeutic antibodies; indeed, eight of the nine antibody products on the US market are recombinant molecules. These molecules are produced in mammalian cell culture using either Chinese hamster ovary (CHO) or mouse myeloma (NS0) cell lines. Although recombinant antibody fragments can also be produced in mammalian cell culture, other systems (e.g. bacterial fermentation) are preferred. Recently, antibody production in transgenic goats, chickens and various plant varieties has been developed to provide a high yield of product at a potentially lower cost of goods than that in mammalian cell culture. The major challenges to be overcome by these transgenic technologies involve the molecular fidelity of the expressed product (principally glycosylation) and the manufacturing regulatory issues raised by the Food and Drug Administration (FDA). This review will discuss the application of the different technologies for the production of therapeutic antibodies and antibody fragments. Focusing on progress made over the past year, our goal is to assess the value of each system with regard to molecular fidelity and cost of goods.

Evolution of antibody technologies

In 1975, Köhler and Milstein [2] established methods to make mouse monoclonal antibodies; however, the utility of these murine antibodies as human therapeutics was limited by their immunogenicity in humans [3,4••]. In the ensuing years, considerable effort was devoted to genetically engineering monoclonal antibodies in order to make them less immunogenic. The evolution of monoclonal antibodies from 1975 to the present day is shown in Figure 1. In 1984, chimeric monoclonal antibodies containing 66% human and 34% mouse sequences were engineered [5]. Approximately half of the therapeutic antibodies currently approved by the FDA are of this design. Between 1988 and 1991, techniques to successfully humanise murine antibodies using complementarity-determining region (CDR) grafting and veneering techniques were established [6,7], reducing the mouse proportion of the sequence to only 5–10%. An alternative approach for producing fully human antibodies is phage display [8]. The initial product is either a single-chain Fv fragment (scFv), in which a short polypeptide is used to directly link the variable heavy and variable light chains, or an Fab antibody fragment (Figure 2) from which a full-length antibody must then be constructed and produced using suitable expression systems [9]. The mid 1990s saw the emergence of transgenic mice that had been genetically engineered to contain a human antibody repertoire [10–12]. This technology allows the use of standard hybridoma techniques to generate fully human antibodies, obviating the need for humanisation altogether. The generation of fully human antibodies has now raised the standards for antibody manufacturing because the protein structure itself should not be immunogenic or have a short half-life.

Factors to be considered during manufacture

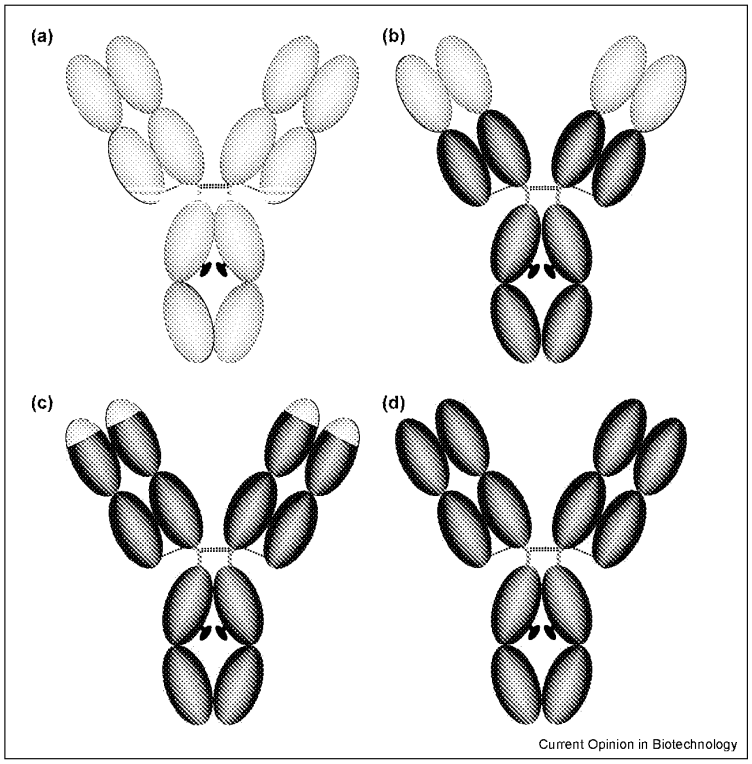
In considering a suitable method for antibody manufacture a variety of factors must be evaluated. These include antibody structure, the importance of carbohydrate, and expression, which includes productivity, ease of purification and cost of goods.

Many different antibody structures have been generated using standard expression technology. These include full-length

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Page 12816

Figure 1

Evolution of monoclonal antibodies from (a) mouse, through (b) chimeric (67% human), (c) humanized (90–95% human) and (d) human (100% human). Mouse-derived sequences (light shading) and human-derived sequences (dark shading) are shown.



antibodies, antibody fragments (Fab or $[Fab']_2$), and scFv (Figure 2). If an antibody molecule of small size is preferred, for example, a fragment with no effector function or limited pharmacokinetic activity, then scFvs or Fab fragments generated in a bacterial system may be sufficient. ScFvs are highly selective for *in vivo* tumours, show good tumour penetration and reduced immunogenicity, and are cleared rapidly from the blood [13]. The use of these molecules is currently being directed towards radioimmunodetection and *in situ* radiotherapy (Table 1) [13,14]. If pharmacokinetic activity in the form of increased half-life is required for therapeutic purposes, however, then a full-length antibody is preferred. For immunoglobulin G (IgG), the molecule can be one of four subclasses: γ1, γ2, γ3 or γ4. If a full-length antibody with effector function is needed, a γ1 subclass is preferred. The γ1 and γ3 subclasses exhibit potent effector function, complement activation [15], and promote antibody-dependent cell-mediated cytotoxicity (ADCC) through interaction with specific Fc receptors [16,17].

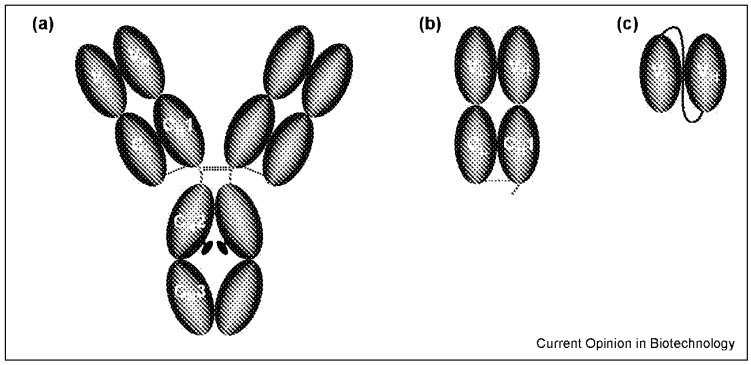
Effector function in these subclasses requires the presence of an accessible carbohydrate structure at Asn297, within the Fc region of the antibody molecule. Unlike bacterial expression, animal cell culture and transgenic animal systems have the greatest potential to produce oligosaccharides similar to those contained in human antibodies. A comprehensive analysis has been conducted on 12 IgGs from different animals showing varying patterns of glycosylation [18••]. The complex biantennary structure of the *N*-linked oligosaccharide at Asn297 is constant across most animal species (Figure 3). Differences arise principally because of the presence or absence of fucose and bisecting *N*-acetylglucosamine (GlcNAc), and the presence or absence and type of sialic acid. Both human and chicken antibodies can contain oligosaccharides with only the sialic acid *N*-acetylneuraminic acid (NANA), whereas all other species can produce antibodies containing only the sialic acid *N*-glycosylneuraminic acid (NGNA) or a mixture of NGNA and NANA. Additionally, human, rat and chicken antibodies contain bisecting GlcNAc oligosaccharides. This structure is required for optimal γ1 effector function [19••]. Although CHO cells do not normally contain the enzyme activity (*N*-acetylglucosaminyltransferase-III) that leads to the bisecting GlcNAc moiety, a CHO cell can be selected or genetically engineered to display this activity [18••,19••].

Expression systems

There are various expression systems that can be used for the production of whole antibodies and antibody fragments. These include bacterial or mammalian cell culture

Samsung Bioepis Exhibit No. 1002
Page 12817

Figure 2



Structural summary of antibodies and antibody-derived proteins that are clinically useful. (a) A full-length antibody of the IgG subclass contains both heavy (V_H, C_H1, C_H2 and C_H3 domains) and light (V_L and C_L domains) chains. Interchain disulfide bonds are indicated (dotted lines). The single oligosaccharide chain (shaded knob) is attached to Asn297 within the C_H2 domain. (b) An Fab fragment contains V_H, V_L, C_L and C_H1 domains, along with a portion of the hinge region. Single-site pegylation can occur via a hinge thiol. (c) A scFv contains V_H and V_L domains connected via a polypeptide linker. Increased stability of scFv can be achieved by the introduction of an additional engineered disulfide bond. Fusion constructs of these molecules with nonimmunoglobulin domains have also been reported [37].

and transgenic animals or plants. As described above, the expression system of choice is partially dependent upon the intended use of the antibody, as well as the antibody yield derived from each system. This yield affects the cost of goods, which is comprised principally of two factors: the cost of the upstream process that generates the antibody, and the cost of the downstream process, that is, purification and final fill of the active pharmaceutical ingredient. For the sake of this review, only the cost associated with the upstream production process will be discussed.

Bacterial fermentation

Table 1 highlights the various expression systems used for the production of therapeutic antibodies. Bacterial systems are suitable for the expression of scFvs and Fabs (Figure 2). Because bacteria lack the cellular machinery to glycosylate proteins, only aglycosyl-antibody fragments are produced from bacterial fermentation. Recombinant fragments can be localised intracellularly or within the periplasm. The yield of scFvs in bacterial expression systems is usually low, primarily as a result of incorrectly folded protein retained either at the inner cell membrane or as an insoluble aggregate in the periplasm. Sánchez *et al.* [20] described the generation of 27–30 μg/ml of active scFv expressed in bacterial cytosol. Although the insoluble periplasmic protein can be extracted and refolded, high periplasmic expression can cause toxicity and cell death [20,21].

ScFvs have also been expressed in insect cells [13,20–24] (see Table 1). Functional scFvs have been secreted into the growth medium of a stably transformed *Drosophila* expression system at 25 μg/ml [23], and intracellularly in insect cells using the baculovirus expression system [23].

In contrast to bacterial and insect cells, there is some debate as to the ability of yeast cells to express functional antibodies; indeed, the glycosylation pattern in yeast is very different from that in mammalian systems [13,21].

Bacterial expression systems are cost-effective for the production of antibody fragments where no effector function or extended pharmacokinetic activity is required. To take economic advantage of bacterial expression, pegylation of the antibody fragment can be performed to increase the half-life of the antibody fragments in humans [25]. Because the assembly and glycosylation of full-length antibodies is not possible in bacterial systems, mammalian cell culture or transgenic organisms are better suited for production of these molecules.

Mammalian cell culture

Any human antibody IgG subclass can be generated in mammalian cell culture systems using either CHO cells, requiring methotrexate amplification, or NS0 cells, requiring methionine sulphoxime amplification (using glutamine synthetase selection in NS0 cells [26]). When expressing γ1 antibodies in a recombinant or transgenic system, the system must be chosen to maintain antibody effector function. An optimal effector function is dependent upon the correct carbohydrate structure at Asn297, including the presence of bisecting GlcNAc [19••] (see Figure 3). It must be appreciated that the structure and composition of oligosaccharides in immunoglobulins can vary considerably with the host cell or transgenic system chosen for expression.

In general, productivity in mammalian cell culture continues to increase because of improved recombinant expression vectors, the identification of 'hot integration spots' within the genome and the enhancement of biomass accumulation. This has resulted in cell-culture processes achieving yields of 1–2 g/L of unpurified antibody [27]. Further increases in the productivity of mammalian cell culture could be achieved by enhancing cell growth and

Table 1

Summary of antibody expression systems.

System	Antibody form	Source	Use	References
Bioreactor				
Escherichia coli	Mu scFv	Cytosol, periplasm	Diagnostic, therapeutic	[20–22]
Pichia pastoris	Mu scFv	Medium	Diagnostic, therapeutic	[13,21]
Drosophila melanogaster	Mu scFv	Medium	Diagnostic	[23]
Mammalian (CHO/NS0)	Ch IgG_1	Medium	Therapeutic	[38–41]
	Ch Fab			
	Hz IgG_1	Medium	Therapeutic	[42–44]
Hybridoma	Mu IgG_2	Medium	Therapeutic	[45,46]
	Mu IgM			
	Hu IgG_2	Medium	Therapeutic	[1,47]
Transgenic organism				
Animals				
Mouse	Ch IgG_1	Milk	Research	[28••]
Goat	Ch IgG_1	Milk	Therapeutic	[28••]
	Hu IgG_2			
Plants				
Tobacco	SIgA/G: Ch	Leaf	Therapeutic	[35,36]
Maize	Hz IgG	Seed	Therapeutic	[33]
Soy	Hz IgG	Pod, seed, stem, leaf	Therapeutic	[34]
Rice	Mu scFv	Seed	Diagnostic, therapeutic	[24]
Wheat	Mu scFv	Seed	Diagnostic, therapeutic	[24]

Ch, chimeric; Hu, human; Hz, humanized; Mu, murine; SIgA/G, secretory IgA/G.

the inherent specific productivity of the manufacturing cell line. Increasing the yield of antibody from a manufacturing process is particularly important where the product is to be used chronically and therapeutic doses are high. For some high-dose indications, >200 kg of purified bulk material may be required annually at a cost of goods of >$500/g. Assuming a productivity of 2 g/L with a 50% process yield, at least twenty 10 kL bioreactor runs per year would be required to meet this output. In order for the industry to maintain an acceptable margin on future production, the cost of goods must be reduced by 1–2 orders of magnitude — to tens of dollars per gram. The future cost of goods target for mammalian cell culture is below $50/g of final purified material.

Transgenic organisms

An alternative method for the large-scale production (e.g. hundreds of kilograms) of antibody is expression in transgenic animals or plants.

Goats

The generation of a transgenic goat herd able to produce antibody for phase I clinical trials takes up to 24 months. Antibody DNA fused to a milk-specific regulatory element is inserted into a single cell embryo by microinjection. Transmission of the mammary gland-specific transgene is achieved using Mendelian genetics [28••]. At this time, several monoclonal antibodies expressed in transgenic goat milk are in early-to-late stage development and clinical testing (Table 1). There is, as yet, limited clinical data on the efficacy and safety of antibodies generated in goat milk [28••]. Current figures suggest that, at 1000 kg/year, antibodies could be produced in goat milk for a cost of approximately $40/g [29], compared with mammalian cell culture in which the cost is $300–1000/g (at 100 kg/year assuming a titer of 0.5 g of antibody/L) [30]. The cost-effective advantage of transgenic animals is realised only at higher production requirements in excess of 75–100 kg/year; price model analyses that include both upstream and downstream process costs have concluded that, for only 10 kg of material in milk, the cost would be $300/g [30]. At this scale, mammalian cell culture is the more cost-effective option.

Chickens

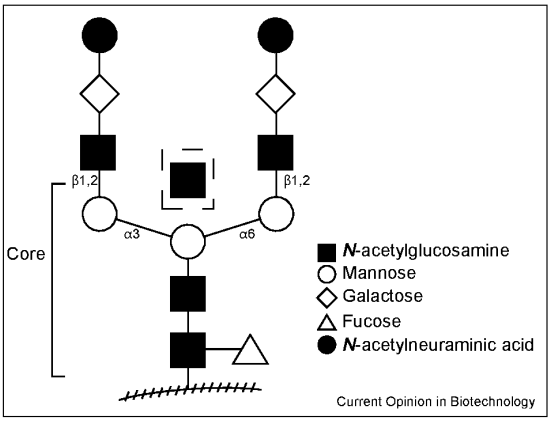
The transgenic production of antibodies in egg white has been reported to take approximately 18 months. This expression system has the potential to supply large quantities of material for clinical trials relatively inexpensively [31]. For example, a flock of 5000 chickens is estimated to produce 125 kg of unpurified antibody/year (100 mg antibody/egg and 250 eggs/chicken/year). The commercial cost of chicken eggs (produced under conditions that do not comply with current good manufacturing practice [cGMP]) is currently $0.05/egg [31]. Hence, the cost of generating unpurified material from transgenic chickens is calculated at $0.5/g. Although this cost appears low, it does not account for the production of material under cGMP conditions. There are, as yet, no clinical data to support the production of therapeutic antibodies using this system.

Plants

The generation of transgenic plants for preclinical and phase I studies takes approximately 20 months. Antibody DNA is introduced into the plant using either

Samsung Bioepis Exhibit No. 1002
Page 12819

Figure 3



Representation of typical human Fc-associated oligosaccharide structures. A conserved oligosaccharide core, linked to asparagine, is composed of three mannose (Man) and two GlcNAc monosaccharide residues. Additional GlcNAcs are normally β1,2-linked to α6Man and α3Man, whereas the monosaccharide residues *N*-acetylneuraminic acid, galactose, fucose and the bisecting GlcNAc (boxed) can be present or absent, depending on the heterologous expression system that is used.

Agrobacterium infection or gene bombardment in the presence of a carrier molecule and gold particles. In the case of corn, antibody is produced in the seed; in tobacco plants, antibody is synthesised in the leaf. Recent advances with inducible promoters allow controlled expression only in harvested plant tissue so that antibody is generated in a GMP facility overnight and not out in the field [32•]. Although expression levels can be quite high, the carbohydrate structures generated in plants are quite distinct in composition and structure from human glycoproteins. To overcome this problem, aglycosyl-antibodies are typically produced in transgenic plants [33]. For IgG1 subclasses requiring effector function, this type of expression has obvious limitations; however, an aglycosyl mutein of IgG2 or IgG4, both of which lack significant effector function, might be successful.

The antibody huNR-LU-10 mAb, for example, generated in corn, has been genetically engineered to knockout the glycosylation site. The aglycosyl molecule was comparable in function to its glycosylated counterpart, although *in vitro* antibody-dependent cell cytotoxicity was reduced [31,33]. In addition, a humanised aglycosyl IgG1 to treat herpes simplex virus 2, produced in soybean, was compared with the glycosylated molecule produced in murine cells. Both antibodies were similar in affinity, neutralising activity and stability [34]. Also, a monoclonal IgA for the oral treatment of tooth decay, produced in transgenic tobacco, demonstrated higher functional activity and longer survival times than the murine IgG equivalent [31,33,35,36]. A rudimentary cost analysis conducted for plant-produced antibodies gave a figure of $100/g [30]. Growth in the field versus the greenhouse makes a difference in production cost. For field crops, production costs of only $43/g have been reported, whereas the generation of the same material in plants cultivated in greenhouses rises to $500–600/g [32•].

Conclusions

At this time, bacterial expression systems are only useful for the generation of antibody fragments. A full-length antibody molecule cannot yet be generated in this way; to make these, mammalian expression is the system of choice. Mammalian expression systems have been proven to generate safe and effective antibody molecules with serum half-lives equivalent to those observed for naturally occurring antibodies. Although there are differences in glycosylation patterns between antibodies generated in CHO versus NS0 cell lines, no clinical data suggest these structural differences have any effect on antibody activity *in vivo*. The majority of approved therapeutic antibodies are of subclass IgG1 and are generated in either NS0 or CHO expression systems. Both systems produce antibodies with acceptable effector function and serum half-life; moreover, human antihuman antibody (HAHA) responses owing to unusual carbohydrate structures have not been observed. Enhanced effector function can be obtained if an expression system is used that is able to generate antibodies featuring a bisecting GlcNAc structure. Transgenic production can achieve a lower cost of goods for large-scale manufacturing. Recent advances in the expression of antibodies in transgenic goats, chickens and plants — with respect to productivity, competitive timelines and cost of goods — suggest the need to seriously evaluate these recombinant systems as alternative platforms. If the productivity of mammalian cell culture continues to improve (e.g. to 2–5 g/L), so that the cost of goods can be reduced to tens of dollars per gram, then transgenics cease to be advantageous from a cost of goods standpoint, even for large-scale production. This assumes that there is no further reduction in the cost of goods for transgenic systems.

Comparing cost of goods analyses between cell culture and the various transgenic production systems, expression in transgenic chickens appears to show great promise when compared with goats and plants. With a growing number of antibodies moving into clinical evaluation, the utility of transgenic production will be evaluated alongside mammalian cell culture for the production of therapeutic antibodies.

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Samsung Bioepis Exhibit No. 1002
Page 12821

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Chain of Custody Log: US

1.0 Samples were received at 860 Centennial Avenue, Piscataway, NJ 08854, sent from ATCC. Samples were received frozen by Alan Chau on Friday, 11/08/2019 TRK# 447046152160. The package came in a box (total weight 8.55lb) including 2kg dry ice.

1.1 Samples were shipped to China office in a dry shipper on 11/08/2019 by Cindy Wu. Cells were kept at -80C in dry shipper during the duration of the shipment.

1.2 The sample was immediately transferred to Yuling Li, antibody sequencing team, antibody drug discovery department, Genscript, 28 Yongxi Road, Jiangning, Nanjing, Jiangsu Province, China. Sample was kept in -800C freezer (GR19013096, 3rd floor, box 17) before it was taken out for experiment.

Created by: Sabrina Iadarola, Sales Manager, GenScript USA, Inc.

Date: 11/19/2019

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Theory and Practice

Edited by
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Mark C. Manning

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Samsung Bioepis Exhibit No. 1002
Page 12825

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Samsung Bioepis Exhibit No. 1002
Page 12829

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Samsung Bioepis Exhibit No. 1002
Page 12830

1

Practical Approaches to Protein Formulation Development

Byeong S. Chang and Susan Hershenson

INTRODUCTION

As is the case with other pharmaceuticals, formulation development is one of the critical steps in developing a protein as a therapeutic product. Development of stable protein formulations may require even more resources and effort than conventional small molecule pharmaceuticals. Proteins typically have more stability issues as a result of their complexity and delicate structural stability. Fortunately, a great deal of research regarding protein stability has been conducted and this information is readily available in the literature (reviewed by Manning et al., 1989; Chen, 1992; Ahern and Manning, 1992a, 1992b; Arakawa et al., 1993; Cleland et al., 1993; Wang and Pearlman, 1993; Pearlman and Wang, 1996; Volkin and Middaugh, 1997). Ultimately, it would be ideal to be able to develop a pure pharmaceutical containing only the native protein. However, it is not practical to have only the native form of a protein in the formulation because the protein must be purified from a complex biological mixture containing a pool of other proteins which includes misfolded, denatured, and degraded forms of the same protein. Furthermore, a major challenge is to maintain the integrity of the purified protein during routine pharmaceutical processing, storage, handling, and delivery to the patient. One could envision achieving this goal by developing a formulation with

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Samsung Bioepis Exhibit No. 1002
Page 12831

perfect stability, i.e., no physical and chemical change in the protein. Because proteins are complex molecules composed of numerous reactive chemical groups and delicate three-dimensional structures, identifying a set of conditions to keep all components stable is virtually impossible. In general, commercial therapeutic protein formulations are developed under the assumption that some degree of physicochemical changes will occur during storage and handling.

Realizing that it is impossible to develop a perfectly stable formulation, especially while meeting an aggressive product development timeline, the main objective then becomes one of maintaining the appropriate safety and efficacy of the product. In order to achieve this objective, it is imperative to understand the broad spectrum of degradation pathways affecting proteins, and to have available equipment and expertise in an extensive repertoire of analytical methods. Formulation development focuses on determining the potential degradation pathways, assessing the significance of each and optimizing variables to minimize the degradation products that are clinically significant.

Regulatory guidelines also are critical elements for guiding formulation development. They provide information about how to conduct studies and obtain useful results for evaluating formulations. The results obtained allow formulation scientists to write an appropriate developmental pharmaceutics section in regulatory filings. The guidelines also help to evaluate the significance of some inevitable degradation products that are produced during manufacturing, shipping and storage. For example, if the degradation products have properties comparable to those of the desired product with respect to activity, efficacy, and safety, they can be classified as product-related substances. This classification is significantly different from considering the degradation product as an impurity when there is not sufficient supporting evidence to justify classification as a product-related substance (Appendix, Regulatory Document 1). Understanding of these practical issues of regulatory requirements is critical for formulation scientists during design, implementation, evaluation and reporting of their studies.

In addition to insight into the scientific and regulatory issues, developing commercial formulations requires a clear understanding of the potential market. For example, indication, patients, method of delivery, frequency of dosing, typical dose requirement, market distribution and other business-related information will provide directions for the design of a successful formulation. Also, it is important to consider the competitiveness of the formulation as compared to other products available in the market.

In this chapter, an overview of critical factors affecting the design of therapeutic protein formulations and a general guide to developing commercially viable dosage forms for protein pharmaceuticals will be discussed. Since the majority of practical issues are not covered very well in the scientific literature, this chapter also includes information from regulatory guidance documents (see Appendix), labels from marketed products and routine industrial experience.

Samsung Bioepis Exhibit No. 1002
Page 12832

PREPARATION FOR FORMULATION DEVELOPMENT

Resource Requirements for Formulation Development

A list of resources that should be available before starting formulation development is summarized in Table 1. Some resources may not be as critical as others, depending on the nature of problems encountered, but it is important to have sufficient resources to discover major formulation issues as early as possible in the product development process. Without the appropriate equipment and personnel, the development of an acceptable formulation can be greatly hampered, potentially to such a degree that the product is never brought to market. Of course, not all of the resources need to be at the company developing the therapeutic protein, but if outside contractors are employed it is essential that timely access to resources is available. In addition, the quality of raw materials should be carefully evaluated because unexpected impurities may introduce unnecessary

Table 1.
Resource Requirements for Initial Protein Formulation Development

Resources	Requirement	Example
Purified protein	Representative of manufacturing process; sufficient quantity to cover dose bracket, formulation variables, and stress conditions; minimum complication by impurity (precipitation of impurity, degradation by impurity like proteolytic cleavage).	Purified bulk, sample from final purification process
Qualified excipients	Pharmaceutically acceptable quality, manufacturers with qualified production procedures and sufficient scale, specifications on critical impurities, quality that can be carried on to clinical studies and commercial distribution.	USP, Ph. Eur, JP
Access to fill finish facility	Capability to sterilize container/closure components; fill/finish under aseptic environment; head-space purge system; drying equipment	Sterile hood, filling machine, lyophilizer
Analytical instruments	Structural analyses; concentration determination, chromatographic analyses; electrophoresis; bioassays; other microcharacterizations.	CD, UV, fluorescence, HPLCs, mass-spectrometry, SDS-PAGE
Facility to accommodate stability studies	Controlled temperature, controlled light exposure, controlled relative humidity, devices to provide controlled agitation.	Freezer, refrigerator, incubator, light chamber, RH incubator, agitator

Table 2.
Examples of Information Useful for Designing Formulation Studies

Information	Examples
Clinical indication	Site of treatment (self-administration, office visit, hospital), methods of delivery, concomitant medication, competition.
Patient population	Age, strength, tolerability, capability to manipulate devices, sensitivity to excipient
Typical routes of delivery	Injectables (IV, SC, IM, IP, ICV, IT, IO), topical, inhalation, nasal, oral, etc.
Dose requirement	PK profile, frequency of dosing, variable vs. fixed dose, single-dose/multidose
Drug interaction	Co-administration with other drug, dilution or reconstitution with other solution; presence of undesirable compounds like reducing sugars, preservatives
Typical dosage forms	Liquid, lyophilized, spray-dried, aerosol by liquid or powder, other novel carrier; stability, physical properties, reconstitution art
Container/closure	Vial/stoppers, prefilled syringes, prefilled cartridges, dual-chamber cartridges, blister packages, product contact material, leacheates, breakage, light sensitivity, moisture penetration
Delivery device	Syringes, prefilled-syringes, pen injectors, auto-injectors, needle-free injectors, inhalation devices, infusion pumps

complications in the stability profile that is determined during formulation development and testing.

Useful Information for Designing Formulations

The configuration of a protein formulation is affected by how the drug will be used as a product. If such information is available when designing formulation studies, it is recommended to consider the limitations and challenges associated with each application. Examples of such information are listed in Table 2.

PREFORMULATION DEVELOPMENT

It is important to understand the critical properties of a protein before starting large studies to design and test the final formulation. Preformulation studies are designed to learn about the protein's susceptibility to a variety of pharmaceutically relevant stresses. The main objectives of preformulation research

Samsung Bioepis Exhibit No. 1002
Page 12834

Table 3.
Information Obtained from Pre-formulation Studies for Protein Pharmaceuticals

Characterization	Examples
Physical properties	Primary, secondary, tertiary and quaternary structures, solubility, viscosity, self-association, hydrophobicity, molecular weight, extinction coefficient, glycosylation, effects of ionic strength, etc.
Biological properties	Substrate or receptor affinity, in vitro activity model, *in vivo* preclinical model, etc.

include: general characterization of the product; investigation of potential stability issues; development of relevant analytical methods; establishment of a stability profile with stability-indicating assays; and identification of major formulation challenges. A summary of these issues will be presented in this section.

Characterization of Protein Pharmaceuticals

There is available in the literature extensive coverage of analytical methods and their principles for the characterization of proteins (e.g., Jones, 1993; Reubsaet et al., 1998; Herron et al., 1995). General points to consider when characterizing a protein as an active ingredient are listed in Table 3. As a protein's biological activity is dependent on its structure, significant emphasis has been given to structural properties and stability against various stresses.

Accelerated Stability Studies

In order to predict potential stability problems within a short period of time and to develop appropriate analytical methods, proteins are exposed to stronger-than-real stresses and various degradation products induced by the stresses are examined. The results obtained from these so-called "accelerated stability studies" might also be useful to predict the kinetics of the degradation processes under real handling conditions, when there are not sufficient real-time results available because of time and resource constraints. However, the accelerated stability study is not acceptable to determine expiry of the product, so it is best used to rank order the importance of different degradation pathways. Approaches and cautions in the extrapolation of data from accelerated stability testing to real-time stability and normal handling conditions are discussed in detail below.

Table 4.
Various Conditions Used to Accelerate Protein Degradation

Stresses	Routine ranges	Practical applications	Problems to monitor
Temperature	0–50°C	Storage, shipping, handling, delivery	Structural changes (precipitation, aggregation, recovery loss), solubility, increased reaction rates for all degradations
Light	>1.2 million lux hrs illumination, >200 watt hrs/square meter UV energy	Light exposure, container, package	Oxidation, cleavage
Freezing	Multiple freeze-thaw, liquid nitrogen freeze	Frozen storage, accidental freezing, lyophilization	Precipitation, aggregation, pH change, crystallization of excipients
Oxidation	Oxygen purge, peroxide spike	Storage, excipient stability, impurity	Oxidations, inactivation
Humidity	0–100% RH	Storage, container integrity, powder	Moisture content, moisture related degradations
Mechanical stresses	Vortex, agitation, shear-stress ($3000\,s^{-1}$)	Manufacturing, filling, shipping, handling, delivery	Precipitation, aggregation, recovery loss
Other denaturants	—	Impurities, pH, denaturing excipients	Precipitation, aggregation, recovery loss, structural changes

Conditions to accelerate various degradation reactions in protein products and potential problems to monitor are listed in Table 4. Proteins contain numerous amino acid side chains and delicate three-dimensional structures, which can be susceptible to different stresses. Therefore, it is important to test the protein under a variety of physical and chemical stresses in order to provide a good simulation of the degradation products that can be generated.

Development of Analytical Methods

A brief summary of typical analytical methods is presented in Table 5. It is essential to have a wide range of analytical methods available to identify and characterize degradation products. The analytical methods should be further selected and customized to accommodate the specific needs for each protein product.

Samsung Bioepis Exhibit No. 1002
Page 12836

Table 5.
Typical Methods Used to Characterize Proteins and Degradation Products

Methods	Examples	Applications
Column chromatography	HPLC, FPLC, low pressure LC; size-exclusion, reversed-phase, ion-exchange, hydrophobic, affinity columns; coupled with UV, fluorescence, RI, and other analytical instruments as detectors	Most physical and chemical degradations, excipient impurities, leacheates
Electrophoresis	SDS-PAGE, native PAGE, isoelectric focusing, capillary electrophoresis, etc.	Degradations with changes in size and/or charge
Spectroscopy	CD, fluorescence, FTIR, UV, Raman, NMR, etc.	Structural changes, chemical modifications of side groups
Thermal analysis	Differential scanning calorimetry, thermogravimetric analysis, thermomechanical analysis, etc.	Protein structure, lyophilized cake structure, powder characterizations
Light scattering/turbidity	Dynamic light scattering, other light scattering devices, turbidity, particle size determination, particle counter, etc.	Aggregation, precipitation, molecular weight determination
Other microcharacterization methods	Peptide mapping, peptide sequencing, amino acid analysis, mass spectrometry, other specific analyses for individual reactive groups	Identification of impurities and chemical degradation, analysis of complex proteins, e.g., antibody and glycoprotein

Evaluation of the Significance of Problems

As stated earlier, it would be ideal to have a pure protein in an absolutely stable formulation. In reality, however, scientists have to design formulation based on compromises that deal with several different potential problems. To make matters worse, the formulation needs to be recommended long before it is evaluated fully, because of typical aggressive timelines in the industry. In general, the formulation will have to be optimized based on assumptions and extrapolations of results obtained during a limited time. Therefore, it is important to utilize the given time efficiently, by collecting as much relevant information as possible for evaluating the significance of each problem.

Due to the marginal stability of proteins, it is possible to create rapidly a variety of degradation products during accelerated stability testing. However, not

all the degradation products that are observed will be significant under normal handling, shipping and storage conditions. Furthermore, the rank order of different degradation processes under accelerated stability testing will NOT be the same under practical handling conditions, because each reaction has a different temperature dependency, i.e., reaction order and activation energy. Another important thing to keep in mind when evaluating different degradation processes is the contribution to the pharmaceutical quality of the product. Critical degradation products should be designated not on the quantity obtained during accelerated stability studies, but on a comprehensive understanding of their contributions to the quality of the product.

Quantitative Assessment. Usually, the rate of each degradation reaction during real storage conditions (e.g., at 4–8°C) should be very slow. In order to predict the rate under real storage conditions, reaction rates obtained under accelerated stability conditions can be extrapolated by using the Arrhenius equation.

Predicting the correct reaction rate requires a proper understanding of the reaction order, because the amount of the degradation product does not linearly increase over time unless the reaction follows zero-order kinetics. One way to determine the reaction order is to calculate the linearity between the concentration of residual native protein and time. The reaction order can be calculated from:

$$dC/dt = kC^n \tag{1}$$

where, C is the protein concentration, t is the time, k is the reaction rate constant, n is the reaction order. For a zero order reaction $n = 0$ and $C_0 - C = k \cdot t$. For a first order reaction $n = 1$ and $\log C_0 - \log C = k \cdot t$. For a second order reaction $n = 2$ and $1/C - 1/C_0 = k \cdot t$. For each reaction order a characteristic transformation of concentration will show a linear relationship with time, e.g., $\log C$ will show a linear relationship with time for a first order reaction, whereas $1/C_0$ will be linear versus time for second order reactions.

After obtaining the reaction rate constants for different temperatures, the activation energy can be found by using with the Arrhenius equation.

$$k = A \cdot e^{(-Ea/RT)} \tag{2}$$

The activation energy is obtained by plotting (log k) vs (1/T) and determining the slope of the plot. Using the activation energy, the reaction rate constant for real storage condition, e.g., 2–8°C for refrigerated storage, can be estimated by extrapolation.

Care must be taken when extrapolating the rate constants because there are numerous cases when the Arrhenius relationship does not apply. The Arrhenius reaction applies only to irreversible reactions where the product is accumulated as a single quantifiable species. If the degradation product is the result of serial

Samsung Bioepis Exhibit No. 1002
Page 12838

reactions, the reaction order and rate constant will be determined only by the rate-limiting reaction at the testing condition. If the rate-limiting reaction changes or another significant variable is introduced at the extrapolated condition, then the extrapolated rate constant will be in error. Such complications routinely can be found in various degradation pathways that are affected by temperature-sensitive reactions such as structural changes, pH changes, by physical changes such as the glass transition of an amorphous phase in a lyophilized formulation and by changes in reactants like dissolved oxygen. For example, proteins have relatively high activation energies for structural changes. Thus, many reactions that are dependent on a major perturbation of the native protein structure tend to cause substantial damage under accelerated storage conditions, e.g., higher temperature. However, many of these reactions are not necessarily major problems when the product is stored at 2–8°C where the protein maintains its native conformation. In contrast, degradation reactions with lower activation energies, which might not be coupled to protein conformational changes (e.g., oxidation of surface methionine residues), tend to be much more problematic in the development of protein formulations.

Results from stresses (e.g., agitation) other than heat imposed in accelerated stability studies potentially could be extrapolated in a similar way to storage and actual handing conditions. The major challenge is the ability to assess quantitatively the magnitude of the stress so that the stress-stability relationship can be established. To date there are not published guidelines for such quantitation.

Qualitative Assessment. Not all of the degradation products are equivalent in terms of their contribution to the pharmaceutical quality of the protein product. Therefore, a qualitative assessment of each degradation product is important when weighing their significance. Regardless of their quantity, some degradation products are generally less acceptable than others. If the degradation product comprises the safety of the product, then it should be considered less acceptable. For example, even at levels of a few percent or less of the total protein population, non-native aggregates can cause adverse reactions in patients such as immune responses and even anaphylactic shock. Also, if the degradation reaction results in the inactivation of protein, it needs to be considered more important than other degradation reactions that do not affect the activity. For example, certain chemical changes (e.g., deamidation) may not alter the activity of a given product, whereas other reactions (e.g., oxidation) may render that product inactive. The relative impact of each degradation product on safety and efficacy cannot be predicted and must be determined for each protein therapeutic.

Information useful for the qualitative evaluation of degradation products includes the identity, clinical and preclinical experiences with the degradation product, biological activity, stability and potential side effects. Regulatory documents also provide clear guidance about what assessment is necessary for protein degradation products (Appendix, Regulatory Documents 2,3). The criteria for

Samsung Bioepis Exhibit No. 1002
Page 12839

identification, reporting and qualification of degradation products are set up based on the total patient exposure and percentage of the degradation products (Appendix, Regulatory Document 3). When certain degradation products cannot be prevented from forming in the formulation, their inclusion in the product must be qualified, which may require that additional information on safety and efficacy be obtained as recommended in the regulatory guidelines (Appendix, Regulatory Documents 2,3). Obtaining this information requires a significant amount of additional work, which may include clinical studies.

FORMULATION DEVELOPMENT

As discussed above, the critical parameters affecting the pharmaceutical quality of a protein therapeutic are defined during the preformulation studies. In formulation development, the effects of formulation variables on the defined critical parameters are examined to optimize protein stability. Which variables are most important depends of the formulation type chosen. For example, resistance to agitation and/or accidental freezing is a critical property for an aqueous formulation, which would not be a concern for a lyophilized formulation. Similarly, choosing excipients that provide a glassy matrix to stabilize the protein is only a concern for dried formulations.

Formulation Options for Protein Pharmaceuticals

Different types of formulations need to be developed based on clinical needs, patient compliance, delivery method, stability of the drug, storage and distribution, and market competitiveness. Having a clear plan about what type of formulation is desired will allow one to design better formulation studies. Liquid formulations have been generally preferred due to the convenience of manufacturing and use. However, protein drugs may not be stable enough to be handled as a liquid formulation. Dried formulations (e.g., lyophilized) or suspension formulations (e.g., insulin zinc suspension) have been successfully used to overcome stability problems. In addition, specific applications and delivery may demand the appropriate type of formulation, e.g., a spray-dried powder for pulmonary delivery. As details of the stability issues are discussed in other chapters in this book, only practical issues regarding these different types of formulations will be summarized here.

Liquid Formulations. It is important to understand that developing conditions to keep proteins stable in a liquid form for a pharmaceutically relevant

Samsung Bioepis Exhibit No. 1002
Page 12840

storage time (e.g., two years) is not a simple task. For most proteins, including relatively stable ones, at least some degradation should be expected even during refrigerated storage. Unless there is strong evidence supporting that the protein remains stable for two years and the evidence is supported by a broad spectrum of analytical methods, one needs to be very careful about the final decision to market a liquid formulation. Physical or chemical changes that have low activation energy should be monitored especially carefully under real storage conditions. If there is a degradation product that can significantly affect the pharmaceutical quality at its minimum concentrations (e.g., formation of particulates) great care must be taken to assure that such a product does reach unacceptable levels during real-time storage. If long-term storage studies are not implemented until late in the product development process, there is a risk that problems due to unacceptable levels of degradation products will not be discovered in time to test alternative formulations. In addition to stability during storage, temporary exposure to temperatures outside the recommended conditions should also be tested because it can affect the quality of the drug. Also, results obtained from multiple freeze-thawing cycles will be useful to determine if the formulation can accommodate unexpected freezing during distribution and storage. Likewise, sensitivity to agitation or surface denaturation needs to be understood to support formulation choices as well as shipping and handling guidelines. For formulations containing low protein concentration, special attention is required to avoid impurity-related stability issues (e.g., oxidation fostered by metal contaminants in excipients).

Solid Dosage Forms. Recent improvements in devices designed for easier use of lyophilized products, e.g., dual chamber syringes, dual chamber cartridges and convenient reconstitution devices, have helped pharmaceutical industries to develop lyophilized products without too many concerns surrounding patient compliance issues. Because lyophilized products have less stability-related issues and have a much greater potential tolerance for room-temperature storage, many biopharmaceutical industries consider the lyophilized formulation as a default option. In fact, lyophilization has been widely utilized to overcome various stability issues of labile proteins. However, it is important to note that lyophilization can present its own challenges, particularly in designing appropriate formulations and economic cycles. Detailed discussion about the rational design of stable lyophilized formulations is available in another chapter in this book.

In addition to the required stability, a successful lyophilized formulation should also have the desired physical properties of the dried powder, e.g., ruggedness of the cake and the maintenance of the physical states for each of the ingredients. For example, crystallization of an initially amorphous excipient during storage can lead to unacceptable degradation of the protein product and loss of cake structure. Furthermore, optimal water content for protein stability should be studied and controlled during storage. It is preferable to define an acceptable

Samsung Bioepis Exhibit No. 1002
Page 12841

range of water contents to provide flexibility in the manufacturing process. To assure that the appropriate water content is maintain, the integrity of container/ packaging should be monitored in a high relative humidity environment.

The identity and volume of the reconstitution medium should also be clearly defined, because the use of injectable fluids other than the recommended one may compromise the quality of the product (e.g., solution tonicity or protein stability). Reconstitution should be convenient and rapid, and the stability of the reconstituted solution during handling and delivery needs to be demonstrated.

Only recently have spray-dried formulations become commonly used with the advent of novel protein delivery technologies. For example, spray-dried powders have been useful for developing products that require uniform particle size (e.g., pulmonary inhalation for systemic delivery). Similar issues to the lyophilized formulation apply to the spray-dried formulation, and the details of development of spray-dried formulations are presented in another chapter in this book. In addition to protein stability, physical properties pertinent to powder processing and powder stability (e.g., flowablity, hygroscopicity, agglomeration, density and crystallization of excipients) need to be well characterized.

Single Dose and Multidose Forms. Most protein pharmaceuticals are marketed as single dose forms. However, multidose formulations are useful when the dose needs to be split (e.g., dose titration or dose combination). Multidose formulations are distinguished by the presence of preservatives in the formulation, which prevent microbial contamination and/or growth during multiple disruptions of container closure integrity. In general, the addition of preservative(s), regardless of the preservative used, significantly changes the stability profiles of proteins (Maa and Hsu, 1996; Fransson et al., 1997; Lam et al., 1997). In some extreme cases, visible precipitation and aggregation have been reported. Therefore, the effect of various preservatives on the stability of protein should be carefully examined. Other experiments required to qualify a multidose formulations include the preservative effectiveness test and the stopper self-sealing test. Detailed procedures and specification are available from the USP (U.S. Pharmacopeia), the Ph. Eur. (European Pharmacopeia) and the JP (Japan Pharmacopeia).

Desired properties of the ideal preservative include: effectiveness at low concentration against a wide variety of organisms; chemical stability; solubility; compatibility with the protein drug, excipients and auxiliary agents; free from objectionable odor, taste, color and stinging; and non-toxic and non-sensitizing both internally and externally at the required concentration. Also, it must not absorb, penetrate, or interact with containers or closures (Thompson, 1998). For further details on preservatives, readers are referred to Regulatory Document 4 in the Appendix and Thompson (1988). Examples of typical preservatives used for parenteral protein pharmaceuticals are benzyl alcohol, phenol, *m*-cresol and benzalkonium chloride.

Samsung Bioepis Exhibit No. 1002
Page 12842

Typical Protein Stability Problems: Causes and Solutions

Table 6 summarizes typical stability problems observed during protein formulation development and potential methods to solve each problem. The list does not represent the complexity of multiple problems that can be experienced with a given protein. Formulation research should be designed to handle each protein based on its unique stability profile.

Optimization of Formulation Variables

Overview of the Process. The optimization of formulation variables for product stability is the most critical part of protein formulation development. Various formulation excipients and buffers (Table 7) can be utilized and must, therefore, be chosen to maximize the pharmaceutical quality of the product (i.e., stability and activity) without introducing significant side effects. Among the listed formulation variables, the most powerful one is pH. Problems associated with the physical properties of a protein, e.g., precipitation due to solubility and/or stability, are generally very difficult to manage by other formulation means. Optimization of pH is a simple but very useful solution for such problems (Kolvenbach et al., 1997). Most chemical reactions also are affected by pH, e.g.,

Table 6.
Typical Stability Problems Observed in Protein Pharmaceuticals

Problems	Potential causes	Possible solutions
Non-covalent aggregation	Solubility, structural changes, heat, shear, surface, denaturants, impurities	pH, ionic additives, amino acids, surfactants, protein concentration, raw material purity
Covalent aggregation	Disulfide scrambling, other unknown mechanisms	pH, inhibit non-covalent aggregation
Deamidation	pH < 5.0 or pH > 6.0	pH optimization
Cyclic imide	pH around 5	pH optimization
Cleavages	Protease impurity, other unknown mechanisms	pH, product purity, inhibitors
Oxidation	Active oxygen species, free radicals, metals, light, impurity	Excipient purity, free-radical scavenger, active oxygen scavengers
Surface denaturation, adsorption	Low protein concentration, specific affinity, protein hydrophobicity	Surfactants, protein concentration, pH

Samsung Bioepis Exhibit No. 1002
Page 12843

Table 7.
Important Components of Protein Formulations

Formulation Variables	Desired attributes	Examples
pH	Provides good physical properties of protein, minimize degradations	
Stabilizer	Inhibit degradations, effective at low concentrations	Surfactants, sugars, salts, antioxidants
Solubilizer	Improve the solubility, effective at low concentrations	Salts, amino acids, surfactants
Buffer	Good buffering capacity, stable to temperature change, stable to freezing, good safety record	Phosphate, acetate, histidine, glutamate
Tonicity modifier; bulking agent	Inert, good safety record	Sodium chloride, sorbitol, mannitol, glycine

deamidation, cyclic imide formation, disulfide scrambling, peptide bond cleavage, and oxidation (see reviews listed above). Other functional excipients should be also carefully evaluated for the benefit of the product (e.g., use of sucrose to stabilize protein during lyophilization and storage in the dried solid).

In addition to their intended use, excipient candidates should be also qualified as appropriate pharmaceutical ingredients. Generally, it is preferred to select excipients that have been used in marketed products with a relevant route of delivery. Further, it is preferable if these excipients have been used with similar frequency of dosing, history of chronic use and similar patient populations. Otherwise, the approval and safety of the excipients need to be carefully examined. If the excipient is considered safe with a solid scientific basis or has a proven clinical safety record, it can be considered equivalent to approved excipients. The list of excipients used for parenteral pharmaceuticals is available in the literature (Powell et al., 1998; Nema et al., 1997; Appendix Regulatory Document 5). When it is necessary to introduce other excipients with minimum safety records, a significant risk associated with the excipients will be added to the product development and additional pre-clinical and clinical studies may be needed.

Another important requirement in qualifying an excipient is the purity of the raw material. Depending on the historical use as a pharmaceutical ingredient, several different pharmaceutical grades are available, e.g., USP (U.S. Pharmacopeia), Ph. Eur. (European Pharmacopeia) and JP (Japan Pharmacopeia). These pharmaceutical grade materials should be considered as a primary resource, but the quality provided may not be good enough for specific product development. For example, significant stability problems can be found with some impurities

Samsung Bioepis Exhibit No. 1002
Page 12844

even at concentrations below their specification, e.g., metal ions, peroxides, proteases and reducing sugars. These problems are more prominent in low protein concentration products due to a high impurity-protein ratio, although problems like visible precipitation of the protein may be independent of protein concentration. If adjustment in the existing specification is necessary, it is critical to look into the availability of GMP quality raw materials with modified specifications as early as possible, once the potential problem is identified.

The use of excipients derived from animals (e.g., Tweens) or humans (e.g., human serum albumin) should be avoided if possible due to the risk associated with transmissible diseases like bovine spongiform encephalopathy, Creutzfeldt-Jakob Disease, hepatitis virus and HIV. Numerous regulatory guidelines have been issued to discourage the use of animal/human-derived excipients (Appendix Regulatory Documents 6,7,8). When animal-derived excipients have to be included in the product, the manufacturer will need to demonstrate that their selection is fully justified.

Design of the Study. A design for the formulation optimization study should be in place before commencing the work. A typical study protocol will include the following information:

- Study title
- Study objective
- Source and quality of drug substance and excipients
- Material preparation
- Formulation matrix
  - Formulation variables
  - Protein concentrations or bracket
- Analytical methods
- Storage conditions (temperature, light, humidity)
- Additional sample handling conditions (temporary exposure to stresses, container orientation, etc.)
- Sampling schedule and expected duration of the study
- Plan for data analysis and report

The study can be more efficiently designed by utilizing experimental design software packages, which will help to minimize the resources required for sample preparation, analyses, and data analysis.

Necessary Studies for Formulation Development

Storage Stability Study. Documenting that the formulation will keep the protein stable until the desired expiry can be the most time-consuming part of

Samsung Bioepis Exhibit No. 1002
Page 12845

formulation development. The expiry requirements are determined by distribution not regulatory requirements. One year is probably too short for effective manufacturing and distribution through normal channels. In general, a shelf life of 18 month is considered acceptable for commercialization. Results obtained from accelerated stability studies are useful for predicting potential degradation products and appropriate analytical methods, but whatever the actual shelf life, it must be supported by sufficient real-time storage data to obtain regulatory approval. Thus, it is important to establish a final formulation and start the real-time storage studies as early as possible during product development.

Process Development. Formulations that can be prepared on a small scale without experiencing any problems may encounter significant problems during the scale-up of the process. For example, mixing solutions in a large stainless steel tank, pumping solutions through stainless steel tubing, filtration and filling through a high-speed filling machine can introduce unexpected stresses to the protein. An increase in the formation of particulates, along with a loss of proteins due to surface adsorption and aggregation, has routinely been observed. It is important to expose the formulation to equivalent stresses and make sure that no formulation adjustment is necessary to accommodate the manufacturing processes. Again, this testing should be done as early in the development process as possible.

Transportation, Handling and Delivery Study. Unexpected environmental changes can be encountered during the distribution and handling of products (e.g., accidental freezing, exposure to temperatures different from the recommended conditions, vigorous agitation, etc). It is critical to develop the formulation with these stresses in mind because they can compromise the quality of the product.

Also, during administration to the patient, proteins can be exposed to different types of stresses introduced by the device and the routes of delivery. Examples include incompatibility with the delivery device (e.g., protein aggregation induced by exposure to tubing surfaces) and/or concomitant medication (e.g., protein aggregation induced by co-administered antibiotics).

Preclinical and Clinical Studies. Results documenting the maintenance of the biophysical and biochemical properties of the protein are essential for a final formulation decision. Before finalizing the formulation, it is also important to confirm that it does not affect critical *in vivo* biological properties of the protein (e.g., activity, pharmacokinetic profile, and toxicity profile). Maintenance of a protein's biophysical properties can be examined using various structural analyses (e.g., circular dichroism, fluorescence and infrared spectroscopies, etc.). It is possible to determine the biochemical equivalence of the protein pharmaceutical by *in vitro* activity and/or preclinical *in vivo* bioassays. Results supporting the toxicity profile of the formulation can be generated by both preclinical and clinical studies.

Samsung Bioepis Exhibit No. 1002
Page 12846

Strategies to Overcome Difficult Formulation Problems

Occasionally, problems are encountered that are difficult to overcome with conventional formulation approaches. It is possible to conduct additional studies to confirm that the problem is pharmaceutically acceptable. On the other hand, unique formulation approaches can be introduced to address specific problems. Examples of this approach are provided below.

Qualification of Degradation Products. If decreasing the amount of degradation product below the specified threshold is not feasible, then the degradation product can be defined as a drug substance by demonstrating that it does not affect the pharmaceutical quality of the drug product, i.e., safety and efficacy (Appendix, Regulatory Document 1). If there is not sufficient information available, additional qualification studies recommended in the regulatory guidance can be carried out (see the discussion above). The experience of having these degradation products in the materials used for clinical studies can sometimes be very useful because the results obtained can provide useful insight into the clinical implication of the degradation products.

Site-directed Mutagenesis to Improve Properties. Some problems related to the intrinsic properties of a protein cannot be overcome unless a change in the sequence is introduced. After careful research is carried out to identify the problematic region or residue, the protein can be engineered for better physical and/or chemical properties. For serious problems like precipitation due to insolubility or poor stability, changes in protein sequence have been proven effective for improving physical properties (Murby et al., 1995; Roig and Kennedy, 1995).

Chemical Modifications. The physical properties of proteins can be improved by modifying problematic amino acid side chains with small compounds or large polymers (e.g., attachment of polyethylene glycol) (Fagain, 1995; Guerra et al., 1998; Francis et al., 1998). In addition, there are other desirable improvements that can be achieved by the conjugation chemistry (e.g., enhanced pharmacokinetic profiles, reduced immunogenecity, enhanced adsorption, etc.).

Unconventional Dosage Forms. Some protein stability problems can be resolved by introducing novel approaches in the formulation. Examples include suspension formulations (Defelippis et al., 1998), microencapsulation with cyclodextrin (Brewster et al., 1991), suspension of dry-powder in non-aqueous vehicle (Knepp et al., 1998), and use of non-aqueous vehicles with hydrophobic ion-pairing (Manning et al., 1995).

FORMULATION IN COMMERCIAL PRODUCT DEVELOPMENT

Critical Formulation Decisions During Pharmaceutical Development

A brief summary of the important phases of a commercial product development is shown in Figure 1. Ideally, a stable formulation would be available during the early discovery research period to ensure that the protein is in its active and stable form during critical feasibility studies. However, development of a stable formulation for each drug candidate is not practically possible because such an approach would take too much time and too many resources. Generally, formulation development starts after the decision is made to start clinical trials. A

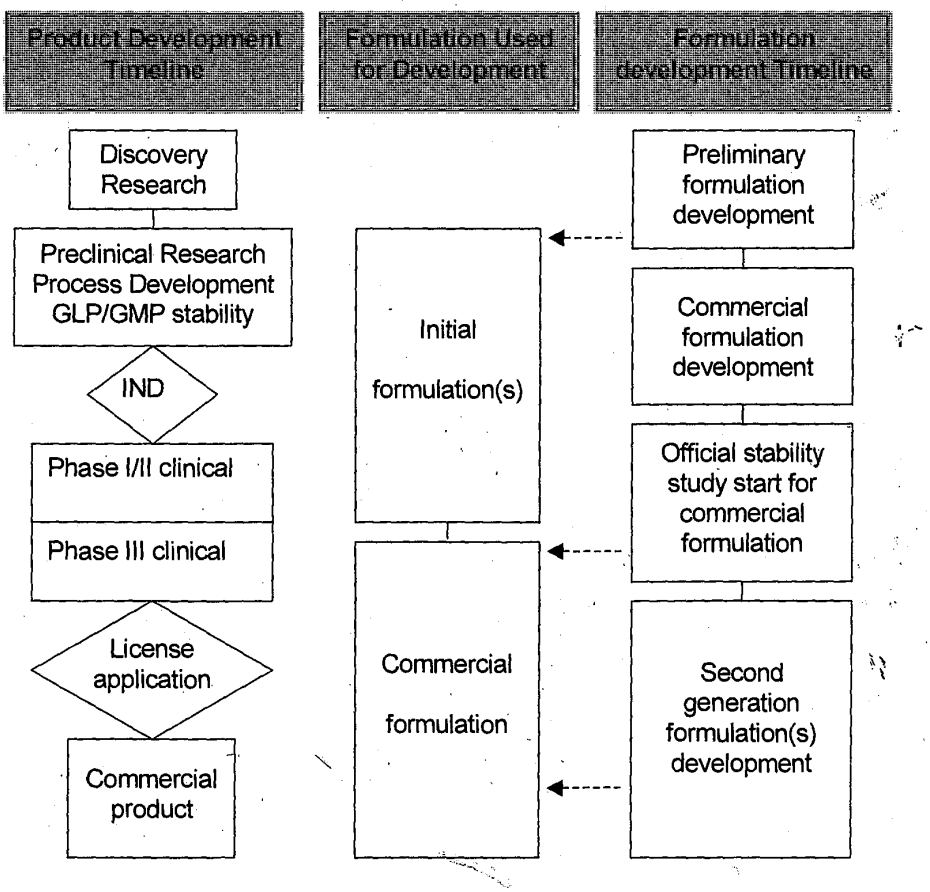


Figure 1. Diagram showing commercial formulation development process.

Samsung Bioepis Exhibit No. 1002
Page 12848

reliable formulation is required to support various preclinical and clinical studies. The formulation can be further improved later to satisfy the clinical, marketing, and regulatory needs. Although formulation development does not necessarily appear rate-limiting during this improvement period, it is important to understand that changing a formulation may require much more supporting work, including additional clinical trials, which can take years.

Formulation for Early Preclinical and Clinical Studies

When a promising protein drug candidate is identified from preliminary feasibility studies, a decision will be made to introduce the drug to clinical studies. In order to obtain regulatory approval to initiate the clinical trials, it is required to demonstrate safety, manufacturing capability, stability of the drug and reproducibility in studying the drug. A sufficiently stable formulation is necessary at this stage because it is important to maintain the quantity and quality of the protein for all research studies from which results will be used for registration of the product with regulatory agencies. Therefore, formulation development becomes a rate-limiting process at this early stage. Formulations can be stored frozen or lyophilized for this purpose. At this stage in product development, the shelf-life requirement is determined by the logistics of supplying drug for clinical trials.

Commercial Formulation

Commercially viable and market competitive formulations have some common features. Most of all, the formulation should maintain the safety and efficacy profile of the protein drug during all the handling and uses specified on the label. Since commercial distribution channels are not equipped for frozen products, shipping and storage at refrigerated temperature or higher are required. Sufficient shelf life needs to be determined under conditions to which the product will be exposed in the commercial distribution system. Various systematic studies need to be carried out to comply with regulatory requirements for registration. It takes 1–2 years to collect all of these results, so the commercial formulation is developed while preclinical studies or early clinical trials (with the preliminary formulation) are in progress. If possible, the commercial formulation should be introduced before the pivotal clinical trial because clinical experience is the most effective way to confirm the safety and efficacy aspects of the formulation. In addition, formulation changes after this point may introduce formidable challenges to the clinical program and to obtaining regulatory approval.

Samsung Bioepis Exhibit No. 1002
Page 12849

Regulatory Issues in Formulation Development

Incorporating regulatory guidelines into the formulation development is not only useful to develop high quality pharmaceutical formulations for maximum benefit to the patients, but also critical to prepare complete documents necessary for regulatory approval for commercialization of the drug. Readers who wish to obtain a comprehensive understanding of the guidelines are referred to the relevant documents published by regulatory agencies. In this section, a brief summary of the guidelines related to the formulation issues is provided.

Guidelines for Stability Studies. Comprehensive guidelines can be obtained from regulatory agencies (Appendix, Regulatory Documents 9–12) and review articles in the literature (Grimm, 1998; Kommanaboyina and Rhodes, 1999; Matthews, 1999). These guidelines generally cover the formal stability studies for bulk drug material, in-process samples and final formulated product. Although some issues may not be relevant for the earlier formulation development work, these guidelines provide key elements for designing stability studies. The guidelines provide information such as what types of experiments should be included in the study protocol, how to propose a stability-indicating profile, and what analytical results are needed to define the purity of the product and the molecular characteristics of degradation products. Another important piece of information provided in the guidelines is the definition of proper experimental conditions, e.g., definition of storage temperature, humidity, light strength, and accelerated and stressed conditions. The guidelines also provide the official protocols to evaluate the results obtained from stability studies.

Results Required to Apply for Regulatory License for a Drug Product. Detailed information regarding the formulation is presented at the Development Pharmaceutics section in the CMC section of regulatory applications (Appendix, Regulatory Docoments 13–16). All of the essential information required to apply for regulatory approval of protein formulations can be found in Note for Guidance on Development Pharmaceutics (Appendix Regulatory Document 17) and Development of Pharmaceutics for Biotechnological and Biological Products (Appendix, Regulatory Document 8). It is important to note that this is currently a European requirement although the international harmonization process may eventually introduce it to U.S. regulatory requirements. A brief summary of the important formulation information is shown in Table 8.

Results Required to File Formulation Amendments. A formulation change can introduce substantial potential adverse effects on the identity, strength, quality, purity or potency of the product as related to the safety or effectiveness of the product. For this reason, it is required that a supplement to the approved license application be submitted. This supplement should include a detailed description of the proposed change. It should also include methods and results for the studies performed to evaluate the effect of the change on the

Samsung Bioepis Exhibit No. 1002
Page 12850

Table 8.
Summary of Information Included in Regulatory Applications

	General information	Comments specific to proteins
Active substance (protein)	Compatibility with excipients and other combined products, and physicochemical characteristics	Structural elements responsible for the biological activity; good coverage of degradations occurring during storage, manufacturing, and delivery.
Excipients	Function of each excipients, justification for their inclusion, and compatibility with other excipients, choice of quality	
Formulated products	Overage, physicochemical parameters, components with appropriate results supporting intended purpose; compatibility with diluent, device, and other drugs in contact before delivery; critical physical properties	Stability of structure in terms of biological activity; formulation optimization for both manufacturing process and stability
Packaging material	Integrity of container and closure during storage, reconstitution, admixture, dilution; sorption to container, leaching, and dose reproducibility	Adsorption, denaturation at the interface, and aggregation of the surface-denatured protein; reconstitution of dry-powder formulation
Manufacturing process	Manufacturing process for the preparation of formulation and its justification, appropriate method of sterilization and justification	Resúlts to support the quality and stability of the protein during the manufacturing process; membrane filtration under aseptic conditions sufficient

product's identity, strength, quality, purity, and potency of the product, as related to the product's safety or effectiveness (Appendix, Regulatory Documents 18–20). When the degradation profile is changed qualitatively or quantitatively, it is recommended to follow the impurity-related guidelines discussed above (Appendix, Regulatory Documents 2,3). The manufacturer must obtain approval of the supplement by FDA prior to distribution of the product made using the change. In general, the following studies (Table 9) can be carried out to confirm

Table 9.
Studies Needed to Support Change in Formulation

Research requirements	Supporting results
Purity	Stability, compatibility, Structural analyses
Potency	*In vitro*/*in vivo* bioassays, preclinical and/or clinical pharmacokinetic comparability , clinical efficacy
Safety	Preclinical safety, clinical safety

Samsung Bioepis Exhibit No. 1002
Page 12851

that the change in the formulation will not affect the safety and effectiveness of the product. It is recommended to consult the regulatory representative to find out how much additional information may be needed for the approval of the changed formulation.

APPENDIX: LIST OF REGULATORY DOCUMENTS

1. International Conference on Harmonization: Guidance on specifications: Test procedures and acceptance criteria for Biotechnological/Biological Products. Federal Register: August 18, Volume 64, Number 159, pp. 44928–44935 (1999).
2. International Conference on Harmonization: Impurities in New Drug Products. FDA Q3B (11/97).
3. Guidance for Industry. ANDAs: Impurities in Drug Products. Draft guidance. FDA (12/98).
4. Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products (CPMP/CVMP/QWP/115/95) EMEA (7/97).
5. Inactive ingredient guide: inactive ingredients for currently marketed drug products. (1996) FOI Services, Inc. Rockville, MD.
6. Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via medicinal products. EMEA (4/99).
7. Note for guidance on plasma-derived medicinal products. EMEA (7/98).
8. Development Pharmaceutics for Biotechnological and Biological Products. Annex to Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96). EMEA (10/1999).
9. International Conference on Harmonization: Stability testing of new drug substances and products. Federal Register, Sept. 22, Volume 59, Number 183, pp. 48754–48759 (1994).
10. International Conference on Harmonization: Final guideline on stability testing of biotechnological/biological products. Federal Register, July 10, Volume 61, Number133, pp. 36466–36469 (1996).
11. Guideline for Industry: Stability testing for drug substances and drug products: draft guidances. FDA, (6/98).
12. International Conference on Harmonization: Guidelines for the photostability testing of new drug substances and products. Federal Register, May 16, Volume 62, Number. 95, pp. 27115–2712 (1997).
13. Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics FDA. (2/87).
14. Guidance for Industry. For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-

Samsung Bioepis Exhibit No. 1002
Page 12852

Derived Biological Products, Animal Plasma or Serum-Derived Products. FDA (2/99).

15. Guidance for Industry. INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products Chemistry, Manufacturing, and Controls Content and Format (Draft guidance) FDA (2/99).
16. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products, FDA (11/95).
17. Note for Guidance on Development of Pharmaceutics (CPMP/BWP/328/99). EMEA (01/1998).
18. Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, April, 1996.
19. Guidance for Industry: Changes to an Approved Application. For Specified Biotechnology and Specified Synthetic Biological Products, 21 CFR 601.12, 314.70; July 24, 1997, Vol 62. No. 142.
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Samsung Bioepis Exhibit No. 1002
Page 12854

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Samsung Bioepis Exhibit No. 1002
Page 12855

Trials@uspto.gov
571-272-7822

Paper 15
Entered: August 30, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

IPR2019-00739
Patent 9,725,504 B2

Before TINA E. HULSE, ROBERT A. POLLOCK, and RYAN H. FLAX, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Amgen Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–10 of U.S. Patent No. 9,725,504 B2 ("the '504 patent," Ex. 1001). Paper 2 ("Pet."). Alexion Pharmaceuticals ("Patent Owner" or "Alexion") timely filed a Preliminary Response. Paper 10 ("Prelim. Resp."). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 13 ("Reply"); Paper 14 ("Sur-Reply").

We review the Petition, Preliminary Response, Reply, Sur-Reply, and accompanying evidence under 35 U.S.C. § 314. An *inter partes* review may not be instituted unless "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Further, a decision to institute may not institute on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018).

After considering the evidence and arguments presented in the Petition and Preliminary Response, Reply, and Sur-Reply, we determine that Petitioner demonstrates a reasonable likelihood of prevailing in showing that at least one of the challenged claims of the '504 patent is unpatentable. Accordingly, we institute an *inter partes* review as to all the challenged claims of the '504 patent on all the grounds of unpatentability set forth in the Petition.

A. Real Parties-in-Interest

Petitioner identifies only itself as the real party-in-interest. Pet. 73. Patent Owner, likewise, identifies only itself as the real party-in-interest. Paper 3, 2.

B. Related Proceedings

The '504 patent shares essentially the same specification with U.S. Patent Nos. 9,718,880 B2 ("the '880 patent) and 9,732,149 ("the '149 patent"). Amgen has filed Petitions for *Inter Partes* Review of the '504, '880, and '149 patents in IPR2019-00739, IPR2019-00740, and IPR2019-00741, respectively. Pet. 73–74; Paper 3, 2.

The '504, '880, and '149 patents are related as follows: The '149 patent issued from application No. 15,284,015, filed January 19, 2017, which is a continuation of application No. 15/260,888 (now the '504 patent), filed on September 9, 2016, which is a continuation of application No. 15/148,839 (now the '888 patent), filed on May 6, 2016, which is a continuation of application No. 13/426,973, filed on March 22, 2012, which is a continuation of application No. 12/225,040, filed as application No. PCT/US2007/006606 on March 15, 2007. The parties do not dispute that March 15, 2007, is the relevant priority date of the challenged patent.

C. The '504 patent and Relevant Background

The '504 patent relates to the use of a humanized anti-C5 antibody (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria. *See* Ex. 1001, Abstract. For reference, we reproduce Figure 1 from the

Balthasar Declaration,[1] illustrating the basic structure of an antibody, such as eculizumab:

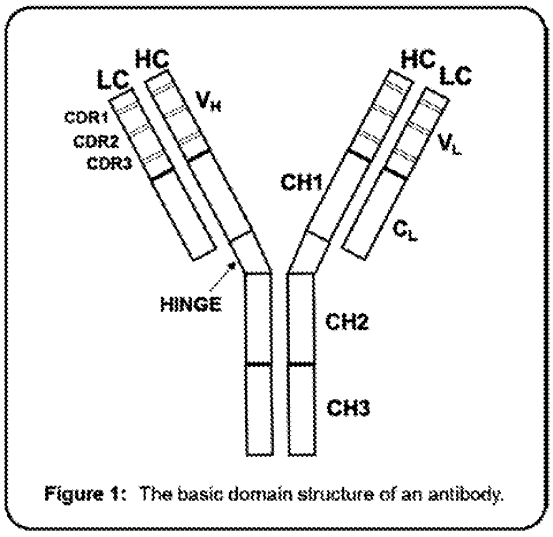


Figure 1: The basic domain structure of an antibody.

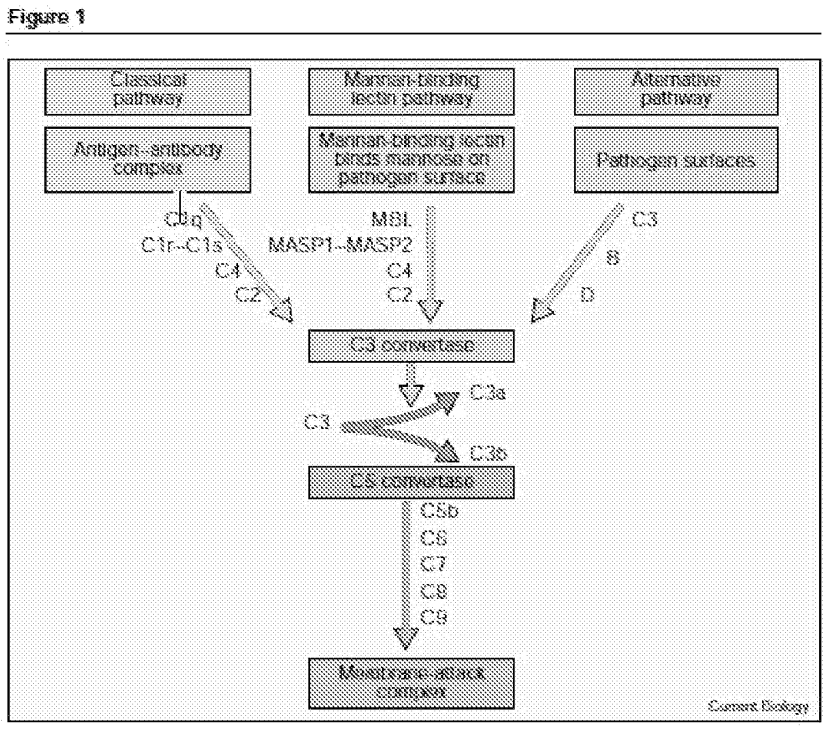
The figure above shows a basic antibody structure having hinged heavy chains (HC) and accompanying light chains (LC), each having constant regions (C_H and C_L) and variable regions (V_H and V_L), all arranged in a general "Y"-shaped structure, as the variable regions and portions of the constant heavy chain regions are hinged away from one another. Ex. 1002 ¶¶ 23–24. The variable regions of each chain also include three complementarity determining regions (CDR), which provide the antibody with antigen-binding specificity. *Id.*

[1] Declaration of Dr. Joseph P. Balthasar, Ph.D. (Ex. 1002, "Balthasar Declaration").

Paroxysmal nocturnal hemoglobinuria or PNH is an acquired hemolytic disease resulting from loss of function in certain cytoprotective proteins. Ex. 1001, 1:27–35; Ex. 1002 ¶ 31. This loss of function renders red blood cells, platelets, and other blood cells highly sensitive to attack via activated complement proteins (explained in detail below). Ex. 1002 ¶ 31. The resultant complement-mediated lysis of blood cells results in anemia, hemoglobinuria, and related symptoms, which impair a patient's quality of life to the extent that "[m]any PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels." Ex. 1001, 1:42–53. As further explained by Petitioner's expert, Dr. Balthasar, "[a]s a result of the destruction of RBCs and the resultant release of free hemoglobin into the blood, `PNH is characterized by hemolytic anemia (a decreased number of red blood cells), hemoglobinuria (the presence of hemoglobin in the urine particularly evident after sleeping), and hemoglobinemia (the presence of hemoglobin in the bloodstream.')" Ex. 1002 ¶ 32 (quoting Ex. 1005 ¶ 7).

"Complement" is a "system of plasma proteins . . . so-named because it complements the activity of antibody in the lysis of bacteria." Ex. 1022 R259; *see generally* Ex. 1001, 7:6–8:56. As part of the immune system, complement "has a central role in host defense against many micro-organisms and in the modulation of inflammatory reactions." *Id.*; *see*

Ex. 1002 ¶ 28. The figure below shows "the main pathways and components of the complement activation system." Ex. 1022, R259.



The above figure illustrates how various complement proteins are organized into the "classical," "mannan-binding," and "alternative" activation pathways. Ex. 1022, R259; *see* Ex. 1001, 7:17–19. All three pathways lead to the cleavage of C3 convertase and the resultant cleavage of C5 convertase into C5a and C5b. Ex. 1022, Fig. 1; *see* Ex. 1002 ¶ 29. As summarized in paragraph 29 of the Balthasar Declaration (Ex. 1002), cleavage of C5 initiates the terminal complement cascade. Conversely, blocking the cleavage of C5 prevents complement activation. *See, e.g.*, Ex. 1001, 10:65–

11:6 ("U.S. Pat. No. 6,353,245 [Evans][2] teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components."); 12:21–29.

According to the Specification, eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5 convertase and, is thus, intended to suppress the terminal activation cascade and resultant complement activation. Ex. 1001, Abstract, 1:56–57 (citing Thomas C. Thomas et al., *Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single-Chain Fv*, 33(17) MOL. IMMUNOL. 1389–401 (1996) (Ex. 1023, "Thomas")). More specifically, "eculizumab" refers to humanized antibodies derived from mouse antibody 5G1.1, sometimes referred to as "murine 5G1.1" or "m5G1.1." *See* Prelim. Resp. 12–13. The term "humanized" refers to an antibody having a human framework, into which CDR regions from a non-human monoclonal antibody (e.g., mouse) are inserted. Ex. 1007, 5:57–67; Ex. 1002 ¶¶ 22–26. Accordingly, humanized versions of non-human antibodies may be indicated by the prefix "h" or "hu" as in "h5G1.1" and "hu5G1.1." *See e.g.*, Pet. 17, n.11, 19; Prelim. Resp. 12; Ex. 1002 ¶ 48.

Claim 1 refers to SEQ ID NO: 2 and SEQ ID NO: 4, which together comprise an eculizumab antibody. *See generally* Prelim. Resp. 1–2. Thus, for example, the '504 patent identifies SEQ ID NO: 2 and SEQ ID NO: 4 as the "Eculizumab Heavy Chain" and "Eculizumab Light Chain,"

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[2] US 6,355,245 B1, issued Mar. 12, 2002 (Ex. 1007).

respectively. Ex. 1001, 30:22–31, 38–44. It is undisputed that SEQ ID NO: 2 encodes a hybrid IgG2/IgG4 heavy chain (i.e., having a genetically engineered heavy chain constant region derived from portions of IgG2 and IgG4 isotype antibodies). *See, e.g.*, Pet. 3; Prelim. Resp. 14; Ex. 1033, 1258 (Figure 2). Eculizumab is the non-proprietary name for Patent Owner's SOLIRIS product, which was approved by the FDA "for treatment of patients with PNH." *See, e.g.*, Prelim. Resp. 1–2, 5–6 (citing Ex. 1033, 1256;[3] Ex. 2005, 1[4]); Pet. 2 (citing Ex. 1009, 2); *see also* Prelim. Resp. 16 ("The '504 patent claims recite the complete amino acid sequence for SOLIRIS® . . . the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001 at cols. 31–33, 35.).").

The '504 patent also discusses the conduct and results of the TRIUMPH trial in which 88 red blood cell transfusion dependent PNH patients were randomly assigned "to receive either placebo or Eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.)." Ex. 1001, 19:51–28:38.

> Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

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[3] Rother et al., "*Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria,*" 25(11) NATURE BIOTECHNOLOGY 1256–1264 (2007).
[4] SOLIRIS Product Label (rev. 3/2007).

Id. at 20:43–50. The Specification concludes that "[t]he results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency." *Id.* at 28:33–38. "[E]culizumab stabilized hemoglobin levels, decreased the need for transfusions, and improved quality of life in PNH patients via reduced intravascular hemolysis." *Id.* at Abstract.

D. Challenged Claims

Petitioner challenges claims 1–10 of the '504 patent, of which claim 1 is independent; claim 1 reads as follows:

> 1. A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

Ex. 1001, 39:2–7. Among the dependent claims, claim 2 requires administration of the compound by intravenous infusion, claims 3 and 8 relate to dosage and dosing protocol, claims 4–6 relate to single unit dosage forms, claim 7 requires that the patient is anemic, and claim 9 and its dependent claim, claim 10, require that "administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH)."

E. Asserted Grounds of Unpatentability

Petitioner asserts the following seven grounds for unpatentability (Pet. 23):

Ground	Claim(s)	Basis	Asserted Reference(s)
1	1–3, 7–10	102(b)[5]	Hillmen[6]
2	4, 5	103(a)	Hillmen and Bell[7]
3	6	103(a)	Hillmen, Bell, and Wang[8]
4	1–5, 7–10	103(a)	Bell, Bowdish,[9] and Evans[10]
5	6	103(a)	Bell, Bowdish, Evans, and Wang
6	1–5, 7–10	103(a)	Bell, Evans, and Mueller[11]
7	6	103(a)	Bell, Evans, Mueller, and Wang

[5] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the `504 patent have an effective filing date before the effective date of the applicable AIA amendments, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103 throughout this Decision.
[6] Hillmen et al., "*Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria,*" 350(6) N. Engl. J. Med. 552–59 (2004). (Ex. 1004).
[7] Bell et al., US 2005/0191298 A1, published Sept. 1, 2005 (Ex. 1005).
[8] Wang, US 2005/0271660 Al, published Dec. 8, 2005 (Ex. 1028)
[9] Bowdish et al., US 2003/0232972 A1, published Dec. 18, 2003 (Ex. 1006).
[10] Evans et al., US 6,355,245 B1, issued March 12, 2002 (Ex. 1007).
[11] Mueller et al., WO 97/11971, published April 3, 1997 (Ex. 1008).

In support of its patentability challenges, Petitioner relies on, *inter alia*, the Declaration of Joseph P. Balthasar, Ph.D. Ex. 1002.

F. Overview of Asserted References

1. Overview of Hillmen (Ex. 1004)

Hillmen discloses that "[p]aroxysmal nocturnal hemoglobinuria (PNH) arises from a somatic mutation of the PIG-A gene in a hematopoietic stem cell and the subsequent production of blood cells with a deficiency of surface proteins that protect cells from attack by the complement system." Ex. 1004, 552.

> Patients with PNH have chronic, often disabling symptoms of fatigue and intermittent episodes of dysphagia, abdominal pain, and hemoglobinuria. These symptoms are thought to be related to the intravascular destruction of PNH type III erythrocytes, which are deficient in complement inhibitors, by autologous complement. The hemolytic anemia frequently renders the patients transfusion-dependent. In addition, patients have an extremely high risk of potentially life-threatening thrombosis, particularly thrombosis of the hepatic and cerebral veins. Approximately 50 percent of patients with PNH die of the disease; the median duration of survival after diagnosis is 10 years.

Id. at 557.

Hillmen reports on the efficacy of eculizumab for "reduc[ing] the incidence of intravascular hemolysis, hemoglobinuria, and transfusion requirements in patients with PNH." *Id.* at 553. "Eleven transfusion-dependent patients with PNH received infusions of eculizumab (600mg) every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12." *Id.* at Abstract, *see id.*

at 554. Based on this treatment, Hillmen concludes:

> Eculizumab is safe and well tolerated in patients with PNH. This antibody against terminal complement protein C5 reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion, with an associated improvement in the quality of life in patients with PNH.

Id. at Abstract.

Hillmen characterizes eculizumab as "a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components." *Id.* (citing, e.g., Thomas (Ex. 1023)). According to Hillmen, the antibody "binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b, thereby preventing the release of the inflammatory mediator C5a and the formation of the cytolyticpore C5b-C9." *Id.* Because eculizumab "specifically prevents cleavage of C5, which is necessary for assembly of the membrane-attack complex, "the treatment "presumably prolongs the survival of type III erythrocytes . . . which are highly sensitive to lysis by complement." *Id.* at 557.

2. Overview of Bell (Ex. 1005)

Bell discloses the treatment of PNH "using a compound which binds to or otherwise blocks the generation and/or activity of one or more complement components. . . . In particularly useful embodiments, the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb (eculizumab), h5G1.1-scFv (pexelizumab) and other functional fragments of hSGl.l." *Id.* ¶ 12; *see also id.* ¶ 52 ("The antibody h5G1.1-mAb is currently undergoing clinical trials under the tradename

eculizumab."). Bell further discloses: "Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in [Evans] and [Thomas] . . . the disclosures of which are incorporated herein in their entirety." *Id.* ¶ 52.

As noted by Dr. Balthasar, the data disclosed in Bell overlaps with that in Hillmen, but further includes data on extension studies in which patients continued treatment for paroxysmal nocturnal hemoglobinuria for a total of two additional years. *See* Ex. 1002 ¶ 39 (citations omitted).[12] Briefly, eleven transfusion-dependent PNH patients received weekly 600 mg doses of eculizumab by infusion for four weeks, followed by "900 mg of eculizumab 1 week later[,] then 900 mg on a bi-weekly basis." Ex. 1005 ¶¶ 81–82. Bell characterizes the first twelve weeks of treatment as a "pilot study." *Id.* ¶ 82. "Following completion of the initial acute phase twelve week study, all patients participated in an extension study conducted to a total of 64 weeks. Ten of the eleven patients participated in an extension study conducted to a total of two years." *Id.* Bell concludes that "[p]atients in the two year study experienced a reduction in adverse symptoms associated with PNH. *Id.* ¶¶ 82, 96.

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[12] Page 38, footnote 17, of the Petition states: "Because the clinical study taught in Bell is the same C02-001 study disclosed in Hillmen, which discloses the eculizumab amino acid sequences of SEQ ID NOs: 2 and 4, Bell, too, therefore anticipates claims 1–4 and 7–10 for the same reasons discussed above for Hillmen." Despite this assertion, Petitioner's sole anticipation-based Ground in this IPR relies on Hillmen. *See* Pet. 23.

3. Overview of Wang (Ex. 1028)

Wang discloses formulations of eculizumab suitable for nebulization and pulmonary delivery. *See, e.g.*, ¶¶ 25, 62, 67. Wang discloses formulations comprising from 1 to 30 mg/ml eculizumab, and provides evidence that a formulation having 30 mg/ml eculizumab can be effectively and efficiently delivered using a conventional nebulizer. *Id.* ¶¶ 171–173, Fig. 10.

4. Overview of Bowdish (Ex. 1006)

Bowdish discloses "[i]mmunoglobulins or fragments thereof hav[ing] a peptide of interest inserted into a complementarity determining region (CDR) of an antibody molecule," whereupon, "[t]he antibody molecule serves as a scaffold for presentation of the peptide and confers upon the peptide enhanced stability." Ex. 1006 ¶ 6. In certain "embodiments, the peptide replacing the amino acids of a CDR is an agonist TPO [thrombopoeitin] peptide." *Id.* ¶ 17.

In Example 4, Bowdish describes a TPO mimetic peptide graft into the heavy chain CDR3 of antibody framework 5G1.1, described in Evans, which Bowdish incorporates by reference. *Id.* ¶¶ 191–193. According to Bowdish:

> Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated herein by reference.[13] The sequence was cloned into 5G1.1 in such a fashion as to replace the native CDR3 . . . [wherein t]he peptide graft translated into amino acids is Leu Pro Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Arg Ala

[13] U.S. Application Ser. No. 08/487,283 matured into U.S. Patent No. 6,355,245 B1, referenced herein as Evans (Ex. 1007).

> Pro Val (SEQ. ID. NO: 66). The 5G1+peptide was produced as a whole IgG antibody (See FIGS. 13A and 13B).

Id. ¶ 191. "Purified 5G1.1+peptide antibody as well as the parental 5G1.1 were analyzed for their ability to bind to cMpl receptor by FACS analysis." *Id.* ¶ 192.

In SEQ ID NOs: 69 and 70, respectively, Bowdish discloses the amino acid and nucleotide sequences for the "5G1.1 Light Chain." In SEQ ID NO: 67, Bowdish discloses the amino acid sequence of the "5G1.1 "TPO Heavy Chain," with the substituted TPO mimetic sequence marked in bold. An excerpt of that sequence showing the amino acids of the TPO substitution in bold reads: DTAVYYCAR**LPIEGPTLRQWLAARAPV** WGQGTLVTVSS. Bowdish discloses the corresponding nucleotide sequence in SEQ ID NO: 68.

5. Overview of Evans (Ex. 1007)

Evans discloses anti-C5 antibodies useful in the treatment of glomerulonephritis (GN). Ex. 1007, Abstract. Evans' Example 7 describes the isolation anti-C5 monoclonal antibodies from mouse hybridoma designated 5G1.1. *Id.* at 37:34–39:30. In Figures 18 and 19, respectively, Evans discloses the amino acid sequence of the light and heavy chain variable regions of mouse antibody 5G1.1, with "[t]he complementarity determining region (CDR) residues according to the sequence variability definition or according to the structural variability definition . . . [bolded] and [underlined], respectively." *Id.* at 9:65–10:20. A representation of an excerpt of the heavy chain sequence showing the amino acids of CDR3 so marked reads: DSAVYYCAR**Y<u>FFGSSPNWYFD</u>V**WGAGTTVTVSS.

See id. at Fig. 19.

Evans describes making a series of different humanized 5G1.1 scFv[14] and full-length antibodies containing the CDR regions from the murine 5G1.1 antibody. AMG1007, 37:35-39:30, 42:59-45:33. With respect to the former, Evans discloses that "[p]articularly preferred constant regions . . . are IgG constant regions, which may be unaltered, or constructed of a mixture of constant domains from IgGs of various subtypes, e.g., IgG1 and IgG4." *Id.* at 45:29-33.

In Example 11, Evans discloses steps in the humanization of mouse antibody 5G1.1, including the construction of recombinant antibody, 5G1.1 scFv CO12. *Id.* at 42:59-45:33. According to Dr. Balthasar, the construct "5G1.1 scFv CO12" contains all six 5G1.1 CDR regions and its sequence aligns perfectly with the eculizumab variable regions claimed by the '504 patent." Ex. 1002 ¶ 55 (comparing portions of SEQ ID NO: 2 of the '504 patent with portions of Evans' SEQ ID NO. 2). Dr. Balthasar's Figure 6, for example, shows that both sequences contain the larger of the two overlapping amino acid sequences Evans identifies as CDR3, YFFGSSPNWYFDV. *Id.*

6. Overview of Mueller (Ex. 1008)

Mueller discloses "[a]ntibodies to porcine P-selecting protein, porcine VCAM protein and porcine CD86 protein are useful for diagnosing human

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[14] As Dr. Balthasar notes, "a scFv comprises an antibody's light and heavy chain variable domains connected by a linker." Ex. 1002 ¶ 54, n.4 (citing Ex. 1007, 6:39-41).

rejection of porcine xenotransplants and for improving xenotransplantation of porcine, cells, tissues and organs into human recipients. Ex. 1008, Abstract. According to Mueller, one object of the invention is to provide antibody molecules that neither activate complement nor bind to the FC receptor. *Id.* at 7:28–31. To achieve these and other goals, Mueller points to "[r]ecombinant (chimeric and/or humanized) antibody molecules comprising the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4, such antibodies being referred to hereinafter as `HuG2/G4 mAb.'" *Id.* at 8:23–26. Mueller developed and tested "chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4." *Id.* at 12:19–33. As controls for these experiments, Mueller used "a humanized antibody directed against human C5 (h5G1.1 C012 HuG4 mAb)." *Id.* at 11:34–12:4, 12:34–13:2, Figures 11, 12, 15. On pages 58–61, Mueller discloses the cDNA and amino acid sequence of "Human G2/G4."

II. ANALYSIS

A. Principles of Law

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics,*

Inc., 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). This "single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). "Under the principles of inherency, if the prior art necessarily . . . includes[ ] the claimed limitations, it anticipates." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). Similarly, "[a] reference anticipates a claim if it discloses the claimed invention `such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.' " *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (internal citation and emphasis omitted). Moreover, "it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968); *see Eli Lilly v. Los Angeles Biomedical Res. Inst.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that

subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted).

B. Person of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the

technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus. Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner contends that a person of ordinary skill in the art as of the relevant date would have "had an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in the field." Pet. 21. Patent Owner does not dispute this definition, but suggests that we interpret the relevant field as directed to "engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry." *See* Prelim. Resp. 45 (emphasis omitted).

Petitioner's proposed definition is not inconsistent with the cited prior art. Patent Owner responds, however, that it "does not dispute Amgen's POSA definition, except to clarify that the POSA would have at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry." Prelim. Resp. 45 (emphasis omitted); *see also id.* (arguing that Petitioner cannot prove unpatentability of the challenged claims under either definition).

Considering that each of the asserted references (discussed *infra*) is substantially directed to the development of monoclonal antibodies for the treatment or diagnosis of human disease, Patent Owner's proposed clarification provides useful context. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art)

(quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). Accordingly, we define one of ordinary skill in the art as a person with an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry. Our decision whether to institute, however, does not turn on which party's definition of the skilled artisan is used, and our determinations would be unchanged if we applied Petitioner's definition.

C. Claim Construction

Based on the filing date of the Petition (Feb. 28, 2019), the Board interprets claim terms in an *inter partes* review ("IPR") using the same claim construction standard that is used to construe claims in a civil action in federal district court. *See* 83 Fed. Reg. 51,340 (Nov. 13, 2018) (to be codified at 37 C.F.R. pt. 42).

In construing claims, district courts give claims their ordinary and customary meaning, which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Sources for claim interpretation include "the words of the claims themselves, the remainder of the specification, the prosecution history [i.e., the intrinsic evidence], and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "[T]he claims themselves [may] provide substantial

guidance as to the meaning of particular claim terms." *Id.* However, the claims "do not stand alone," but are part of "a fully integrated written instrument,' consisting principally of a specification that concludes with the claims," and, therefore, the claims are "read in view of the specification." *Id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995)).

At this stage in the proceeding, we need only construe the claims to the extent necessary to determine whether to institute *inter partes* review. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms `that are in controversy, and only to the extent necessary to resolve the controversy.' " (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

Although at this stage of the proceeding no claim term requires express construction, for the sake of clarity, we address Petitioner's unopposed position that "immediate," as used in claim 9, encompasses events occurring within one week after administering eculizumab:

> Claim 9 recites that the claimed method "results in an *immediate* and sustained decrease in mean levels of lactate dehydrogenase (LDH)." AMG1001, claim 9. The '504 patent specification teaches "[t]he impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an *immediate (one week)* and sustained decrease in mean levels of LDH." AMG1001, 22:22-25. Claim 10 depends from claim 9 and further requires that "the immediate decrease occurs *within one week* of administration of the antibody." AMG1001, claim 10. Thus, as Dr. Balthasar explains, a POSA would have understood the term "immediate"

> to include a decrease beginning "within one week" after administering the eculizumab. AMG1002, ¶¶64-65.

Pet. 22. Considering the above-cited portion of the Specification and the dependency of claim 10 noted in the Petition, we agree with Petitioner's assertion that "immediate" as used in claim 9 encompasses within its scope events occurring within one week after administering eculizumab.

D. Anticipation by Hillmen (Ground 1)

In Ground 1, Petitioner challenges claims 1–3 and 7–10 as anticipated by Hillmen. Pet. 25–37. Patent Owner opposes. Prelim. Resp. 45–51. For this Ground, here we focus on claim 1.

1. The Parties' Contentions

Petitioner contends "Hillmen discloses all the limitations of claim 1, either expressly or inherently, and is enabling." Pet. 25 (citing Ex. 1002 ¶¶ 75–84). In particular, Petitioner argues that Hillmen *explicitly* discloses every element of claim 1, except for eculizumab's amino acid sequence. *Id.* at 26. With respect to that amino acid sequence, Petitioner contends "Hillmen's antibody necessarily `comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4' because Alexion admitted that Hillmen's eculizumab possesses those very amino acid sequences." *Id.* at 26–27 (citing Ex. 1014, 765, 767 (Boone Declaration ¶¶ 5–6)[15]; Ex. 1024, 109; Ex. 1025, 2 (these exhibits identify a trial "CO2-

[15] Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone, dated May 11, 2017 (submitted during the prosecution of U.S. Application No. 15/148,839, which became the '149 patent) (Ex. 1014, 763–70, "Boone Declaration").

001 as testing SOLIRIS). The Boone Declaration, cited by Petitioner, in relevant portion, states first that study C02-001 was a study of the effect of eculizumab (h5G1.1-mAb) on patients with PNH, that Dr. Boone had reviewed the eculizumab antibody used in that study and its amino acid sequence, and that Dr. Boone concluded that the antibody (eculizumab) used in each of the studies . . . contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4. Ex. 1014, 764 67 (¶¶ 5 6).

Although Petitioner does not argue that Hillmen literally and expressly disclosed the claimed antibody structure with SEQ ID NOs: 2 and 4 (which, we note, it does not), Petitioner's position is that, because Hillmen disclosed a trial of the SOLIRIS eculizumab antibody, and because Patent Owner conceded that the eculizumab antibody used is the claimed anti-C5 antibody, that Hillmen inherently discloses the claimed sequences. Pet. 27 29 (citing *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004)).

Petitioner's inherency rationale, based on the general knowledge in the relevant field (*id.* at 31), is summarized as follows. Contemporaneous with Hillmen's disclosure, the skilled artisan would have known that Bowdish disclosed the entire amino acid sequence of eculizumab, but for a heavy chain CDR3 region, which Bowdish disclosed as substituted with a TPO (thrombopoietin) amino acid sequence; the skilled artisan, however, would have known that Evans disclosed the amino acid sequences of eculizumab's heavy and light chain variable domains, including heavy chain CDR3 region absent from Bowdish; alternatively, the skilled artisan would have understood that Mueller disclosed the hybrid IgG2/IgG4 heavy chain and light chain constant domains of eculizumab, whereas Evans disclosed

the respective variable domains. Pet. 29–31 (citing Ex. 1004, 553–554; Ex. 1006 ¶¶ 191–193, Figs. 13A, 13B; Ex 1007, 44:4–13; Ex. 1008, 52–53, 58–61; Ex. 1002 ¶¶ 60, 81–84). With this knowledge in hand, the skilled artisan would have known that Hillman discloses a method of treatment using eculizumab– which was necessarily the claimed anti-C5 antibody with the claimed SEQ ID NOs: 2 and 4. *Id.*

Petitioner also appears to argue that Hillmen inherently discloses the hybrid IgG2/IgG4 heavy chain portion of SEQ ID. NO: 2, because one of ordinary skill in the art would have known that eculizumab contains this structure. Pet. 17 (citing Ex. 1034, 1279; Ex. 1049, 838–839; Ex. 1002 ¶¶ 46–49). Petitioner argues, for example, that Tacken explicitly describes eculizumab as containing an IgG2/IgG4 constant region. *Id.* (quoting Ex. 1034, 1279); *see, e.g.*, Ex. 1002 ¶ 46 ("Tacken confirms that eculizumab contains a hybrid IgG2/IgG4 constant region. AMG1034, 1278-1279. Tacken describes using `h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals)' containing an `IgG2/IgG4 constant region.' AMG1034, 1279.").

Petitioner also relies on statements made by Patent Owner on the record during the prosecution of U.S. Patent Application Ser. No. 11/127,438, where, in arguing that disclosures upon which the applicant relied for priority were supportive of the then-pending claims, Alexion stated:

> Applicant respectfully disagrees and asserts that the priority applications provide ample written support for the claimed descriptions. For example, the priority documents each describe that "Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-

> scFv and functional fragments of h5G1.1 are *described in U.S. Patent No. 6,355,245* [Evans], the disclosures of which are incorporated herein in their entirely [*sic*] by this reference . . . Applicant submits that h5G1.1 . . . [was] *well-known to one of ordinary skill in the art as eculizumab* . . . at the time of filing of priority applications.

See Pet. 10 (quoting Ex. 1049, 838–39 (emphasis Petitioner's)). Thus, Petitioner argues, Alexion represented to the Patent Office that the antibody structure disclosed in Evans was well-known to the skilled artisan so that such a person of skill would have considered this structure to be the eculizumab in Hillmen, and which was publically disclosed before the March 15, 2007 priority date of the '504 patent.

Patent Owner takes the position that, "[p]rior to March 15, 2007, the priority date of the '504 patent, the unique amino acid sequence of SOLIRIS® was not publicly known or disclosed in the prior art." Prelim. Resp. 1.

> If a POSA were searching for the sequence of "eculizumab" as described in the art, the literature as of March 15, 2007 identified an amino acid sequence and corresponding structure that is very different from what the '504 patent claims. In particular, publications describing the safety, efficacy, and clinically relevant biological activity of "eculizumab" consistently directed a POSA to the 1996 "Thomas" publication (AMG1023) for the structure and design of the antibody, which in turn described a humanized antibody constructed with a naturally-occurring "IgG4" heavy chain constant region. The claimed antibody of the '504 patent has a very different, uniquely engineered, non-naturally occurring constant region that was nowhere described in Thomas or the prior art literature showing the safety and efficacy of "eculizumab."

Id. at 2–3 (emphasis omitted).

It is Patent Owner's position that, reading Hillmen's disclosure of "eculizumab" and Hillmen's reference to Thomas, the skilled artisan would not have been directed to the version of eculizumab encompassed by claim 1 of the '504 patent, but would have understood Hillmen to refer to Thomas's disclosed eculizumab, which is an IgG4 isotype antibody, which does not have the hybrid IgG2/IgG4 heavy chain sequence as described in SEQ ID NO: 2. *Id.* at 3, 11–13 (referencing Ex. 1023). In particular, Patent Owner notes that Hillmen cites Thomas as *the* reference for eculizumab. *Id.* at 3, 12 (citing Ex. 1004, 533 (which cites Ex. 1023 as reference "15")).

> Thomas . . . described the design and testing of a humanized anti-C5 antibody (termed "humanized 5G1.1" or "h5G1.1") featuring an "IgG4" heavy chain constant region, which was selected because the IgG4 isotype was thought to avoid activating human complement. (AMG1023 at 1396, 1399.) Thomas reported data showing that the IgG4 humanized antibody had suitable affinity and specificity, and was as effective as the original mouse antibody (termed "murine 5G1.1" or "m5G1.1") in an *in vitro* assay showing activity blocking C5 cleavage and preventing lysis of blood cells due to complement activity. (AMG1023 at 1396.)

Id. at 12–13 (emphasis omitted).

Patent Owner states that "[t]oday, but not prior to the March 15, 2007 priority date for the '504 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in the claims of the '504 patent, namely, `a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'" *Id.* at 15 (emphasis omitted). Patent Owner argues that, as of the critical date, Hillmen did not

> enable[ ] a POSA to make and use the specific antibody recited in claims 1-3 and 7-10 without undue experimentation, because

> Hillmen guided a POSA as of March 15, 2007 to make and use a very different antibody – the ***IgG4*** isotype antibody of Thomas. *See, e.g.*, *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (for a reference to anticipate, "[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation").

Id. at 46–47. Patent Owner further argues that

> [t]he mere naming of an investigational product (*e.g.*, "eculizumab") in a prior art publication does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as of the priority date.

Id. at 48–49 (citing *Endo Pharm. Solutions, Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378–83 (Fed. Cir. 2018)).

2. Analysis

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has not carried its burden to show a reasonable likelihood of anticipation of claim 1 of the '504 patent under Ground 1.

Petitioner concedes Hillmen does not expressly disclose the claimed antibody; instead, Petitioner relies on the doctrine of inherency and a post-priority-date admission by Patent Owner that the pharmaceutical (eculizumab) referenced in Hillmen was actually the claimed antibody.

Hillmen "tested the clinical efficacy of eculizumab, a humanized antibody that inhibits the activation of terminal complement components, in patients with PNH." Ex. 1004, 552. Hillmen teaches that "[e]culizumab is a recombinant humanized monoclonal antibody that was designed to block the

activation of terminal complement components.[14,15] It binds specifically to the terminal complement protein C5. *Id.* at 553. Citation [14] of Hillmen refers to Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 NATURE 323–27 (1988). This reference is not an exhibit in this proceeding and Petitioner does not suggest that it mentions eculizumab. Citation [15] of Hillmen refers to Thomas (Ex. 1023), which discloses a monoclonal antibody (5G1.1) that recognizes the human complement protein C5, which was shown to effectively block C5 cleavage. *See* Ex. 1023, 1389.

Thomas discloses the process of developing a humanized antibody (h5G1.1 HuG4) for human C5. Thomas summarizes this work in a section titled "*Construction of a humanized h5G1.1 antibody*":

> Having demonstrated the effective humanization of the 5G1.1 variable regions, an intact humanized antibody (IgG4 isotype) was constructed and produced in 293-EBNA cells. The avidity of this humanized antibody (h5G1.1 HuG4) for human C5, was compared to the murine 5G1.1 mAb by determining the ability of each to compete binding of biotinylated 5G1.1 mAb to C5 (Fig. 9). The humanized h5G1.1 mAb had a two-fold lower avidity than the murine antibody. However, the humanized h5G1.1 HuG4 antibody was equipotent with the murine antibody at protecting PAEC from lysis by human serum, with a 0.5-fold molar ratio of antibody to C5 (1:1 ratio of antibody binding sites to C5) completely inhibiting lysis of the PAEC (Fig. 10).

Id. at 1396.[16] We find nothing in Thomas that expressly discloses or alludes

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[16] Patent Owner argues that as of the '504 patent's priority date, many other references cited Thomas when referring to eculizumab. *See* Prelim. Resp. 24–29, Table 1. Without going into detail, we find Patent Owner has accurately shown how other, contemporaneous prior art references cited Thomas for this purpose.

to a hybrid IgG2/IgG4 antibody. *See generally* Ex. 1023.

We also consider Dr. Balthasar's assertion that one of ordinary skill in the art "would have known that eculizumab contains a hybrid IgG2/IgG4 heavy chain constant region" because Tacken "describes using `h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals)' containing an `IgG2/IgG4 constant region.'" Ex. 1002 ¶ 46 (citing Ex. 1034, 1279).

In seeking to address this assertion, Patent Owner takes the position that Tacken (also addressed in the context of Petitioner's obviousness challenges) is non-analogous art because it "does not involve the same field as the '504 patent, and would not have been reasonably pertinent to the particular problem addressed by the '504 patent." Prelim. Resp. 37; Sur-Reply 2–3. On the present record, we do not find Patent Owner's argument persuasive. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (mere lawyer's arguments and conclusory statements that are unsupported by factual evidence are entitled to little probative value).

"Prior art is analogous if it is from the same field of endeavor or if it is reasonably pertinent to the particular problem the inventor is trying to solve." *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1335 (Fed. Cir. 2015). In the present case, Tacken discloses the development of "a humanized antibody, hD1V1G2/G4 (hD1), directed against the C-type lectin DC-specific intercellular adhesion molecule 3 "grabbing nonintegrin (DC-SIGN) to explore its capacity to serve as a target receptor for vaccination purposes." Ex. 1034, Abstract. Given Patent Owner's position that the relevant field of the '504 patent encompasses the "engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry"

(*see* Section II(B), above), Tacken's development of the monoclonal antibody hD1V1G2/G4 (hD1) "for vaccination purposes" would appear to be in the same field of endeavor. Moreover, because Tacken's antibodies employ the same IgG2/IgG4 constant region as SEQ ID NO. 2 of claim 1, we disagree that Tacken is not reasonably pertinent to the '504 patent.

With reference to its hD1V1G2/G4 (hD1) antibody, Tacken discloses that, "[a]n isotype control antibody, h5G1.1-mAb (5G1.1, eculizumab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5." Ex. 1034, 1279. Although, as Patent Owner points out, Tacken then cites to Thomas, Patent Owner does not address why Tacken would use an eculizumab having the IgG4 constant region as set forth in Thomas as "[a]n isotype control antibody" for one having an IgG2/IgG4 constant region. Dr. Balthasar, however, testifies that Tacken also cites Mueller II[17] "as providing information about the hybrid IgG2/IgG4 constant region portion of eculizumab." Ex. 1002 ¶ 56 (citations omitted); *see* Ex. 1034, 1279 (indicating that in the construction of hD1V1G2/G4 (hD1), "humanized variable heavy and variable light regions were [ ] genetically fused with a human hybrid IgG2/IgG4 constant domain," as set forth in Mueller II (reference 17)). On the present record, we read Tacken as disclosing that humanized monoclonal antibody 5G1.1, known as eculizumab, encompasses

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[17] John P. Mueller et al., *Humanized porcine VCAM-specific monoclonal antibodies with chimeric IgG2/G4 constant regions block human leukocyte binding to porcine endothelial cells*, 34 Mol. Immunol. 441–52 (1997) (Ex. 1031).

a molecule having a hybrid IgG2/IgG4 constant domain.

That Tacken, Bowdish, and Mueller suggest that eculizumab may include an IgG2/IgG4 constant domain, however, does not necessarily lead to the conclusion that Hillmen discloses the same molecule. Rather, the present record indicates that "eculizumab" is not a single, fixed chemical entity. To the contrary, the art identified as "eculizumab" at least two such compounds that differed in the heavy chain constant region: one having the IgG4 isotype (as evidenced in Thomas), and a second having a hybrid IgG2/IgG4 isotype (as evidenced by, e.g., Tacken).

Patent Owner made the above dichotomy explicit in an official representation to the Patent Office. During Alexion's prosecution of Application No. 11/127,438, an application outside of the chain of priority of the '504 patent, but claiming the use of eculizumab for the treatment of pulmonary conditions, the Examiner took the position that "the description of `eculizumab or pexelizumab' as well as `the mutated Fc portions' in the priority documents is not readily apparent." Ex. 1049, 741, 830–834 (representative claim amendments). In response, Alexion asserted that

> **eculizumab was first constructed in the IgG4 isotype**, see, e.g., the bridging paragraph of the left and right columns of page 1396 of Thomas et al. (1996) [Ex. 1023], . . . **and then into the G2/G4 format**, see Mueller et al. (1997) *Molecular Immunology,* Vol. 34, No.6, pages 441-452 [Ex. 1031], . . . while **in either form** the h5G1.1 antibody was well known to be incapable to activate human complement, see, e.g., the right column, lines 27-28, of page 1399 of Thomas et al., 1996, *Id.,* and the bridging paragraphs of pages 446 to 448 and 450 to 451 of Mueller et al, 1997, *Id.* Thus, Applicant submits that it was well-known to one of ordinary skill in the art at the time of filing

> of priority applications that eculizumab has a G2/G4 Fc portion, i.e., a mutated Fe portion.

Id. at 838–839 (bolding added). Alexion's statement, above, supports both Thomas's disclosure of eculizumab in the IgG4 isotype as the first construction of eculizumab, as well as an understanding that "eculizumab" referred to and refers to a genus of antibodies, including one with the hybrid IgG2/IgG4 isotype of the challenged claims. Accordingly, in view of the record before us, we conclude that "eculizumab" referred to and refers to a class or category of anti-C5 antibodies, also called 5G1.1 or h5G1.1 mAbs.

Upon considering the facts here in view of Petitioner's reliance on *Crish*, 393 F.3d 1253, and Patent Owner's reliance on *Endo Pharms.*, 894 F.3d 1374, we find the latter case analogous here. In *Crish*, the Federal Circuit found that a claim to the nucleotide sequence of the hINV gene promoter region was inherently disclosed by prior art that "specifically identified [the promoter region] by size and location" because "[t]he starting material plasmid necessarily contain[ed] the gene of interest, including the promoter region." *Crish*, 393 F.3d at 1257–59. Here, however, Hillmen does not "specifically identify" an eculizumab antibody containing the hybrid IgG2/IgG4 sequence of SEQ ID NO: 2, as required by claim 1.

Endo Pharms. compels a different result under the facts here. In *Endo Pharms.*, the issue was again inherency (in the context of obviousness) where prior art scientific articles described clinical trials for a testosterone undecanoate composition, but did not disclose its specific, and later claimed, formulation including a particular mixture of castor oil and benzyl benzoate. *Endo Pharms.*, 894 F.3d at 1278. It was later confirmed that the

composition of the clinical trials described in the prior art articles did, indeed, have the claimed mixture of castor oil and benzyl benzoate. *Id.* The Federal Circuit held that because it was not demonstrated that a skilled artisan could extrapolate the vehicle formulation (a mixture of castor oil and benzyl benzoate) used in the prior art articles based on reported pharmacokinetic performance data, such performance could not have only been attributed to the claimed formulation and the generic disclosure of the pharmaceutical formulation in the prior art did not inherently disclose the claimed formulation. *Id.* at 1281□83. Furthermore, *Endo Pharms.* distinguished *Crish* because it was about the inherent properties of a known prior art product rather than a product that was named but not known or determinable based on the prior art disclosure of its performance characteristics. *Id.* at 1383.

In Ground 1, the prior art reference, Hillmen, discloses a clinical trial of □eculizumab□but does not otherwise identify the structure of the antibody tested, other than by referencing Thomas. Ex. 1004, 552, 553 (citing Ex. 1023). Thomas discloses a version of eculizumab different from that claimed (an IgG4 isotype rather than a hybrid IgG2/IgG4 antibody). Even accepting that a skilled artisan would have known of a hybrid IgG2/IgG4 antibody, as claimed (*see, e.g.*, Ex. 1002 ¶ 13), Hillmen's mere reference to □eculizumab□would have at least invoked a molecule having the IgG4 isotype taught in Thomas. Thus, Hillmen's disclosure of □eculizumab□ would not have necessarily led the skilled artisan to the claimed antibody with □a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.□ Moreover, none of the references teaching or suggesting

an IgG2/IgG4 isotype (e.g., Bowdish, Evans, Tacken, Mueller, or Mueller II) is cited in Hillmen. *See id.* at 559. We disagree with Petitioner's position that such references' teaching would have somehow overridden Hillmen's direct invocation of Thomas's disclosure of eculizumab so as to point the skilled artisan to some alternative antibody structure.[18] Accordingly, under *Endo Pharms.*, as discussed above, there is no inherent anticipation of claim 1 over Hillmen.

To summarize, as we presently understand the art as of the filing date of the '504 patent, one of ordinary skill understood that eculizumab encompassed molecules by both IgG4 isotypes and IgG2/IgG4 hybrid structures, whereas a plain reading of Hillmen suggests that it specifies the former. Accordingly, one of ordinary skill in the art would not have necessarily understood Hillmen to disclose a version of eculizumab having the IgG2/IgG4 heavy chain constant region of SEQ ID No. 2. For the above reasons, Petitioner has not demonstrated a reasonable likelihood that claim 1, the sole independent claim of the '504 patent, is unpatentable under Ground 1.

E. Obviousness in view of Hillmen, Bell, and Wang (Grounds 2 and 3)

In Grounds 2 and 3, Petitioner challenges claims 4 and 5 as obvious in view of Hillmen and Bell, and claim 6 further in view of Wang. Pet. 37–45.

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[18] We need not address here Patent Owner's non-trivial argument that Petitioner "has improperly attempted to shoehorn" the obviousness arguments of Grounds 4–7 into its anticipation contentions. Prelim. Resp. 47.

Patent Owner opposes. Prelim. Resp. 52–55. Pertinent to each of Grounds 2–7, we address Patent Owner's secondary considerations evidence in section II(H), below.

For Grounds 2 and 3, Petitioner states: "Bell disclosed a Phase 2 Pilot Study involving 11 PNH patients treated with eculizumab over a period of 12 weeks" identical to that disclosed in Hillmen. . . . Given the substantial overlap, a POSA would have had ample reason to combine Hillmen and Bell, with a reasonable expectation of success at achieving the claimed subject matter." Pet. 37–38 (citations omitted). Responding to these contentions, Patent Owner notes that, "Grounds 2 and 3 rely upon Hillmen as the sole prior art allegedly disclosing the claimed element of an antibody comprising `a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4' . . . . [but] Hillmen did not disclose the claimed antibody sequence either expressly or inherently." Prelim. Resp. 52–53. Patent Owner's point is well taken.

As discussed in Section II(D)(2), above, Petitioner has not established that Hillmen inherently discloses the IgG2/IgG4 heavy chain constant region of SEQ ID NO: 2, and the Petition sets forth no additional argument on that subject in support of Grounds 2 and 3. Petitioner also does not argue, nor do we discern, where the required sequence is taught in Bell or Wang. Accordingly, Petitioner has not demonstrated a reasonable likelihood that claims 4–6 are unpatentable over the combinations of Hillmen, Bell, and Wang set forth in Grounds 2 and 3.

F. Obviousness in view of Bell, Bowdish, Evans, and Wang (Grounds 4 and 5)

Petitioner challenges claims 1–5 and 7–10 as obvious in view of Bell, Bowdish, and Evans (Ground 4), and claim 6 further in view of Wang (Ground 5). Pet. 45–60. Patent Owner opposes. Prelim. Resp. 56–61; *see also id.* at 55. For the purpose of institution, we focus on claim 1.

1. The Parties' Contentions

With respect to Ground 4, Petitioner contends that Bell taught all limitations of claim 1 but for eculizumab's amino acid sequence. Pet. 45–47. Petitioner points, for example, to Bell's disclosure that preferred treatments for PNH included "an *anti-C5 antibody* selected from the group consisting of *h5G1.1-mAb (eculizumab)* . . .' suitable for treating PNH, and also that the antibody `h5G1.1-mAb' was `undergoing clinical trials under the tradename *eculizumab*.'" *Id.* at 46 (citing Ex. 1005 ¶¶ 12, 52). Petitioner then argues that one of ordinary skill in the art would have looked to Bowdish and Evans to obtain the amino acid sequence of eculizumab. *See* Pet. 47–54.

Petitioner contends that the skilled artisan would have looked to Bowdish for the light and most of the heavy chain sequence of eculizumab in light of Bowdish's use of an "anti-C5 antibody as the starter `scaffold' antibody sequence for creating a recombinant TPO-mimetic" antibody. Pet. 47; Ex. 1002 ¶¶ 130–135. According to Petitioner, Bowdish disclosed "the full antibody amino acid sequence for such a 5G1.1 antibody [i.e., an anti-C5 antibody] except for the heavy chain CDR3 (HCDR3) sequence, which Bowdish replaced with the TPO-mimetic peptide sequence,

LPIEGPTLRQWLAARAPV." *Id.* (citing Ex. 1006 ¶¶ 191"193, Figs. 13A (SEQ ID NO: 67; "5G1.1 "TPO Heavy Chain (Bold Denotes TPO mimetic) Amino acid sequence"), 13B (SEQ ID NO: 69; "5G1.1 Light Chain Amino Acid Sequence"). In particular, Petitioner argues:

> A POSA . . . would have understood that the only portion of the "scaffold"5G1.1 antibody sequence not expressly disclosed in Bowdish is the HCDR3 sequence because Bowdish taught that "[t]he TPO mimetic peptide graft in Fab clone X4b has been *transplanted into the heavy chain CDR3* of another antibody framework, *5G1.1* . . . The sequence was *cloned into 5G1.1* in such a fashion as to *replace the native CDR3*."

Pet. 50 (citing Ex. 1006 ¶ 191; Ex. 1002 ¶ 137 (emphasis Petitioner's)).

Petitioner further argues that to obtain the CDR3 sequence missing from Bowdish, one of ordinary skill in the art would have looked to Evans "because both Bell and Bowdish explicitly direct the artisan there for information on how the h5G1.1 antibody was originally created." *Id.* at 53 (citing Ex. 1002 ¶ 142; Ex. 1006 ¶ 191). Alternatively, Petitioner argues, one of ordinary skill in the art would have readily identified the entire IgG2/IgG4 heavy chain sequence from Bowdish alone, because Bowdish incorporates Evans by reference. *Id.* at 5, 18 (citing Ex. 1006 ¶ 191; Ex. 1002 ¶¶ 54"55).

According to Petitioner, "a POSA would have understood that *each* of the 5G1.1 antibody heavy chain variable regions in Evans contain *the same CDR3 sequence*: YFFGSSPNWYFDV. Thus, regardless of which `version' of Evans' humanized 5G1.1 the POSA selected to combine with Bowdish, that heavy chain would contain the YFFGSSPNWYFDV CDR3 sequence." *Id.* at 51 (internal citations omitted) (*citing e.g.*, Ex. 1002 ¶ 136). In sum,

the "prior art would have led a POSA to make a simple substitution of one known element for another" i.e., replace the TPO-mimetic peptide sequence in Bowdish's antibody with the HCDR3 sequence from Evans" to yield predictable results: a humanized anti-C5 antibody." Pet. 53"54.

Petitioner relies on the Balthasar Declaration as support and further explanation as to how one of ordinary skill in the art would derive the claimed antibody based on the asserted art. *See* Pet. 47"51. Dr. Balthasar provides a number of illustrations useful to understanding Petitioner's argument.

Figure 4 from Dr. Balthasar's report, relating to the eculizumab light chain sequence, is reproduced below.

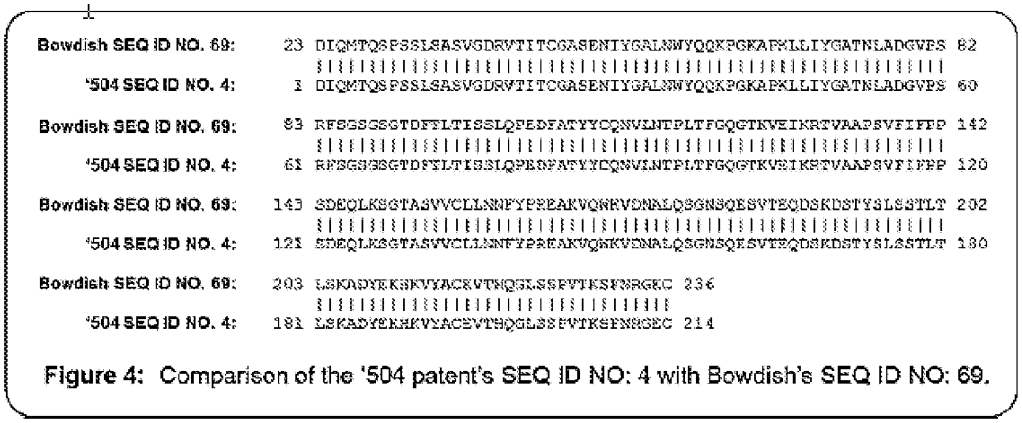


Figure 4: Comparison of the '504 patent's SEQ ID NO: 4 with Bowdish's SEQ ID NO: 69.

Ex. 1002 ¶ 52. Figure 4 purports to show identity between the mature peptide sequence[19] of the eculizumab light chain disclosed in Bowdish and

[19] Dr. Balthasar notes that Bowdish's Figures 13A and 13B identify leader sequences, not included in the comparisons of Figures 4 and 5 because one of ordinary skill in the art "would have understood that leader sequences are cleaved off as a standard part of the maturation of an antibody." *Id.*

SEQ ID NO. 4 of the '504 patent. *Id.*

Figure 5 from Dr. Balthasar's report, relating to the heavy chain sequence of eculizumab, is reproduced below.

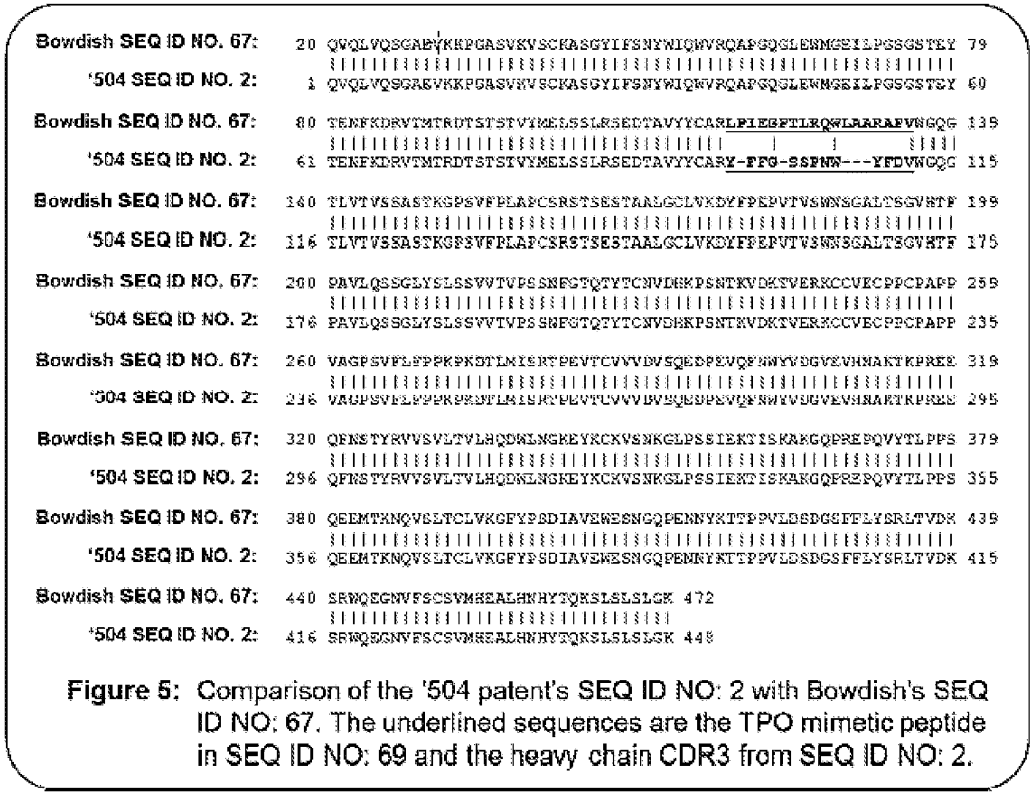


Figure 5: Comparison of the '504 patent's SEQ ID NO: 2 with Bowdish's SEQ ID NO: 67. The underlined sequences are the TPO mimetic peptide in SEQ ID NO: 69 and the heavy chain CDR3 from SEQ ID NO: 2.

Id. ¶ 55. According to Dr. Balthasar, "Figure 5 shows that the mature portion of SEQ ID NO: 67 from Bowdish (*i.e.*, amino acids 20 to 472) aligns perfectly with SEQ ID NO: 2 from the `504 patent outside of the heavy chain CDR3 region." *Id.*

Figure 6 of Dr. Balthasar's declaration, relating to the heavy chain CDRs of eculizumab, is reproduced below.

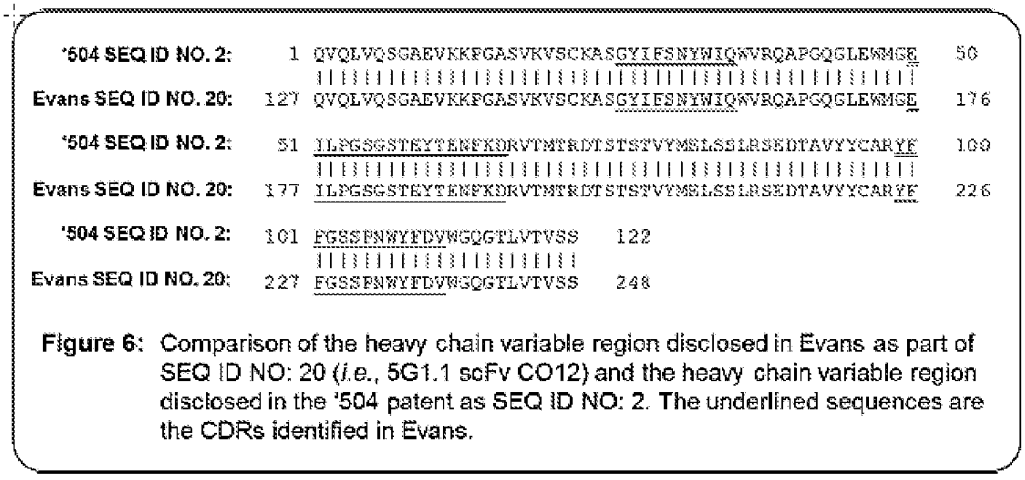


Figure 6: Comparison of the heavy chain variable region disclosed in Evans as part of SEQ ID NO: 20 (*i.e.*, 5G1.1 scFv CO12) and the heavy chain variable region disclosed in the '504 patent as SEQ ID NO: 2. The underlined sequences are the CDRs identified in Evans.

Ex. 1002 ¶ 53. According to Dr. Balthasar, Figure 6 shows an alignment of SEQ ID NO: 2 of the '504 patent with the heavy chain CDRs identified in Evans underlined, including the YFFGSSPNWYFDV sequence of CDR3. *Id.* ¶¶ 55, 136.

Figure 11 of Dr. Balthasar's declaration, relating to the relationship between the heavy chain CDR3 and Bowdish's TPO peptide, is reproduced below.

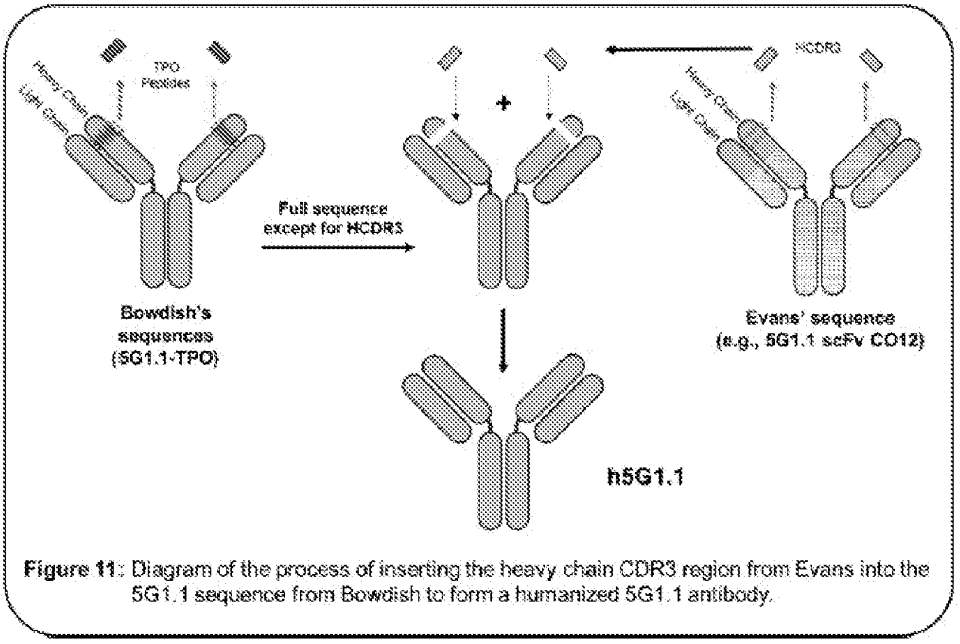


Figure 11: Diagram of the process of inserting the heavy chain CDR3 region from Evans into the 5G1.1 sequence from Bowdish to form a humanized 5G1.1 antibody.

Ex. 1002 ¶ 120. Figure 11 shows the original Bowdish scaffold antibody, including the location of eculizumab heavy chain CDR3; the use of Evans as a source of the HCDR3; and the replacement of Bowdish's TPO peptide with Evan's HCDR3. *Id.* According to Dr. Balthazar, Figure 11 "illustrate[s] how a POSA would have arrived at the claimed sequence (*i.e.*, eculizumab) by placing the heavy chain CDR3 disclosed in Evans into the 5G1.1 antibody sequence disclosed in Bowdish." *Id.*

With respect to reason to combine, Petitioner appears to argue that, because the combination of Bowdish and Bell taught the use of eculizumab for the treatment of PNH, the skilled artisan would have looked to Evans to recreate the molecule used in those successful studies. *See* Pet. 53; Ex. 1002 ¶¶ 122, 139–142. Moreover, with respect to the specific sequence of SEQ ID NO: 2, Petitioner asserts that, as of the filing date of the '504 patent, it

was well known that antibodies with a hybrid IgG2/IgG4 constant region carried certain benefits, such as a reduced ability to elicit unwanted inflammatory events and lessened propensity to activate the complement system. Pet. 17 (citing Ex. 1032, 11, 19, 28; Ex. 1031, 451; Ex. 1002 ¶¶ 47, 57). As noted by Dr. Balthasar, for example:

> A POSA would have been aware that the HuG2/G4 antibody design should prove useful in humanization of other antibodies intended for human use where elimination of FcR binding and C [*i.e.*, complement] activation may be desirable. AMG1031, 451; *see also*, AMG1034, 1280. Because the goal of using eculizumab in treating PNH is to reduce the level of complement activation, using a heavy chain constant region that avoids a counter-productive activation of complement by the therapeutic antibody aligns well with the desired outcome. AMG1005, ¶¶[0003], [0012].

Ex. 1002 ¶ 47.

Patent Owner argues that, absent impermissible hindsight, the skilled artisan would not have combined, or reasonably expected success in combining the asserted references. Prelim. Resp. 4–5, 56–61. Patent Owner argues that Bell, like Hillmen, taught eculizumab was the antibody of Thomas and nothing in the other references would point the skilled artisan toward a different antibody, e.g., the IgG2/IgG4 hybrid covered by the claim. *Id.* Patent Owner also argues Thomas taught away from the claimed invention because Thomas described an "eculizumab" with an IgG4 constant region. *Id.* at 57.

Patent Owner argues that even assuming one of ordinary skill did combine Bowdish and Evans to obtain eculizumab having the claimed sequence, "a POSA would not have reasonably expected the resulting

compound to work in a pharmaceutical composition for preventing C5 cleavage and safely and effectively treating PNH . . . . [because] even small changes to the amino acid sequence could have a substantial impact on the binding properties and the safety and efficacy of an antibody intended for human administration.□ *Id.* at 60 (citing *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051 (Fed. Cir. 2019). Patent Owner thus contends that, in view of this complexity and unpredictability, the skilled artisan would not have ventured away from Thomas's known antibody; i.e., would not have looked to Bowdish and Evans for an isotype variant of that antibody. *Id.* at 41.

2. Analysis

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has carried its burden to show a reasonable likelihood that claims 1 and 6 of the '504 patent would have been obvious under Grounds 4 and 5, respectively.

Regarding Patent Owner's argument that the combination of Bell, Bowdish, and Evans involves improper hindsight and that the combination fails to render the challenged claims obvious because Bell's disclosed antibody would necessarily be that of Thomas's disclosure, we are not convinced. As summarized in Section I(F)(2), above, Bell extols the virtues of eculizumab for the treatment of PNH, but does not identify the antibody's amino acid sequence. Bell does cite to and incorporates by reference both Evans and Thomas. *See* Ex. 1005 ¶ 52. Accordingly, Thomas's IgG4 isotype antibody would be one type of eculizumab contemplated by Bell. But, as discussed in section II(D)(2), one of ordinary skill in the art would

have understood that "eculizumab" encompassed multiple isotypes, including one having the hybrid IgG2/IgG4 isotype noted in Tacken and Bowdish. Here, Bowdish discloses a substantial portion of the anti-C5 antibody 5G1.1 and points to Evans as evidencing the remaining amino acid sequence. And with respect to Patent Owner's argument that neither Bowdish nor Evans uses the term "eculizumab" (Prelim. Resp. 58–59), on the present record, we accept from Dr. Balthasar's Declaration that one of ordinary skill in the art would have looked to those references for the structure of eculizumab, particularly given that Bowdish incorporates Evans by reference for the construction of 5G1.1. *See*, *e.g.*, Ex. 1006 ¶ 191; Ex. 1002 ¶¶ 43–46, 51, 54, 56, 122; *see also* Ex. 1001, 39:1–32 (the '504 patent's claims also do not use the term "eculizumab"). Accordingly, Petitioner's arguments rely on the disclosures of the prior art and no improper hindsight is necessarily invoked under Petitioner's rationale.

As for Patent Owner's contention that Thomas taught away from the claimed invention (or, somehow taught away from the prior art combination), we disagree. A "teaching away" requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *Id.* at 1200 (citation and emphasis omitted). "The prior art's mere disclosure of more than one alternative does not constitute a teaching away from . . .

alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed. *Id.* at 1201. Thomas does not criticize, discredit, or discourage the claimed invention or the prior art combination. Thomas, at most, teaches the original eculizumab construction, an alternative to the version as taught by Bowdish and Evans.

On the present record, we are not persuaded by Patent Owner's argument that "[e]ven if Bowdish and Evans were combined . . . , a POSA would not have reasonably expected the resulting compound to work in binding to C5 or safely and effectively treating PNH because even small changes could substantially impact an antibody's binding properties, safety, and efficacy for human administration, we disagree. *See* Prelim. Resp. 60.

As an initial matter, it is not clear whether claim 1 requires any showing of safety and efficacy as these are standards for FDA approval of new drugs rather than of patent law. *Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 855 F.3d 1356, 1372–73 (Fed. Cir. 2017), *cert. granted*, 138 S. Ct. 2678 (2018), and *aff'd*, 139 S. Ct. 628 (2019) ("Approval of a new drug by FDA, however, is a more demanding standard than that involved in the patents-in-suit. The patents here make no reference to FDA standards and broadly claim a palonosetron formulation for reducing the likelihood of emesis and CINV.").

Further, Bell teaches that a variety of compounds containing the variable regions of a humanized 5G1.1 are useful to the treatment of PNH, stating: "In particularly useful embodiments, the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb (eculizumab), h5G1.1-scFv (pexelizumab) and other functional fragments of h5Gl.l."

Ex. 1005 ¶ 12. Moreover, Bell touts the benefits of "eculizumab" in a long-term clinical trial, indicating that the treatment is suitable for treatment of patients suffering from PNH, as set forth in claim 1. As noted above, one of ordinary skill in the art understood eculizumab to encompass a humanized 5G1.1 antibody having the IgG2/IgG4 isotype indicated in SEQ ID NO: 2.

Although we recognize Patent Owner's argument that "sequence changes outside of the antigen-binding site, *e.g.*, in the heavy chain constant region" may influence antibody affinity, specificity, and immunogenicity, this is counterbalanced by Petitioner's citation to eculizumab of the IgG2/IgG4 isotype and its reasoned argument that the skilled artisan would look to the hybrid sequence because it was known "that antibodies with a hybrid IgG2/IgG4 constant region carried certain benefits, such as a reduced ability to elicit unwanted inflammatory events and lessened propensity to activate the complement system." *See* Prelim. Resp. 11; Pet. 17 (citing Ex. 1032, 11, 19, 28; Ex. 1031, 451; Ex. 1002 ¶¶ 47, 57).

On balance, the present record suggests that a person of ordinary skill in the art would have reasonably expected a version of eculizumab having a heavy chain consisting of SEQ ID NO: 2 to work for the purpose set forth in claim 1 ("treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH)"). The parties are invited to further address this issue during trial.

We take note of Patent Owner's arguments relating to and evidence of objective indicia of non-obviousness, discussed above at Section II(E). Although we noted that there was some evidence to support Petitioner's contentions of commercial success, long-felt but unmet need, and industry

praise, we also noted some potential shortcomings in Patent Owner's presentation, including the rebutability of the presumption of a nexus between their evidence and the claimed and novel subject matter. We expect this issue will be further developed at trial.[20]

Again, to summarize, based on the evidence presented at this stage in the proceedings, it has been shown that there is a reasonable likelihood that claim 1 of the '504 patent would have been obvious over Bell, Bowdish, and Evans under Ground 4. With respect to Ground 5, which challenges only dependent claim 6, we await further development of the parties' positions in the Patent Owner Response and Petitioner's Reply.

G. Obviousness in view of Bell, Evans, Mueller, and Wang (Grounds 6 and 7)

Petitioner challenges claims 1–5 and 7–10 as obvious in view of Bell, Evans, and Mueller (Ground 6), and claim 6 further in view of Wang (Ground 7). Pet. 61–73. Patent Owner opposes. Prelim. Resp. 61–63; *see also id.* at 55. For the purpose of institution, we focus on claim 1.

1. The Parties' Contentions

In sum, Petitioner asserts, "the only element of claim 1 not expressly taught in Bell is that its humanized anti-C5 antibody `comprises a heavy

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[20] In addition to challenging Petitioner's positions with respect to claim 1, Patent Owner also raises non-trivial arguments in response to Petitioner's contentions specific to dependent claims 5 and 6, which we need not address at this stage of the proceeding. *See* Pet. 39–45 (citing e.g., Ex. 1005 ¶ 58, 89–96; Ex. 1002 ¶¶ 104–109), 60–61 (citing Ex. 1027, 1638 (¶ 3.5), Ex. 1004 (¶ 5.3.9); Ex. 1028, Fig. 10, ¶ 67; Ex. 1029, Table 1; Ex. 1030, Table 1; Ex. 1002 ¶¶ 168; Prelim. Resp. 55, 60–61.

chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.' Pet. 62. According to Petitioner, Evans disclosed the complete amino acid sequences of the heavy and light chain variable domains of a humanized anti-C5 antibody, whereas Mueller disclosed the amino acid sequence of a light chain constant region and the hybrid IgG2/IgG4 heavy chain constant region. *Id.* at 62–63 (citing Ex. 1007, 44:4–13, SEQ ID NO: 20; Ex. 1002, ¶¶172–173, 183–185; Ex. 1008, 58–61). Petitioner further argues:

> Knowing that chimeric IgG2/IgG4 constant regions that were known not to activate the complement system (AMG1008, 7:28-31, 8:23-26, 12:27-32), a POSA reading Bell and Evans also would have looked to Mueller for h5G1.1 sequence information. Mueller taught methods for making chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4 . . . (HuG2/G4 mAb). AMG1008, 12:27-30; *see also, id.,* 8:23-26. In particular, Mueller described a control antibody h5G1.1 CO12 HuG2/G4 mAb, which a POSA would have readily identified as a humanized anti-C5 antibody because of the h5G1.1 nomenclature coupled with the hybrid IgG2/IgG4 constant region (HuG2/G4). AMG1008, 12:37, FIG. 15; AMG1005, ¶[0052]; AMG1034, 1279; AMG1049, 838-839; AMG1002, ¶190.

Id. at 64.

Figure 14 from the Balthasar Declaration is reproduced below.

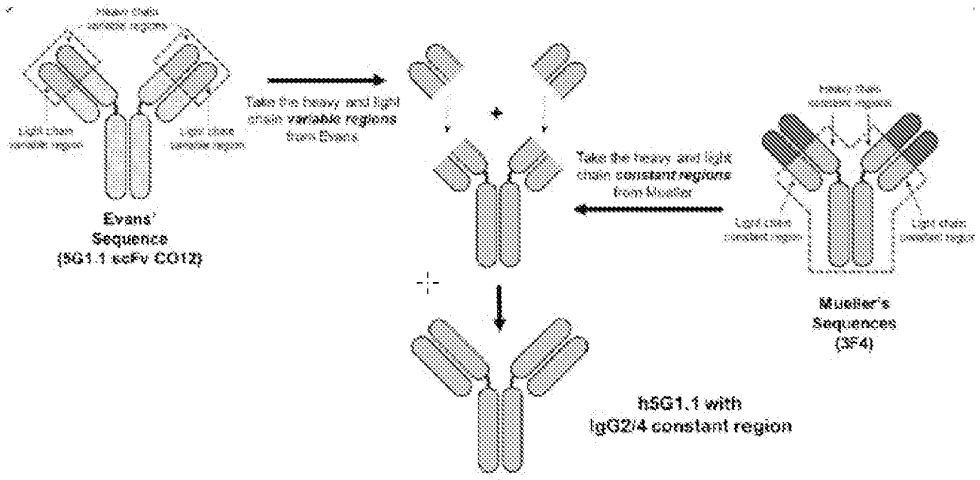


Figure 14.

Ex. 1002 ¶ 173. According to Petitioner, the above figure presents an overview of how one of ordinary skill in the art would have combined the teachings of Evans and Mueller to arrive at the eculizumab antibody described in claim 1. *Id.*

Relying on Dr. Balthasar's testimony, Petitioner argues that "Mueller disclosed the amino acid sequence of a hybrid IgG2/IgG4 heavy chain constant domain when Mueller disclosed the sequence of the chimeric anti-VCAM `3F4' antibody." Pet. 64 (citing Ex. 1002 ¶ 186; Ex. 1008, 58–61). According to Petitioner, one of ordinary skill in the art would have aligned Mueller's chimeric 3F4 HuG2/G4 heavy chain and mature 3F4 heavy and light chain variable regions such that a skilled artisan aligning the two would identify the 3F4 variable regions (at Figure 9) as amino acids 20–137 of the 3F4 HuG2/G4 heavy chain and amino acids 20–131 of the 3F4 light chain. *Id.* at 65 (citing Ex. 1008, 51–53, 58–61, Figure 9; Ex. 1002 ¶ 186).

Petitioner contends that the skilled artisan "would have immediately known that the remainder of the 3F4 HuG2/G4 heavy chain (amino acids 138-463 is the hybrid IgG2/IgG4 constant region of that antibody, and that the remainder of the 3F4 chain (amino acids 132–238) is the light chain constant region of that antibody." *Id.* at 65–66 (citing Ex. 1002 ¶¶ 179, 186, Figure 15; Ex. 1008, 52–53, 56–57). With this understanding of the heavy and light chain constant domain sequences in mind, Petitioner contends the skilled artisan would have looked to Evans to complete the whole antibody using Evans's variable regions identified from its SEQ ID NO: 20, particularly because Evans uses the same "CO12" nomenclature to refer to its 5G1.1 scFv as Mueller does in referring to h5G1.1. *Id.* at 66–67 (citing Ex. 1002 ¶¶ 173, 180–182).

Petitioner's argued rationale for combining Mueller and Evans is that Mueller taught antibodies with lower immune response and identified an antibody as h5G1.1 CO12 HuG2/G4 mAb, which the skilled artisan would have known is eculizumab. Further, Petitioner argued, Evans taught the complementary parts of this anti-C5 antibody, so, by combining the elements of the two references, a complete antibody would have been created having the SEQ ID NO: 2 and SEQ ID NO: 4 of the claim. *Id.* at 64; *see also id.* at 69–70 (further discussing why one of ordinary skill in the art would have combined the cited references with a reasonable expectation of success).

Patent Owner argues "[a] POSA would have understood that Mueller could have used ***any*** antibody with an IgG4 or IgG2/G4 isotype as a `negative control' for its *in vitro* experiments, as long as it did not bind to

VCAM, meaning, there would be no reason to incorporate the variable regions taught by Evans. *Id.* at 62 63. And, without improper hindsight, Mueller and Evans would not have been combined by the skilled artisan. Prelim. Resp. 61. Patent Owner argues [a] POSA as of March 15, 2007 considering the problem addressed by the '504 patent developing an antibody that prevents cleavage of C5 and can safely and effectively treat patients suffering from PNH would have had no reason to look at Mueller, which had nothing to do with that problem. *Id.* (citing *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013) (While a prior art reference may support any finding apparent to a person of ordinary skill in the art, prior art references that address different problems may not, depending on the art and circumstances, support an inference that the skilled artisan would consult both of them simultaneously.).

2. Analysis

In contrast to Grounds 4 and 5, where Bowdish expressly incorporated Evans by reference, thereby rendering the combination unquestionable, in Grounds 6 and 7 we find no express link between the teachings of Mueller and Evans. Although such a combination is possible, the mere fact that prior art can be combined does not establish that one of ordinary skill would have done so. *See, e.g.*, *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (The mere fact that the prior art may be modified in the manner suggested . . . does not make the modification obvious unless the prior art suggested the desirability of the modification.).

Grounds 6 and 7 present a close question on whether there would have been motivation to combine Mueller and Evans in the manner argued by Petitioner. Upon review of the Balthasar Declaration, it is apparent that Mueller's 3F4 heavy chain provides a match for part of the claimed SEQ ID NO: 2. *See* Ex. 1002 ¶ 58, Figure 8. Further, Mueller's 3F4 light chain provides a match for part of the claims SEQ ID NO: 4. *Id.* ¶ 59, Figure 9. The Balthasar Declaration provides an illustration as its Figure 10, reproduced below, showing the extent that each of Evans and Mueller (and Bowdish, per Grounds 4 and 5) discloses the claimed SEQ ID NOs: 2 and 4.

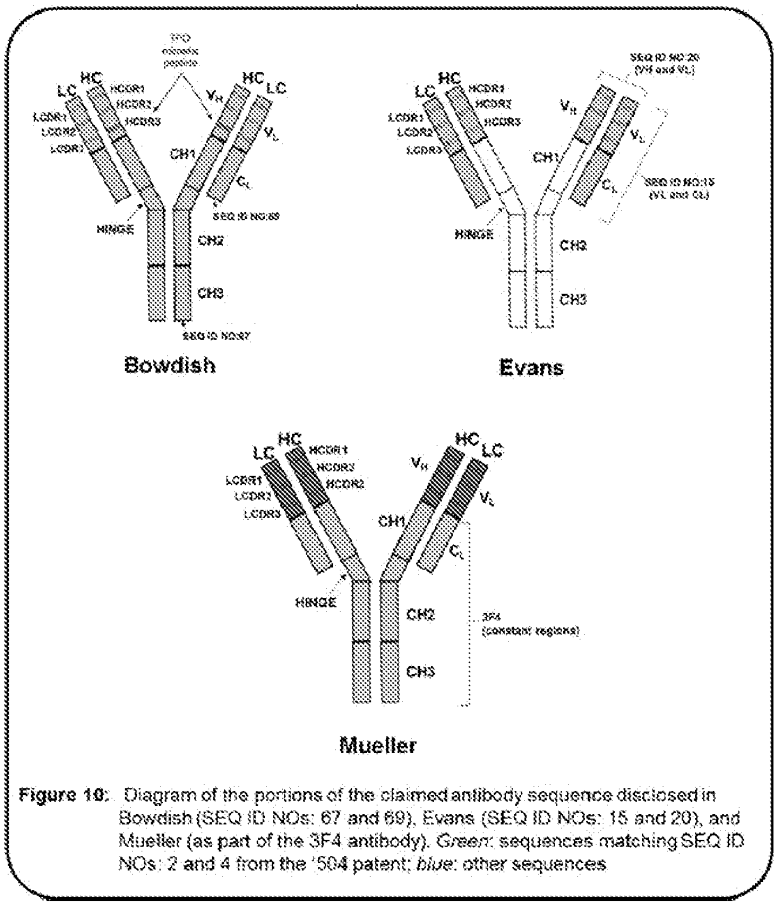


Figure 10: Diagram of the portions of the claimed antibody sequence disclosed in Bowdish (SEQ ID NOs: 67 and 69), Evans (SEQ ID NOs: 15 and 20), and Mueller (as part of the 3F4 antibody). *Green*: sequences matching SEQ ID NOs: 2 and 4 from the '504 patent; *blue*: other sequences

Ex. 1002 ¶ 60. Dr. Balthasar's Figure 10 shows three antibody structures: Bowdish top-left, Evans top-right, and Mueller bottom center. The Figure shows identity with SEQ ID NOs: 2 and 4 of the '504 patent in green and differences in blue.

Based on the above figure, Petitioner's rationale for combining the teachings of Mueller and Evans is somewhat tenuous. In particular, we are concerned with the proposed reasons one of ordinary skill in the art would have paired Evans with Mueller, choosing precisely those portions of Evans's and Mueller's constructs to create an antibody having exactly the sequences set forth SEQ ID NOs: 2 and 4. At this stage in the proceedings, based on the evidence before us, the answer is not entirely clear and Patent Owner's argument regarding improper hindsight makes some sense. True, Mueller discloses "a humanized antibody directed against human C5 (h5G1.1 CO12 HuG4 mAb)," but little else regarding its structure. *See* Ex. 1008, 12. It is not apparent that the skilled artisan, knowing of Evans, would have looked to Mueller, or vice versa.

Based on our understanding of the evidence presented at this stage in the proceedings, Petitioner has not sufficiently demonstrated a reasonable likelihood that claim 1 of the '504 patent would have been obvious over the combinations set forth in Grounds 6 and 7.

H. Objective Evidence of Non-Obviousness

Factual considerations that underlie the obviousness inquiry include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any

relevant secondary considerations. *See Graham*, 383 U.S. at 17–18. Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR*, 550 U.S. at 406, (2007). Although evidence pertaining to secondary considerations must be taken into account whenever present, it does not necessarily control the obviousness conclusion. *See*, *e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

Petitioner contends no objective indicia of nonobviousness support patentability of the challenged claims. Pet. 37, 38, 45, 60–62, 71–73. In particular, Petitioner notes that during the prosecution of the '504 patent, Alexion argued that the claimed heavy chain of eculizumab, i.e., the hybrid IgG2/IgG4 constant domain, provided surprising and unpredictable results, such as decreased effector function, reduced immunogenicity, and increased half-life. Pet. 72 (citing Ex. 1014, 588, 593 (¶ 8)). However, Petitioner contends, because eculizumab's hybrid IgG2/IgG4 constant region was well known in the art (as evidenced by Tacken), the allegedly surprising and unpredictable features of the antibody have no nexus to the challenged claims. *Id.* (citing Ex. 1034, 1279).

Petitioner further contends that one of ordinary skill in the art would not have found surprising the alleged beneficial results of using the hybrid constant region because, in view of Mueller II, antibodies with the claimed hybrid IgG2/IgG4 heavy chain were known not to bind FcR and to be less immunogenic, whereas it was well known that antibodies with this claimed hybrid heavy chain would have an increased half-life. *Id.* (citing Ex. 1031,

488, 451; Ex. 1032 ("Rother"), 5, 19[21]; Ex. 1002 ¶ 210–212); *see*, *e.g.*, Ex. 1032, 5–6 (disclosing that antibodies having "an engineered constant region that includes an IgG2-derived portion and an IgG4-derived portion . . . maintain the function of the non-Fc component and/or have increased half-life compared to the non-Fc component alone and/or lack unwanted antibody Fc-mediated cell activating and inflammatory properties including events resulting from Fc-receptor antibody engagement and complement activation").

Patent Owner contends that evidence of commercial success, long-felt, but unmet need, and industry praise support the non-obviousness of the challenged claim. Prelim. Resp. 63. Patent Owner argues that SOLIRIS, the product embodying the claimed antibody, is a commercial success, having annual net product sales in excess of $1 billion in 2018. *Id.* at 64. (citing Ex. 2018, 70). Patent Owner further contends that this commercial success "has a direct nexus to the patented features of the '504 patent, which claims the uniquely-engineered, non-naturally occurring antibody responsible for the drug's clinical (and therefore commercial) success as a treatment for PNH, as well as complement-mediated hemolytic condition aHUS." *Id.*

At this stage in the proceedings, based on the evidence presented by Patent Owner, it is apparent that SOLIRIS is a successful product. "[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP,*

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[21] Rother et al., WO 2005/007809 A2, published Jan. 27, 2005 (Ex. 1032).

LLC v. Kohler Co., 829 F.3d 1317, 1329 (Fed. Cir. 2016). This "presumption of nexus is rebuttable: a patent challenger may respond by presenting evidence that shows the proffered objective evidence was `due to extraneous factors other than the patented invention.'" *Id.* Here, the parties appear to agree that the claim of the '149 patent is directed to the commercial product SOLIRIS. However, commercial success "is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996).

Patent Owner argues that because SOLIRIS is "the first FDA-approved treatment to reduce hemolysis in patents with PNH," there is evidence that the claimed antibody fulfilled a long-felt, unmet need in the market. Prelim. Resp. 64 (citing Ex. 2019, 1270).

At this stage in the proceeding, the available evidence supports that anti-C5 antibodies were considered potential therapeutic options for "many years" before 2007, and that Alexion's eculizumab product "is currently the only complement-specific antibody on the market" and is the "first and only approved therapy for PNH." Ex. 2019, 1270. Again, it may be presumed that there is a nexus between the claimed and novel elements of the SOLIRIS product and the meeting of the long-felt need. However, "[w]here the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Patent Owner also contends "SOLIRIS® also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade . . . ." Prelim. Resp. 64--65 (citing Ex. 2020; Ex. 2021).

As with the other two contended bases for indicia of non-obviousness, while it is apparent there was high praise for the SOLIRIS product from the relevant industry, there is a rebuttable presumption that this praise has a nexus with the claimed subject matter. *Cf. In re Kao*, 639 F.3d at 1068.

Given the early stage of these proceedings, we decline to accord much weight to Patent Owner's substantially untested evidence of objective indicia of nonobviousness. The parties will have the opportunity to further develop these facts during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

I. The Board's Discretion to Deny Institution under 35 U.S.C. §§ 325(d) and 314(a)

1. The Parties' Positions

Patent Owner argues the "Petition should also be denied institution under 35 U.S.C. §§ 325(d) and 314(a), because Amgen's Grounds rely on the `same or substantially the same prior art or arguments' previously presented to the PTO" "[i]n the course of patent prosecution leading to issuance of the '504 patent, as well as prosecution of related U.S. Patent Nos. 9,719,880 (`the '880 patent') and 9,732,149 (`the '149 patent'). Prelim. Resp. 17, 65"66; *see id.* at 65"66 (asserting that the Examiner considered Hillmen, Evans, and Wang; and further reviewed Bell ("cumulative of Bowdish"), and Mueller II ("cumulative of Mueller").

Patent Owner argues that in the course of prosecution leading to the issuance of the '504 patent, the Examiner:

> - Expressly discussed Amgen's asserted references Hillmen 2004 (AMG1004), Evans (AMG1007), and Wang (AMG1028) as a basis for rejection, before ultimately finding the claims to be allowable over the art (*see, e.g.*, AMG1014 at 557-561, 623-628, 738-743);
> - Considered Amgen's asserted reference Bell (AMG1005), which Alexion submitted to the PTO (*see, e.g.*, AMG1014 at 566);
> - Considered U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen relies here (*see, e.g.*, AMG1014 at 565); and
> - Considered the "Mueller II" article (AMG1031), which is cumulative of Amgen's asserted "Mueller" reference (AMG1008) because, as Amgen's declarant recognized, it "discloses the same antibodies" as Mueller. (*See, e.g.*, AMG1014 at 499; AMG1002 ¶ 182 & n.14.)

Prelim. Resp. 18.

Petitioner's position on this issue is that "[t]he arguments and evidence presented herein were not before the examiner during prosecution and, therefore, do not constitute `the same or substantially the same prior art or arguments' under 35 U.S.C. §325(d).' " Pet. 24. In particular, Petitioner argues that

> the examiner rejected Alexion's claims as (i) anticipated by Hillmen in view of Thomas; (ii) obvious over Hillmen, Thomas and Evans; and (iii) obvious over Hillmen, Thomas, Evans, and Wang. AMG1014, 557-561. Those rejections rested solely on disclosures in Thomas and Evans for eculizumab sequence information. *Id.* The examiner later allowed the '504 patent

> claims mistakenly believing because of Alexion's mischaracterization of the art that the sequence and structure of eculizumab were not already known.
>
> Though Hillmen, Evans, and Wang were referenced by the examiner during prosecution, this Petition presents them in a different light, along with new references Bell, Bowdish, and Mueller, which teach the IgG2/IgG4 constant region missing from the art combination raised during prosecution.
>
> Bell and a parent application to Bowdish (US 2003/0049683 A1) was cited but not relied upon during prosecution, and Mueller was not cited at all. The art combinations here, which were not raised by the examiner during prosecution, provide the complete sequence of eculizumab, thereby teaching the very thing the examiner mistakenly concluded was missing from the prior art. Consequently, this Petition is not the same/substantially the same as or cumulative of any previous arguments and § 325(d) does not preclude instituting this Petition.

Id. at 24–25.

2. Analysis

Regarding the Board's discretion under 35 U.S.C. § 325(d), in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, the Board enumerated non-exhaustive factors to be considered in exercising discretion under 35 U.S.C. § 325(d) on whether to institute *inter partes* review. Case IPR2017-01586, slip op. at 17–18 (PTAB Dec. 15, 2017) (Paper 8) (precedential as to § III.C.5, first paragraph). The non-exhaustive *Becton* factors are:

> 1. the similarities and material differences between the asserted art and the prior art involved during examination;
>
> 2. the cumulative nature of the asserted art and the prior art evaluated during examination;

> 3. the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> 4. the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> 5. whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> 6. the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Id. (numbering added). The *Becton* factors are not dispositive, but are part of a balanced assessment of the relevant circumstances in a particular case and we do not simply default to a tally of each factor to determine whether or not an IPR should be instituted.

Here, Patent Owner has not clearly identified how its arguments fall under the above-noted factors, but has generally argued that the prior art before us now was considered by the prosecuting Examiner either directly or as being cumulative of references that were so considered, and has further argued that the unpatentability issues presented in the Petition are the same as those at issue before the Examiner. Upon review of this evidence, we note that the Examiner considered Hillmen in rejecting a claim for obviousness-type double patenting and for anticipation. *See* Ex. 1014, 482, 557□561. As discussed above, at this stage in the proceedings, the anticipation Ground 1 over Hillmen, on its own, is not considered sufficient to institute IPR; therefore, Hillmen's consideration during prosecution is not determinative here. Rather, we focus on the Bell, Bowdish, and Evans□ the references of Ground 4, upon which we base our institution decision.

As an initial matter, Alexion did address the substance of Evans during prosecution. *See* Ex. 1014, 588. But, according to Patent Owner, the Examiner "[c]onsidered" Bell and "U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen relies here." Prelim. Resp. 18. Both of these citations, however, are to an Information Disclosure Statement signed by the Examiner. *See id.* (citing Ex. 1014, 565, 566). Patent Owner does not direct us to, nor do we discern, where either Bell or some version of Bowdish was substantively considered during prosecution. The Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution. *See, e.g.*, *Amneal Pharms. LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, slip op. at 40 (PTAB Nov. 7, 2018) (Paper 8) (declining to deny institution based on Section 325(d) where the reference was listed on the face of the patent, but Patent Owner provided no evidence "about the extent to which the Examiner evaluated" the reference during prosecution); *Digital Check Corp. d/b/a ST Imaging v. E-Imagedata Corp.*, IPR2017-00178, slip op. at 12–13 (PTAB Apr. 25, 2017) (Paper 6) (acknowledging that a prior art reference was cited in an IDS, but granting institution because there was no indication that the claims were rejected based on those references or that the Examiner substantively discussed those references during prosecution); *Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, slip op. at 7–9 (PTAB Apr. 3, 2017) (Paper 8) (refusing to deny institution based on Section 325(d) for grounds based on a prior art reference that was simply cited in an IDS and

not considered at any length); *Praxair Distribution, Inc. v. INO Therapeutics LLC*, IPR2015-00893, slip op. at 8 (PTAB Sept. 22, 2015) (Paper 14) (granting institution even though the references were previously cited in an IDS because patent owner failed to identify with specificity where the references were considered); *HyperBranch Medical Technology, Inc. v. Confluent Surgical, Inc.*, IPR2018-01099, slip op. at 17 (PTAB Nov. 27, 2018) (Paper 14) (instituting IPR because, *inter alia*, "[t]he Examiner does not appear to have considered the combined teachings of Spero and Haber during examination of the '021 patent.").

Based on the evidence presented by Patent Owner, *Becton* factors 1–6 weigh in favor of not exercising our discretion not to institute here. Therefore, based on the evidence cited by Patent Owner and for the reasons above, we decline to exercise our discretion under section 325(d) to deny institution here.

Other than the heading of Section VI of the Preliminary Response and that section's first sentence invoking the statute, Patent Owner presents no arguments or evidence directed to the Board's discretion under 35 U.S.C. § 314(a). *See* Prelim. Resp. 65–66. *Therefore*, we also decline to exercise our discretion under Section 314(a) to deny institution.

III. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of prevailing on Ground 4 in showing that claim 1 of the '504 patent is obvious over the combination of Bell, Bowdish, and Evans. Given this determination, we institute trial on all

challenged claims raised in the Petition.[22] *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review "require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

Our decision at this stage derives from our preliminary review of the challenged claims, the asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration. We emphasize that at this stage of the proceeding, we have not made a final determination as to the construction of any claim term or the patentability of the instituted claims. Our final decision will be based on the full record developed during trial.

IV. ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of claims 1–10 of U.S. Patent No. 9,725,504 B2, in accordance with each ground on which the challenge to each claim is based in the Petition, is hereby *instituted*; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of the '504 patent will commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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[22] In view of the complexity of the art and arguments presented, the parties are, nevertheless, invited to negotiate an agreement to focus on some subset of the asserted claims and Grounds.

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Paper 15
Entered: August 30, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

IPR2019-00740
Patent 9,718,880 B2

Before TINA E. HULSE, ROBERT A. POLLOCK, and RYAN H. FLAX, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314(a)

I. INTRODUCTION

Amgen Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1–3 of U.S. patent No. 9,718,880 B2 ("the '880 patent," Ex. 1001). Paper 2 ("Pet."). Alexion Pharmaceuticals ("Patent Owner" or "Alexion") timely filed a Preliminary Response. Paper 10 ("Prelim. Resp."). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 13 ("Reply"); Paper 14 ("Sur-reply").

We review the Petition, Preliminary Response, Reply, Sur-Reply, and accompanying evidence under 35 U.S.C. § 314. An *inter partes* review may not be instituted unless "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Further, a decision to institute may not institute on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018).

After considering the evidence and arguments presented in the Petition and Preliminary Response, Reply, and Sur-Reply, we determine that Petitioner demonstrates a reasonable likelihood of prevailing in showing that at least one of the challenged claims of the '880 patent is unpatentable. Accordingly, we institute an *inter partes* review as to all the challenged claims of the '880 patent on all the grounds of unpatentability set forth in the Petition.

A. Real Parties-in-Interest

Petitioner identifies only itself as the real party-in-interest. Pet. 70. Patent Owner, likewise, identifies only itself as the real party-in-interest. Paper 3, 2.

B. Related Proceedings

The '880 patent shares essentially the same specification with U.S. Patent Nos. 9,725,504 B2 ("the '504 patent) and 9,732,149 ("the '149 patent"). Amgen has filed Petitions for *Inter Partes* Review of the '504, '880, and '149 patents in IPR2019-00739, IPR2019-00740, and IPR2019-00741, respectively. Pet. 70; Paper 3, 2.

The '504, '880, and '149 patents are related as follows: The '149 patent issued from application No. 15,284,015, filed January 19, 2017, which is a continuation of application No. 15/260,888 (now the '504 patent), filed on September 9, 2016, which is a continuation of application No. 15/148,839 (now the '880 patent), filed on May 6, 2016, which is a continuation of application No. 13/426,973, filed on March 22, 2012, which is a continuation of application No. 12/225,040, filed as application No. PCT/US2007/006606 on March 15, 2007. The parties do not dispute that March 15, 2007, is the relevant priority date of the challenged patent.

C. The '880 patent and Relevant Background

The '880 patent relates to the use of a humanized anti-C5 antibody (eculizumab) for the treatment of paroxysmal nocturnal hemoglobinuria. *See* Ex. 1001, Abstract. For reference, we reproduce Figure 1 from

paragraph 26 of the Balthasar Declaration,[1] illustrating the basic structure of an antibody such as eculizumab:

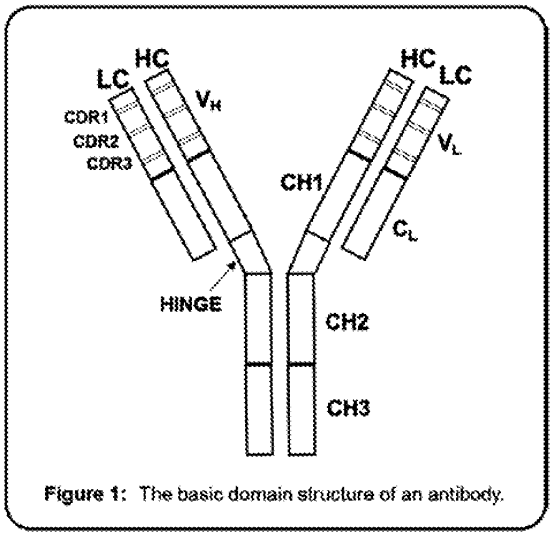


Figure 1: The basic domain structure of an antibody.

Figure 1 shows a basic antibody structure having hinged heavy chains (HC) and accompanying light chains (LC), each having constant regions (C_H and C_L) and variable regions (V_H and V_L), all arranged in a general "Y"-shaped structure, as the variable regions and portions of the constant heavy chain regions are hinged away from one another. Ex. 1002 ¶¶ 23–25. The variable regions of each chain also include three complementarity determining regions (CDR), which provide the antibody with antigen-binding specificity. *Id.* ¶ 25.

[1] Declaration of Dr. Joseph P. Balthasar, Ph.D. (Ex. 1002, "Balthasar Declaration").

Paroxysmal nocturnal hemoglobinuria or PNH is an acquired hemolytic disease resulting from loss of function in certain cytoprotective proteins. *Id.* at 1:27–35; Ex. 1002 ¶¶ 32–33. This loss of function renders red blood cells, platelets and other blood cells highly sensitive to attack via activated complement proteins (explained in detail below). *Id.* The resultant complement-mediated lysis of blood cells results in anemia, hemoglobinuria, and related symptoms, which impair a patient's quality of life to the extent that "[m]any PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels." Ex. 1001, 1:42–53. As further explained by Petitioner's expert, Dr. Balthasar, "[a]s a result of the destruction of RBCs and the resultant release of free hemoglobin into the blood, `PNH is characterized by hemolytic anemia (a decreased number of red blood cells), hemoglobinuria (the presence of hemoglobin in the urine particularly evident after sleeping), and hemoglobinemia (the presence of hemoglobin in the bloodstream.')" Ex. 1002 ¶ 33 (quoting Ex. 1005 ¶ 7).

"Complement" is a "system of plasma proteins . . . so-named because it complements the activity of antibody in the lysis of bacteria." Ex. 1022 R259; *see generally* Ex. 1001, 7:6–8:56. As part of the immune system, complement "has a central role in host defense against many micro-organisms and in the modulation of inflammatory reactions." *Id.*; *see* Ex. 1002 ¶ 29. The figure below, reproduced at paragraph 30 of the

Balthasar Declaration, shows "the main pathways and components of the complement activation system." Ex. 1022, R259.

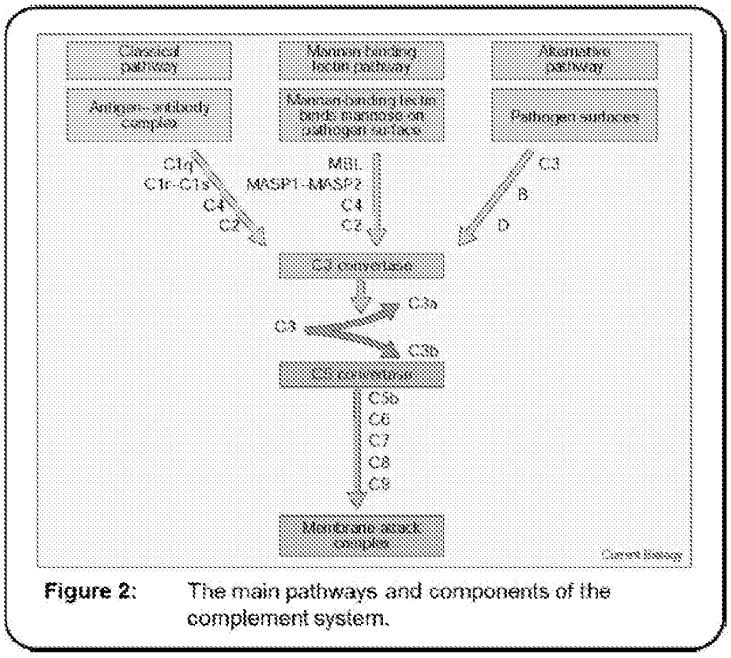


Figure 2: The main pathways and components of the complement system.

The above figure illustrates how various complement proteins are organized into the "classical," "mannan-binding," and "alternative" activation pathways. Ex. 1022, R259; *see* Ex. 1001, 7:17–19. All three pathways lead to the cleavage of C3 convertase and the resultant cleavage of C5 convertase into C5a and C5b. Ex. 1022, Fig. 1; *see* Ex. 1002 ¶ 30. As also summarized in the Balthasar Declaration, cleavage of C5 initiates the terminal complement cascade. Ex. 1002 ¶ 30. Conversely, blocking the cleavage of C5 prevents complement activation. *See, e.g.*, Ex. 1001, 10:57–65 ("U.S. Pat. No. 6,353,245 [Evans][2] teaches an antibody which binds to C5 and

[2] US 6,355,245 B1, issued Mar. 12, 2002 (Ex. 1007).

inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components."); 12:6–10.

According to the Specification of the '880 patent, eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5 convertase and is, thus, intended to suppress the terminal activation cascade and resultant complement activation. Ex. 1001, Abstract, 1:56–57 (citing Thomas C. Thomas et al., *Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single-Chain Fv*, 33(17) MOL. IMMUNOL. 1389–401 (1996) (Ex. 1023, "Thomas")). More specifically, "eculizumab" refers to humanized antibodies derived from mouse antibody 5G1.1, sometimes referred to as "murine 5G1.1" or "m5G1.1." *See* Prelim. Resp. 12–13. The term "humanized" refers to an antibody having a human framework, into which CDR regions from a non-human monoclonal antibody (*e.g.*, mouse) are inserted. Ex. 1007, 5:57–67; Ex. 1002 ¶¶ 27. Accordingly, humanized versions of non-human antibodies may be indicated by the prefix "h" or "hu" as in "h5G1.1" and "hu5G1.1." *See e.g.*, Pet. 11, 13, 14, n.9; Prelim. Resp. 12; Ex. 1002 ¶ 46.

Claim 1 refers to the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 4, which together comprise an eculizumab antibody. *See generally* Prelim. Resp. 1–2. Thus, for example, the '880 patent identifies SEQ ID NO: 2 and SEQ ID NO: 4 as the "Eculizumab Heavy Chain" and "Eculizumab Light Chain," respectively. Ex. 1001, 30:14–31, 39–46 (subject to Certificate of Correction dated October 24, 2017). It is undisputed that SEQ ID NO: 2 encodes a hybrid IgG2/IgG4 heavy chain (i.e., having a genetically engineered heavy chain constant region derived

from portions of IgG2 and IgG4 isotype antibodies). *See, e.g.*, Pet. 3; Prelim. Resp. 14–16; Ex. 1033, 1258 (Figure 2). Eculizumab is the non-proprietary name for Alexion's SOLIRIS product, which was approved by the FDA for treatment of patients with PNH. *See, e.g.,* Prelim. Resp. 1–2, 6–8 (citing Ex. 1033, 1256;[3] Ex. 2005, 1[4]); Pet. 2–3 (citing Ex. 1009, 2); *see also* Prelim. Resp. 16 ("The '880 patent claims recite the complete amino acid sequence for SOLIRIS® . . . the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001 at cols. 31-33, 35.).")

The '880 patent also discusses the conduct and results of the TRIUMPH trial in which 88 red blood cell transfusion dependent PNH patients were randomly assigned to receive either placebo or Eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.). *Id.* at 19:41–28:31.

> Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7± 1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Id. at 20:29–40. The Specification concludes that "[t]he results of the TRIUMPH study indicate that terminal complement inhibition with

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[3] Rother et al., "*Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria,*" 25(11) NATURE BIOTECHNOLOGY 1256–64 (2007).
[4] SOLIRIS Product Label (rev. 3/2007).

eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency." *Id.* at 28:26–31. "[E]culizumab stabilized hemoglobin levels, decreased the need for transfusions, and improved quality of life in PNH patients via reduced intravascular hemolysis." *Id.* at Abstract.

D. Challenged Claims

Petitioner challenges claims 1–3 of the '880 patent, which read as follows:

> 1. A pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a sterile, preservative free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> 2. A pharmaceutical composition comprising an anti-C5 antibody, wherein the anti-C5 antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> 3. The pharmaceutical composition of claim 2, wherein the pharmaceutical composition is a sterile, preservative free 300 mg single-use dosage form.

Ex. 1001, 39:2–16.

E. Asserted Grounds of Unpatentability

Petitioner asserts six grounds of unpatentability (Pet. 22–23):

Ground	Claim(s)	Basis	Asserted Reference(s)
1	2	102(b)[5]	Hillmen[6]
2	2	102(b)	Hill '05[7]
3	1 and 3	103(a)	Hillmen, Bell,[8] and Wang[9]
4	1 and 3	103(a)	Hill '05, Bell, and Wang
5	1–3	103(a)	Bell, Bowdish, [10] Evans, [11] and Wang
6	1–3	103(a)	Bell, Evans, Mueller[12], and Wang

[5] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the `880 patent have an effective filing date before the effective date of the applicable AIA amendments, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103 throughout this Decision.

[6] Hillmen et al., "*Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria,*" 350(6) N. ENGL. J. MED. 552–59 (2004) (Ex. 1004).

[7] Anita Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 BLOOD 2559–65 (2005) (Ex. 1047).

[8] Bell et al., US 2005/0191298 A1, published Sept. 1, 2005 (Ex. 1005).

[9] Wang, US 2005/0271660 Al, published Dec. 8, 2005 (Ex. 1028)

[10] Bowdish et al., US 2003/0232972 A1, published Dec. 18, 2003 (Ex. 1006).

[11] Evans et al., US 6,355,245 B1, issued March 12, 2002 (Ex. 1007).

[12] Mueller et al., WO 97/11971, published April 3, 1997 (Ex. 1008).

In support of its patentability challenges, Petitioner relies on, *inter alia*, the Declaration of Joseph P. Balthasar, Ph.D. Ex. 1002.

F. Overview of Asserted References

1. Overview of Hillmen (Ex. 1004)

Hillmen discloses that "[p]aroxysmal nocturnal hemoglobinuria (PNH) arises from a somatic mutation of the PIG-A gene in a hematopoietic stem cell and the subsequent production of blood cells with a deficiency of surface proteins that protect cells from attack by the complement system." Ex. 1004, 552.

> Patients with PNH have chronic, often disabling symptoms of fatigue and intermittent episodes of dysphagia, abdominal pain, and hemoglobinuria. These symptoms are thought to be related to the intravascular destruction of PNH type III erythrocytes, which are deficient in complement inhibitors, by autologous complement. The hemolytic anemia frequently renders the patients transfusion-dependent. In addition, patients have an extremely high risk of potentially life-threatening thrombosis, particularly thrombosis of the hepatic and cerebral veins. Approximately 50 percent of patients with PNH die of the disease; the median duration of survival after diagnosis is 10 years.

Id. at 557.

Hillmen reports on the efficacy of eculizumab for "reduc[ing] the incidence of intravascular hemolysis, hemoglobinuria, and transfusion requirements in patients with PNH." *Id.* at 553. "Eleven transfusion-dependent patients with PNH received infusions of eculizumab (600mg) every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12." *Id.* at Abstract, *see id.*

at 554. Based on this treatment, Hillmen concludes:

> Eculizumab is safe and well tolerated in patients with PNH. This antibody against terminal complement protein C5 reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion, with an associated improvement in the quality of life in patients with PNH.

Id. at Abstract.

Hillmen characterizes eculizumab as "a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components." *Id.* (citing, e.g., Thomas (Ex. 1023)). According to Hillmen, the antibody "binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b, thereby preventing the release of the inflammatory mediator C5a and the formation of the cytolyticpore C5b-C9." *Id.* Because eculizumab "specifically prevents cleavage of C5, which is necessary for assembly of the membrane-attack complex, "the treatment "presumably prolongs the survival of type III erythrocytes . . . which are highly sensitive to lysis by complement." *Id.* at 557.

2. Overview of Hill '05 (Ex. 1047)

Hill '05 reports the results of a follow up study to Hillmen (reference 2) "to assess the long-term efficacy and safety of patients with PNH." Ex. 1047, 2559. "After completion of an initial 12-week study [described in Hillmen], all patients chose to participate in the 52-week extension study. Eculizumab, administered at 900 mg every 12 to 14 days, was sufficient to completely and consistently block complement activity in all patients." *Id.* at Abstract.

3. Overview of Bell (Ex. 1005)

Bell discloses the treatment of PNH "using a compound which binds to or otherwise blocks the generation and/or activity of one or more complement components . . . . In particularly useful embodiments, the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb (eculizumab), h5G1.1-scFv (pexelizumab) and other functional fragments of h5G1.1." *Id.* ¶ 12; *see also id.* ¶ 52 ("The antibody h5G1.1-mAb is currently undergoing clinical trials under the tradename eculizumab."). Bell further discloses: "Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in [Evans] and [Thomas] . . . the disclosures of which are incorporated herein in their entirety." *Id.* ¶ 52.

As noted by Dr. Balthasar, the data disclosed in Bell overlaps with that in Hillmen, but further includes data on extension studies in which patients continued treatment for paroxysmal nocturnal hemoglobinuria for a total of two additional years. *See* Ex. 1002 ¶ 40 (citations omitted).[13] Briefly, eleven transfusion-dependent PNH patients received weekly 600 mg doses of eculizumab by infusion for four weeks, followed by "900 mg of eculizumab 1 week later[,] then 900 mg on a bi-weekly basis." Ex. 1005

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[13] Page 37, footnote 16, of the Petition states: "Because the clinical study taught in Bell is the same C02-001 study disclosed in Hillmen, which discloses the eculizumab amino acid sequences of SEQ ID NOs: 2 and 4, Bell, too, therefore anticipates claims 1–4 and 7–10 for the same reasons discussed above for Hillmen." Despite this assertion, Petitioner's sole anticipation-based Grounds in this IPR are based on Hillmen (Ground 1) and Hill '05 (Ground 2). *See* Pet. 22–23.

¶¶ 81–82. Bell characterizes the first twelve weeks of treatment as a "pilot study." *Id.* ¶ 82. "Following completion of the initial acute phase twelve week study, all patients participated in an extension study conducted to a total of 64 weeks. Ten of the eleven patients participated in an extension study conducted to a total of two years." *Id.* Bell concludes that "[p]atients in the two year study experienced a reduction in adverse symptoms associated with PNH. *Id.* ¶¶ 82, 96.

4. Overview of Wang (Ex. 1028)

Wang discloses formulations of eculizumab suitable for nebulization and pulmonary delivery. *See, e.g.*, ¶¶ 25, 62, 67. Wang discloses formulations comprising from 1 to 30 mg/ml eculizumab, and provides evidence that a formulation having 30 mg/ml eculizumab can be effectively and efficiently delivered using a conventional nebulizer. *Id.* ¶¶ 171–173, Fig. 10.

5. Overview of Bowdish (Ex. 1006)

Bowdish discloses "[i]mmunoglobulins or fragments thereof hav[ing] a peptide of interest inserted into a complementarity determining region (CDR) of an antibody molecule," whereupon, "[t]he antibody molecule serves as a scaffold for presentation of the peptide and confers upon the peptide enhanced stability." Ex. 1006 ¶ 6. In certain "embodiments, the peptide replacing the amino acids of a CDR is an agonist TPO [thrombopoeitin] peptide." *Id.* ¶17.

In Example 4, Bowdish describes a TPO mimetic peptide graft into the heavy chain CDR3 of antibody framework 5G1.1, described in Evans,

which it incorporates by reference. *Id.* ¶¶ 191–193. According to Bowdish:

> Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated herein by reference.[14] The sequence was cloned into 5G1.1 in such a fashion as to replace the native CDR3 . . . [wherein t]he peptide graft translated into amino acids is Leu Pro Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Arg Ala Pro Val (SEQ. ID. NO: 66). The 5G1+peptide was produced as a whole IgG antibody (See FIGS. 13A and 13B).

Id. ¶ 191. "Purified 5G1.1+peptide antibody as well as the parental 5G1.1 were analyzed for their ability to bind to cMp1 receptor by FACS analysis." *Id.* ¶ 192.

In SEQ ID NOs: 69 and 70, respectively, Bowdish discloses the amino acid and nucleotide sequences for the "5G1.1 Light Chain." In SEQ ID NO: 67, Bowdish discloses the amino acid sequence of the "5G1.1–TPO Heavy Chain," with the substituted TPO mimetic sequence marked in bold. An excerpt of that sequence showing the amino acids of the TPO substitution in bold reads: DTAVYYCAR**LPIEGPTLRQWLAARAPV** WGQGTLVTVSS. Bowdish discloses the corresponding nucleotide sequence in SEQ ID NO: 68.

6. Overview of Evans (Ex. 1007)

Evans discloses anti-C5 antibodies useful in the treatment of glomerulonephritis (GN). Ex. 1007, Abstract. Evans' Example 7 describes the isolation anti-C5 monoclonal antibodies from mouse hybridoma designated 5G1.1. *Id.* at 37:34–39:30. In Figures 18 and 19, respectively,

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[14] U.S. Application. Ser. No. 08/487,283 matured into U.S. Patent No. 6,355,245 B1, referenced herein as Evans (Ex. 1007).

Evans discloses the amino acid sequence of the light and heavy chain variable regions of mouse antibody 5G1.1, with "[t]he complementarity determining region (CDR) residues according to the sequence variability definition or according to the structural variability definition . . . [bolded] and [underlined], respectively." *Id.* at 9:65–10:20. A representation of an excerpt of the heavy chain sequence showing the amino acids of CDR3 so marked reads: DSAVYYCAR**YFFGSSPNWYFDV**WGAGTTVTVSS.

Evans describes making a series of different humanized 5G1.1 scFv[15] and full-length antibodies containing the CDR regions from the murine 5G1.1 antibody. Ex. 1007, 37:35–39:30, 42:59–45:33. With respect to the former, Evans discloses that "[p]articularly preferred constant regions . . . are IgG constant regions, which may be unaltered, or constructed of a mixture of constant domains from IgGs of various subtypes, e.g., IgG1 and IgG4." *Id.* at 45:29–33.

In Example 11, Evans discloses steps in the humanization of mouse antibody 5G1.1, including the construction of recombinant antibody, 5G1.1 scFv CO12. *Id.* at 42:59–45:33. According to Dr. Balthasar, the construct "5G1.1 scFv CO12" contains all six 5G1.1 CDR regions and its sequence aligns perfectly with the eculizumab variable regions claimed by the '880 patent." Ex. 1002 ¶ 55 (comparing portions of SEQ ID NO: 2 of the '880 patent with portions of Evans' SEQ ID NO: 2). Dr. Balthasar's Figure 6, for

[15] As Dr. Balthasar notes, "a scFv comprises an antibody's light and heavy chain variable domains connected by a linker." Ex. 1002 ¶ 54, n.4 (citing Ex. 1007, 6:39-41).

example, shows that both sequences contain the larger of the two overlapping amino acid sequences Evans identifies as CDR3, YFFGSSPNWYFDV. *Id.*

7. Overview of Mueller (Ex. 1008)

Mueller discloses "[a]ntibodies to porcine P-selecting protein, porcine VCAM protein and porcine CD86 protein are useful for diagnosing human rejection of porcine xenotransplants and for improving xenotransplantation of porcine, cells, tissues and organs into human recipients." Ex. 1008, Abstract. According to Mueller, one object of the invention is to provide antibody molecules that neither activate complement nor bind to the FC receptor. *Id.* at 7:28–31. To achieve these and other goals, Mueller points to "[r]ecombinant (chimeric and/or humanized) antibody molecules comprising the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4, such antibodies being referred to hereinafter as `HuG2/G4 mAb.'" *Id.* at 8:23–26. Mueller developed and tested "chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4." *Id.* at 12:19–33. As controls for these experiments, Mueller used "a humanized antibody directed against human C5 (h5G1.1 C012 HuG4 mAb)." *Id.* at 11:34–12:4. 12:34–13:2, Figures 11, 12, 15. On pages 58–61 of the reference, Mueller discloses the cDNA and amino acid sequence of "Human G2/G4."

II. ANALYSIS

A. Principles of Law

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). This "single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). "Under the principles of inherency, if the prior art necessarily . . . includes[ ] the claimed limitations, it anticipates." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). Similarly, "[a] reference anticipates a claim if it discloses the claimed invention `such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (internal citation and emphasis omitted). Moreover, "it is proper to

take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826 (CCPA 1968); *see Eli Lilly v. Los Angeles Biomedical Res. Inst.*, 849 F.3d 1073, 1074–75 (Fed. Cir. 2017).

A claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which that subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan

would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotations and citations omitted).

B. Person of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *Custom Accessories, Inc. v. Jeffrey-Allan Indus. Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

Petitioner contends that a person of ordinary skill in the art as of the relevant date would have had an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in the field. Pet. 21–22. Patent Owner does not dispute this definition, but suggests that we interpret the relevant field as directed to engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry. *See* Prelim. Resp. 43 (emphasis omitted); *see also id.* (arguing that Petitioner cannot prove unpatentability of the challenged claims under either party's definition).

Considering that each of the asserted references (discussed *infra*) is substantially directed to the development of monoclonal antibodies for the

treatment or diagnosis of human disease, Patent Owner's proposed clarification provides useful context. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). Accordingly, we define one of ordinary skill in the art as a person with an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry. Our decision whether to institute, however, does not turn on which party's definition of the skilled artisan is used, and our determinations would be unchanged if we applied Petitioner's definition.

C. Claim Construction

Based on the filing date of the Petition (Feb. 28, 2019), the Board interprets claim terms in an *inter partes* review ("IPR") using the same claim construction standard that is used to construe claims in a civil action in federal district court. *See* 83 Fed. Reg. 51,340 (Nov. 13, 2018) (to be codified at 37 C.F.R. pt. 42).

In construing claims, district courts give claims their ordinary and customary meaning, which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). Sources for claim interpretation include "the words of the claims themselves, the remainder of the specification, the prosecution history [i.e., the intrinsic

evidence], and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "[T]he claims themselves [may] provide substantial guidance as to the meaning of particular claim terms." *Id.* However, the claims "do not stand alone," but are part of "a fully integrated written instrument,' consisting principally of a specification that concludes with the claims," and, therefore, the claims are "read in view of the specification." *Id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995)).

Neither party requests the construction of any claim term. *See, e.g.*, Pet. 21 (citing Ex. 1002 ¶ 64). At this stage in the proceeding, we need only construe the claims to the extent necessary to determine whether to institute *inter partes* review. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms `that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))). At this stage in the proceeding we find it unnecessary to construe the language of any challenged claim because the claim language is readily understandable on its face, within the context of the claims, to the person of ordinary skill in the art.

With this understanding of the claims, as well as the legal principles and our understanding of the definition of the skilled artisan as set forth above in mind, we address the parties' positions below.

D. Anticipation by Hillmen (Ground 1)

In Ground 1, Petitioner challenges claim 2 as anticipated by Hillmen. Pet. 25–31. Patent Owner opposes. Prelim. Resp. 44–51.

1. The Parties' Contentions

Petitioner contends "Hillmen discloses all the limitations of claim 2, either expressly or inherently, and is enabling." Pet. 25 (citing Ex. 1002 ¶¶ 73–81). In particular, Petitioner argues that "Hillmen expressly disclosed a `pharmaceutical composition comprising an antibody that binds C5' as claimed because Hillmen disclosed administering infusion of *eculizumab* formulations to patients, and eculizumab was a known antibody that binds C5. *Id.* at 26–27 (citing Ex. 1004, Abstract). But, with respect to that amino acid sequence of the claimed heavy and light chains, Petitioner contends "Hillmen's antibody necessarily `comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4' because Alexion admitted that Hillmen's eculizumab possesses those very amino acid sequences." *Id.* at 26–27. In particular, Petitioner argues that:

> During prosecution, Alexion submitted a list of eculizumab clinical studies – including Hillmen's Phase 2 Pilot Study (Study "C02-001") – and stated that "the antibody (eculizumab) used in each of the studies – *contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4*." AMG1014, 767(¶6); *see also, id.*, 765 (study number "C02-001").

Id. at 26.

Although Petitioner does not argue that Hillmen literally and expressly disclosed the claimed antibody structure with SEQ ID NOs: 2 and 4 (it does not), Petitioner's position is that, because Hillmen disclosed a trial

of the SOLIRIS eculizumab antibody, and because Patent Owner conceded that the eculizumab antibody used is the same anti-C5 antibody as claimed, that Hillmen inherently discloses the claimed sequences. Pet. 27–29 (citing *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004)).

Petitioner's inherency rationale, based on "the general knowledge in the relevant field" (*id.* at 30), is summarized as follows. Contemporaneous with Hillmen's disclosure, the skilled artisan would have known that Bowdish disclosed the entire amino acid sequence of eculizumab, but for a heavy chain CDR3 region, which Bowdish disclosed as substituted with a TPO (thrombopoietin) amino acid sequence; the skilled artisan, however, would have known that Evans disclosed the amino acid sequences of eculizumab's heavy and light chain variable domains, including heavy chain CDR3 region absent from Bowdish; alternatively, the skilled artisan would have understood that Mueller disclosed the hybrid IgG2/IgG4 heavy chain and light chain constant domains of eculizumab, whereas Evans disclosed the respective variable domains. Pet. 29–31 (citing Ex. 1004, 553–554; Ex. 1006 ¶¶ 191–193, Figs. 13A, 13B; Ex 1007, 44:4–13; Ex. 1008, 52–53, 58–61; Ex. 1002 ¶¶ 60, 78–80). With this knowledge in hand, the skilled artisan would have known that Hillman discloses a method of treatment using eculizumab – which was necessarily the claimed anti-C5 antibody with the claimed SEQ ID NOs: 2 and 4. *Id.*

Petitioner also appears to argue that Hillmen inherently discloses the hybrid IgG2/IgG4 heavy chain portion of SEQ ID NO: 2, because one of ordinary skill in the art would have known that eculizumab contains this structure. Pet. 13 (citing Ex. 1034, 1279; Ex. 1049, 838–839; Ex. 1002

¶¶ 47–50). Petitioner argues, for example, that Tacken explicitly describes eculizumab as "containing an `*IgG2/IgG4 constant region*.' " *Id.* at 13–14 (quoting Ex. 1034, 1279); *see, e.g.*, Ex. 1002 ¶ 47 ("Tacken confirms that eculizumab contains a hybrid IgG2/IgG4 constant region. AMG1034, 1278-1279. Tacken describes using `h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals)' containing an `IgG2/IgG4 constant region.' AMG1034, 1279.").

Petitioner also relies on statements made by Patent Owner before the examiner during prosecution of U.S. Patent Application Ser. No. 11/127,438, where, in arguing that disclosures upon which the applicant relied for priority were supportive of the then-pending claims, Alexion stated:

> Applicant respectfully disagrees and asserts that the priority applications provide ample written support for the claimed descriptions. For example, the priority documents each describe that "Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-scFv and functional fragments of h5G1.1 are *described in U.S. Patent No. 6,355,245* [Evans], the disclosures of which are incorporated herein in their entirely [*sic*] by this reference . . . Applicant submits that h5G1.1 . . . [was] *well-known to one of ordinary skill in the art as eculizumab* . . . at the time of filing of priority applications.

See Pet. 10 (quoting Ex. 1049, 838–39 (emphasis Petitioner's)). Thus, Petitioner argues, Alexion represented to the Patent Office that the antibody structure disclosed in Evans was well-known to the skilled artisan so that such a person of skill would have considered this structure to be the eculizumab in Hillmen, and which was publically disclosed before the March 15, 2007 priority date of the '880 patent.

Patent Owner takes the position that "[p]rior to March 15, 2007, the priority date of the '880 patent, the unique amino acid sequence of SOLIRIS® was not publicly known or disclosed in the prior art." Prelim. Resp. 1.

> If a POSA were searching for the sequence of "eculizumab" as described in the art, the literature as of March 15, 2007 identified an amino acid sequence and corresponding structure that is very different from what the '804 patent claims. In particular, publications describing the safety, efficacy, and clinically relevant biological activity of "eculizumab" consistently directed a POSA to the 1996 "Thomas" publication (AMG1023) for the structure and design of the antibody, which in turn described a humanized antibody constructed with a naturally-occurring "IgG4" heavy chain constant region. The claimed antibody of the '880 patent has a very different, uniquely engineered, non-naturally occurring constant region that was nowhere described in Thomas or the prior art literature showing the safety and efficacy of "eculizumab."

Id. at 2–3 (emphasis omitted).

It is Patent Owner's position that, reading Hillmen's disclosure of "eculizumab" and Hillmen's reference to Thomas, the skilled artisan would not have been directed to the version of eculizumab encompassed by the challenged claims, but would have understood Hillmen to refer to Thomas's disclosed eculizumab, which is an IgG4 isotype antibody and does not have the hybrid IgG2/IgG4 heavy chain sequence as described in SEQ ID NO: 2. *Id.* at 3, 11–13 (referencing Ex. 1023 (Thomas)). In particular, Patent Owner notes that Hillmen cites Thomas as *the* reference for eculizumab. *Id.* at 3, 12 (citing Ex. 1004, 533 (which cites Ex. 1023 as reference "15")).

> Thomas . . . described the design and testing of a humanized anti-C5 antibody (termed "humanized 5G1.1" or "h5G1.1") featuring

> an "IgG4" heavy chain constant region, which was selected because the IgG4 isotype was thought to avoid activating human complement. (AMG1023 at 1396, 1399.) Thomas reported data showing that the IgG4 humanized antibody had suitable affinity and specificity, and was as effective as the original mouse antibody (termed "murine 5G1.1" or "m5G1.1") in an *in vitro* assay showing activity blocking C5 cleavage and preventing lysis of blood cells due to complement activity. (AMG1023 at 1396.)

Id. at 12–13 (emphasis omitted).

Patent Owner states that "[t]oday, but *not* prior to the March 15, 2007 priority date for the '880 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in the claims of the '880 patent, namely, `a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'" *Id.* at 15. Patent Owner argues that, as of the critical date, Hillmen did not

> enable[ ] a POSA to make and use the specific antibody recited in claims 1-3 and 7-10 without undue experimentation, because Hillmen guided a POSA as of March 15, 2007 to make and use a very different antibody – the ***IgG4*** isotype antibody of Thomas. *See, e.g.*, *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (for a reference to anticipate, "[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation").

Id. at 45. Patent Owner further argues that

> [t]he mere naming of an investigational product (*e.g.*, "eculizumab") in a prior art publication does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product (*i.e.*, SEQ ID NOs: 2 and 4), if a POSA could not have ***necessarily*** determined the later claimed structure/composition from the information publicly available as

of the priority date.

Id. at 47 (citing *Endo Pharm. Solutions, Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378–83 (Fed. Cir. 2018)).

2. Analysis

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has not carried its burden to show a reasonable likelihood of anticipation of claim 2 of the '880 patent under Ground 1.

Petitioner concedes Hillmen does not expressly disclose the claimed antibody; instead, Petitioner relies on the doctrine of inherency and a post-priority-date admission by Patent Owner that the pharmaceutical (eculizumab) referenced in Hillmen was actually the claimed antibody.

Hillmen "tested the clinical efficacy of eculizumab, a humanized antibody that inhibits the activation of terminal complement components, in patients with PNH." Ex. 1004, 552. Hillmen teaches that "[e]culizumab is a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components.[14,15] It binds specifically to the terminal complement protein C5." *Id.* at 553. Citation "14" of Hillmen refers to Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 NATURE 323–27 (1988). This reference is not an exhibit in this proceeding and Petitioner does not suggest that it mentions eculizumab. Citation "15" of Hillmen refers to Thomas (Ex. 1023), which discloses a monoclonal antibody (5G1.1) that recognizes the human complement protein C5, which was shown to effectively block C5 cleavage. *See* Ex. 1023, 1389.

Thomas discloses the process of developing a humanized antibody (h5G1.1 HuG4) for human C5. Thomas summarizes this work in a section

titled "*Construction of a humanized h5G1.1 antibody*":

> Having demonstrated the effective humanization of the 5G1.1 variable regions, an intact humanized antibody (IgG4 isotype) was constructed and produced in 293-EBNA cells. The avidity of this humanized antibody (h5G1.1 HuG4) for human C5, was compared to the murine 5G1.1 mAb by determining the ability of each to compete binding of biotinylated 5G1.1 mAb to C5 (Fig. 9). The humanized h5G1.1 mAb had a two-fold lower avidity than the murine antibody. However, the humanized h5G1.1 HuG4 antibody was equipotent with the murine antibody at protecting PAEC from lysis by human serum, with a 0.5-fold molar ratio of antibody to C5 (1:1 ratio of antibody binding sites to C5) completely inhibiting lysis of the PAEC (Fig. 10).

Id. at 1396.[16] We find nothing in Thomas that expressly discloses or alludes to a hybrid IgG2/IgG4 antibody. *See generally* Ex. 1023.

We also consider Dr. Balthasar's assertion that one of ordinary skill in the art "would have known that eculizumab contains a hybrid IgG2/IgG4 heavy chain constant region" because Tacken "describes using `h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals)' containing an `IgG2/IgG4 constant region.'" Ex. 1002 ¶ 47 (citing Ex. 1034, 1279).

In addressing this assertion, Patent Owner takes the position that Tacken (also addressed in the context of Petitioner's obviousness challenges) is non-analogous art because it "does not involve the same field as the '880 patent, and would not have been reasonably pertinent to the

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[16] We note Patent Owner's argument that as of the '880 patent's priority date, many other references cited Thomas when referring to eculizumab. *See* Prelim. Resp. 23–26, Table 1. Without going into detail, we find Patent Owner has accurately shown how other, contemporaneous prior art references cited Thomas for this purpose.

particular problem addressed by the '880 patent. Prelim. Resp. 36–37; Sur-Reply 2–3. On the present record, we do not find Patent Owner's argument persuasive. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (mere lawyer's arguments and conclusory statements that are unsupported by factual evidence are entitled to little probative value).

Prior art is analogous if it is from the same field of endeavor or if it is reasonably pertinent to the particular problem the inventor is trying to solve. *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1335 (Fed. Cir. 2015). In the present case, Tacken discloses the development of a humanized antibody, hD1V1G2/G4 (hD1), directed against the C-type lectin DC-specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN) to explore its capacity to serve as a target receptor for vaccination purposes. Ex. 1034, Abstract. Given Patent Owner's position that the relevant field of the '880 patent encompasses the "engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry" (*see* Section II(B), above), Tacken's development of the monoclonal antibody hD1V1G2/G4 (hD1) "for vaccination purposes" appears to be in the same field of endeavor as the invention of the '880 patent. Moreover, because Tacken's antibodies employ the same IgG2/IgG4 constant region as SEQ ID NO: 2 of the asserted claims, we are unconvinced that Tacken is not reasonably pertinent to the '880 patent.

With reference to its hD1V1G2/G4 (hD1) antibody, Tacken discloses that, "[a]n isotype control antibody, h5G1.1-mAb (5G1.1, eculizumab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5." Ex. 1034, 1279.

Although, as Patent Owner points out, Tacken then cites to Thomas, Patent Owner does not address why Tacken would use an eculizumab having the IgG4 constant region as set forth in Thomas as "[a]n isotype control antibody" for one having an IgG2/IgG4 constant region. Dr. Balthasar, however, testifies that Tacken also cites Mueller II[17] "as providing information about the hybrid IgG2/IgG4 constant region portion of eculizumab." Ex. 1002 ¶ 56 (citations omitted); *see* Ex. 1034, 1279 (indicating that in the construction of hD1V1G2/G4 (hD1), "humanized variable heavy and variable light regions were [] genetically fused with a human hybrid IgG2/IgG4 constant domain," as set forth in Mueller II (reference 17)). On the present record, we read Tacken as disclosing that humanized monoclonal antibody 5G1.1, known as eculizumab, encompasses a molecule having a hybrid IgG2/IgG4 constant domain.

That Tacken, Bowdish, and Mueller suggest that eculizumab may include an IgG2/IgG4 constant domain, however, does not necessarily lead to the conclusion that Hillmen discloses the same molecule. Rather, the present record indicates that "eculizumab" is not a single chemical entity. To the contrary, the art identified as "eculizumab" at least two such compounds that differed in the heavy chain constant region: one having the IgG4 isotype (as evidenced in Thomas), and a second having a hybrid IgG2/IgG4 isotype (as evidenced by, e.g., Tacken).

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[17] John P. Mueller et al., *Humanized porcine VCAM-specific monoclonal antibodies with chimeric IgG2/G4 constant regions block human leukocyte binding to porcine endothelial cells*, 34 Mol. Immunol. 441–52 (1997) (Ex. 1031).

Patent Owner made the above dichotomy explicit in an official representation to the Patent Office. During Alexion's prosecution of Application No. 11/127,438, an application outside of the chain of priority of the '880 patent, but claiming the use of eculizumab for the treatment of pulmonary conditions, the Examiner took the position that "the description of `eculizumab or pexelizumab' as well as `the mutated Fc portions' in the priority documents is not readily apparent." Ex. 1049, 741, 830–834 (representative claim amendments). In response, Alexion asserted that

> **eculizumab was first constructed in the IgG4 isotype**, see, e.g., the bridging paragraph of the left and right columns of page 1396 of Thomas et al. (1996) [Ex. 1023], . . . **and then into the G2/G4 format**, see Mueller et al. (1997) *Molecular Immunology,* Vol. 34, No.6, pages 441-452 [Ex. 1031], . . . while **in either form** the h5G1.1 antibody was well known to be incapable to activate human complement, see, e.g., the right column, lines 27-28, of page 1399 of Thomas et al., 1996, *Id.*, and the bridging paragraphs of pages 446 to 448 and 450 to 451 of Mueller et al, 1997, *Id.* Thus, Applicant submits that it was well-known to one of ordinary skill in the art at the time of filing of priority applications that eculizumab has a G2/G4 Fc portion, i.e., a mutated Fe portion.

Id. at 838–839 (bolding added). Alexion's statement, above, supports both Thomas's disclosure of eculizumab in the IgG4 isotype as the first construction of eculizumab, as well as an understanding that "eculizumab" referred to and refers to a genus of antibodies, including one with the hybrid IgG2/IgG4 isotype of the challenged claims. Accordingly, in view of the record before us, we conclude that "eculizumab" referred to and refers to a class or category of anti-C5 antibodies, also called 5G1.1 or h5G1.1 mAbs.

Upon considering the facts here in view of Petitioner's reliance on *Crish*, 393 F.3d 1253, and Patent Owner's reliance on *Endo Pharms.*, 894 F.3d 1374, we find the latter case analogous here. In *Crish*, the Federal Circuit found that a claim to the nucleotide sequence of the hINV gene promoter region was inherently disclosed by prior art that "specifically identified [the promoter region] by size and location" because "[t]he starting material plasmid necessarily contain[ed] the gene of interest, including the promoter region." *Crish*, 393 F.3d at 1257–59. Here, however, Hillmen does not "specifically identify" an eculizumab antibody containing the hybrid IgG2/IgG4 sequence of SEQ ID NO: 2, as required by claim 2.

Endo Pharms. compels a different result under the facts here. In *Endo Pharms.*, the issue was again inherency (in the context of obviousness) where prior art scientific articles described clinical trials for a testosterone undecanoate composition, but did not disclose its specific, and later claimed, formulation including a particular mixture of castor oil and benzyl benzoate. *Endo Pharms.*, 894 F.3d at 1278. It was later confirmed that the composition of the clinical trials described in the prior art articles did, indeed, have the claimed mixture of castor oil and benzyl benzoate. *Id.* The Federal Circuit held that because it was not demonstrated that a skilled artisan could extrapolate the vehicle formulation (a mixture of castor oil and benzyl benzoate) used in the prior art articles based on reported pharmacokinetic performance data, such performance could not have only been attributed to the claimed formulation and the generic disclosure of the pharmaceutical formulation in the prior art did not inherently disclose the claimed formulation. *Id.* at 1281–83. Furthermore, *Endo Pharms.*

distinguished *Crish* because it was about the inherent properties of a known prior art product, rather than a product that was named, but not known or determinable based on the prior art disclosure of its performance characteristics. *Id.* at 1383.

In Ground 1, the asserted prior art reference, Hillmen, discloses a clinical trial of "eculizumab," but does not otherwise identify the structure of the antibody tested, other than by referencing Thomas. Ex. 1004, 552, 553 (citing Ex. 1023). Thomas discloses a version of eculizumab different from that claimed (an IgG4 isotype rather than a hybrid IgG2/IgG4 antibody). Even accepting that a skilled artisan would have known of a hybrid IgG2/IgG4 antibody, as claimed (*see, e.g.*, Ex. 1002 ¶ 13), Hillmen's mere reference to "eculizumab" would have at least invoked a molecule having the IgG4 isotype taught in Thomas. Thus, Hillmen's disclosure of "eculizumab" would not have necessarily led the skilled artisan to the claimed antibody with "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." Moreover, none of the record references teaching or suggesting an IgG2/IgG4 isotype (e.g., Bowdish, Evans, Tacken, Mueller, or Mueller II) is cited in Hillmen. *See* Ex. 1004, 559. We disagree with Petitioner's position that such references' teaching would have somehow overridden Hillmen's direct invocation of Thomas's disclosure of eculizumab so as to point the skilled artisan to some alternative antibody structure.[18] Accordingly, under *Endo Pharms.*, as discussed above, there is no inherent anticipation of claim 2 by Hillmen.

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[18] We need not address here Patent Owner's non-trivial argument that

To summarize, based on the preliminary record before us, as of the '880 patent's priority date, one of ordinary skill understood that eculizumab encompassed molecules of both IgG4 and IgG2/IgG4 isotypes, and a plain reading of Hillmen suggests that it specifies the former. Accordingly, one of ordinary skill in the art would not have necessarily understood Hillmen to disclose a version of eculizumab having the IgG2/IgG4 heavy chain constant region of SEQ ID NO: 2. For the above reasons, Petitioner has not demonstrated a reasonable likelihood that claim 2 of the '880 patent, is unpatentable under Ground 1.

E. Anticipation by Hill '05 (Ground 2)

In Ground 2, Petitioner challenges claim 2 as anticipated by Hillmen. Pet. 31–36. Patent Owner opposes. Prelim. Resp. 44–51.

1. The Parties' Contentions

In section I.F(2), above, we noted that Hill '05 reports on an extension of the clinical trial disclosed in Hillmen (discussed in part (1) of this same section). Petitioner's Ground 2 is, similarly, an extension of Ground 1 and relies on substantially the same or similar facts and bases in law. *See* Pet. 31–36. Petitioner argues "[a]s in Ground 1, the law also compels finding anticipation in Ground 2." *Id.* at 35 (again citing, *inter alia*, *Crish*, 393 F.3d at 1258).

Petitioner "has improperly attempted to shoehorn" the obviousness arguments of Grounds 5 and 6 into its anticipation contentions. Prelim. Resp. 45–46.

Petitioner contends, "Hill '05 is an Alexion publication describing results from a one-year extension study involving the same 11 patients enrolled in the Hillmen Phase 2 Pilot Study." Pet. 33 (citing Ex. 1047, 2559–60). Petitioner argues Hill '05, like Hillmen, is directed to and discloses administering "eculizumab" to such patients. *Id.* (citing Ex. 1047, 2565). Petitioner's rationale for Hill '05's anticipation of claim 2 is essentially the same as discussed above for Hillmen, only replacing Hillmen's generic disclosure for "eculizumab" with Hill '05's generic disclosure for "eculizumab," paired with the same identified admissions by Patent Owner during prosecution and the same contentions that Bowdish, Evans, and Mueller, rather than Thomas, would be the skilled artisan's basis for the structure of eculizumab. *See* Pet. 31–35 (citing Ex. 1015, 736, 783; Ex. 1047, abstract, 2559–60; Ex. 1002 ¶¶ 82–92; Ex. 1004, abstract, 554; Ex. 1042, Abstract; Ex. 1011, abstract; Ex. 1005 ¶¶ 81–96; Ex. 1012, abstract, 1235; Ex. 1013, abstract; Ex. 1006 ¶¶ 191–193, Figs. 13A, 13B; Ex. 1007, 44:4–13; Ex. 1008, 52–53, 58–61).

Patent Owner argued Grounds 1 and 2 together and, thus, makes essentially the same arguments over Ground 2 as discussed above regarding Ground 1. *See* Prelim. Resp. 44–51.

2. Analysis

At this stage in the proceedings and for the reasons discussed in section II.D above and as set forth below, we find Petitioner has not carried its burden to show a reasonable likelihood of anticipation of claim 2 under Ground 2.

Upon reviewing Hill '05, we find its disclosure to be no more specific or enlightening as to the structure of eculizumab than that of Hillmen. *See generally* Ex. 1047. Hill '05 states, "[w]e previously reported the outcome of an open-label study of eculizumab in patients with PNH.[2]" Ex. 1047, 2559 (reference "2" is Hillmen (Ex. 1004)). Hill '05 further states, "[e]culizumab is a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage.[9]" *Id.* (reference "9" is Thomas (Ex. 1023)). Thus, Hill '05, like Hillmen, invokes Thomas as a reference for eculizumab.

For the same reasons discussed above regarding Ground 1, based on the evidence presented at this stage in the proceedings, Petitioner has not shown that there is reasonable likelihood that claim 2 of the '880 patent is anticipated by Hill '05 under Ground 2.

F. Obviousness in view of Hillmen or Hill '05, combined with Bell and Wang (Grounds 3 and 4)

In Grounds 3 and 4, Petitioner challenges claims 1 and 3 as obvious in view of the combination of Hillmen, Bell, and Wang, and the combination of Hill '05, Bell, and Wang, respectively. Pet. 36–46. Patent Owner opposes. Prelim. Resp. 50–53. Pertinent to each of Grounds 3 and 4, as well as Grounds 5 and6, we address Patent Owner's secondary considerations evidence in section II(I), below.

1. The Parties' Contentions

For Ground 3, Petitioner states: "Bell disclosed a Phase 2 Pilot Study involving 11 PNH patients treated with eculizumab over a period of 12 weeks" identical to that disclosed in Hillmen. . . . Given the substantial

overlap, a POSA would have had ample reason to combine Hillmen and Bell, with a reasonable expectation of success at achieving the claimed subject matter." Pet. 36–37 (citations omitted). With respect to Ground 4, which substitutes Hill '105 for Hillmen, Petitioner again applies essentially "the same reasons discussed above in Ground 3. *See* Pet 44–46; Ex. 1002 ¶¶ 115–120.

Responding to these contentions, Patent Owner notes that, "Grounds 3 and 4 rely upon Hillmen or Hill, respectively, as the sole prior art allegedly disclosing the claimed element of an antibody comprising 'a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4' in claims 1 and 3 of the '880 patent," but "neither Hillmen nor Hill disclosed the claimed antibody sequence either expressly or inherently." Prelim. Resp. 51. Patent Owner's point is well taken.

2. Analysis

As discussed in Sections II(D)(2) and II(E)(2) above, Petitioner has not established that Hillmen or Hill '105 inherently disclose the IgG2/IgG4 heavy chain constant region of SEQ ID No. 2, and the Petition sets forth no additional argument on that subject in support of Grounds 3 and 4. Petitioner also does not argue, nor do we discern, that the required sequence is taught in Bell or Wang. Accordingly, Petitioner has not demonstrated a reasonable likelihood that claims 1 and 3 are unpatentable over the combinations of Hillmen, Hill '10-5, Bell, and Wang set forth in Grounds 3 and 4.

G. Obviousness in view of Bell, Bowdish, Evans, and Wang (Ground 5)

In Ground 5, Petitioner challenges claims 1–3 as obvious over the combination of Bell, Bowdish, Evans, and Wang. Pet. 46–58. Patent Owner opposes. Prelim. Resp. 54–58. For the purpose of determining whether or not to institute inter partes review, we focus on claim 2.[19]

1. The Parties' Contentions

With respect to Ground 5, Petitioner contends that Bell and Wang taught all limitations of the challenged claims but for eculizumab's amino acid sequence. Pet. 45–46. Petitioner argues that one of ordinary skill in the art would have looked to Bowdish and Evans to obtain the amino acid sequence of eculizumab. *See* Pet. 580–55.

Petitioner contends that the skilled artisan would have looked to Bowdish for the light chain and most of the heavy chain sequences of eculizumab in light of Bowdish's use of an "anti-C5 antibody as the starter `scaffold' antibody sequence for creating a recombinant TPO-mimetic" antibody. Pet. 50; Ex. 1002 ¶¶ 140–145. According to Petitioner, "Bowdish provided the full antibody amino acid sequence except for the heavy chain CDR3 (HCDR3) sequence, which was replaced with the TPO-mimetic peptide sequence (LPIEGPTLRQWLAARAPV)." *Id.* (citing Ex. 1006 ¶¶

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[19] In addition to challenging Petitioner's positions with respect to claim 2, Patent Owner also raises non-trivial arguments in response to Petitioner's arguments regarding claims 1 and 3, which we need not address at this stage of the proceeding. *See* Pet. 41–50, 58–59; Prelim. Resp. 5–6, 42–43, 53, 58, 60.

191–193, Figs. 13A (SEQ ID NO: 67; "5G1.1 –TPO Heavy Chain (Bold Denotes TPO mimetic) Amino acid sequence"), 13B (SEQ ID NO: 69; "5G1.1 Light Chain Amino Acid Sequence"); Ex. 1002 ¶¶ 140–145). In particular, Petitioner argues:

> A POSA . . .would have understood that the only portion of the only portion of the heavy chain sequence missing from Bowdish is the HCDR3 sequence because Bowdish taught that "[t]he TPO mimetic peptide graft in Fab clone X4b has been *transplanted into the heavy chain CDR3* of another antibody framework, *5G1.1* . . . The sequence was *cloned into 5G1.1* in such a fashion as to *replace the native CDR3*."

Pet. 50 (citing Ex. 1006 ¶ 191; Ex. 1002 ¶ 144–150 (emphasis Petitioner's)).

Petitioner further argues that to obtain the CDR3 sequence missing from Bowdish, one of ordinary skill in the art would have looked to Evans "because both Bell and Bowdish explicitly direct the artisan there for information on how the h5G1.1 antibody was originally created." *Id.* at 53 (citing Ex. 1002 ¶ 142; Ex. 1006 ¶ 191. Alternatively, Petitioner argues, one of ordinary skill in the art would have readily identified the entire IgG2/IgG4 heavy chain sequence from Bowdish alone, because Bowdish and Bell expressly cite and "incorporate[] by reference Evans for making eculizumab." *Id.* at 5 & n.2, 15, 53; Ex. 1006 ¶ 191; Ex. 1005 ¶ 52; Ex. 1002 ¶¶ 145–147.

According to Petitioner, "a POSA would have understood that *each* of the 5G1.1 antibody heavy chain variable regions in Evans contain *the same CDR3 sequence*: YFFGSSPNWYFDV. Thus, regardless of which `version' of Evans' humanized 5G1.1 the POSA selected to combine with Bowdish, that heavy chain would contain the YFFGSSPNWYFDV CDR3 sequence."

Id. at 54 (internal citations omitted) (*citing e.g.*, Ex. 1002 ¶ 146). In sum, the "prior art would have led a POSA to make a simple substitution of one known element for another" i.e., replace the TPO-mimetic peptide sequence in Bowdish's antibody with the HCDR3 sequence from Evans" to yield predictable results: a humanized anti-C5 antibody." Pet. 56–57.

Petitioner relies on the Balthasar Declaration as support and further explanation as to how one of ordinary skill in the art would derive the claimed antibody based on the asserted art. *See* Pet. 50–58. Dr. Balthasar provides a number of illustrations useful to understanding Petitioner's argument.

Figure 4 from Dr. Balthasar's report, relating to the eculizumab light chain sequence, is reproduced below.

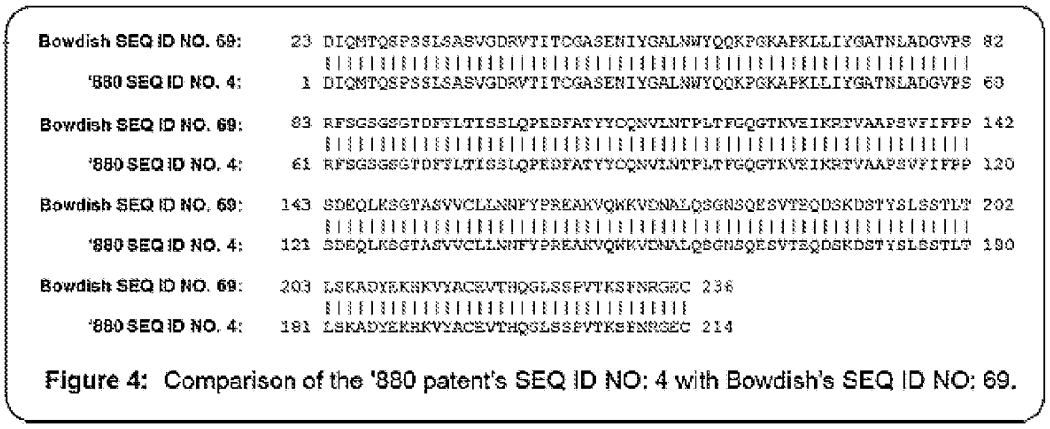


Figure 4: Comparison of the '880 patent's SEQ ID NO: 4 with Bowdish's SEQ ID NO: 69.

Ex. 1002 ¶ 53. Figure 4 purports to show identity between the mature peptide sequence[20] of the eculizumab light chain disclosed in Bowdish and

[20] Dr. Balthasar notes that Bowdish's Figures 13A and 13B identify leader sequences, not included in the comparisons of Figures 4 and 5 because one

SEQ ID NO: 4 of the '880 patent. *Id.*

Figure 5 from Dr. Balthasar's report, relating to the heavy chain sequence of eculizumab, is reproduced below.

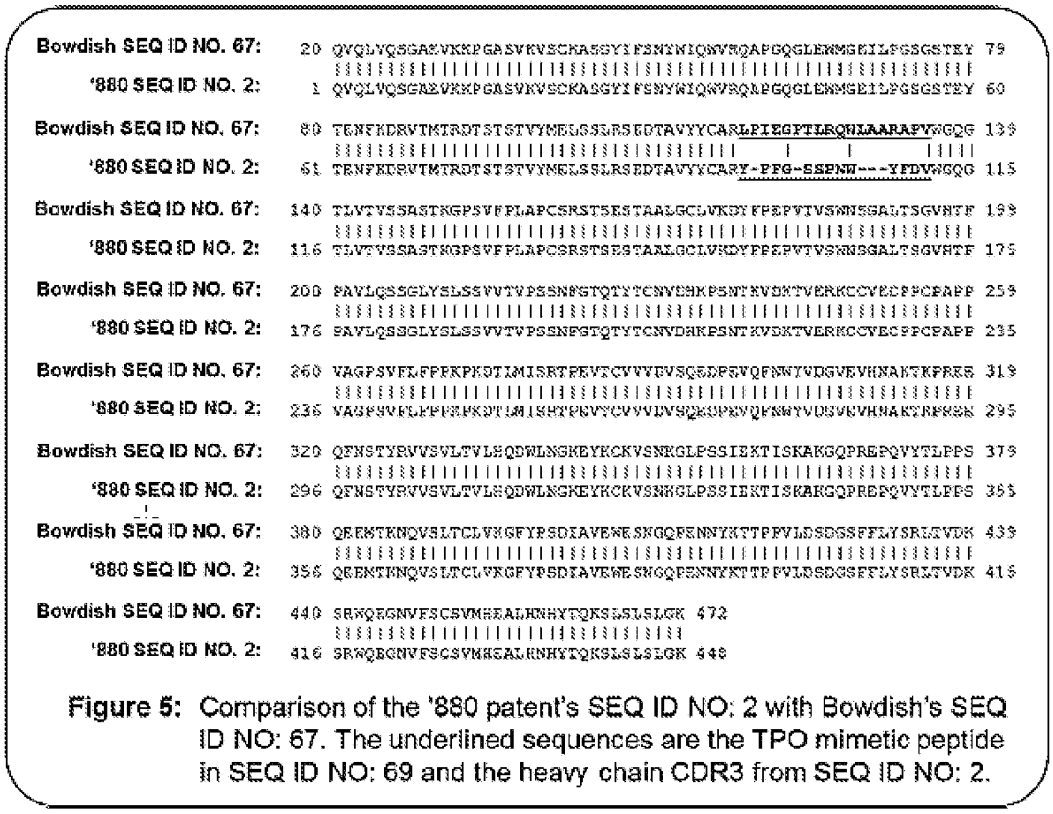


Figure 5: Comparison of the '880 patent's SEQ ID NO: 2 with Bowdish's SEQ ID NO: 67. The underlined sequences are the TPO mimetic peptide in SEQ ID NO: 69 and the heavy chain CDR3 from SEQ ID NO: 2.

Id. According to Dr. Balthasar, "Figure 5 shows that the mature portion of SEQ ID NO: 67 from Bowdish (*i.e.*, amino acids 20 to 472) aligns perfectly with SEQ ID NO: 2 from the `880 patent outside of the heavy chain CDR3 region." *Id.*

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of ordinary skill in the art "would have understood that leader sequences are cleaved off as a standard part of the maturation of an antibody." *Id.*

Figure 6 of Dr. Balthasar's declaration, relating to the heavy chain CDRs of eculizumab, is reproduced below.

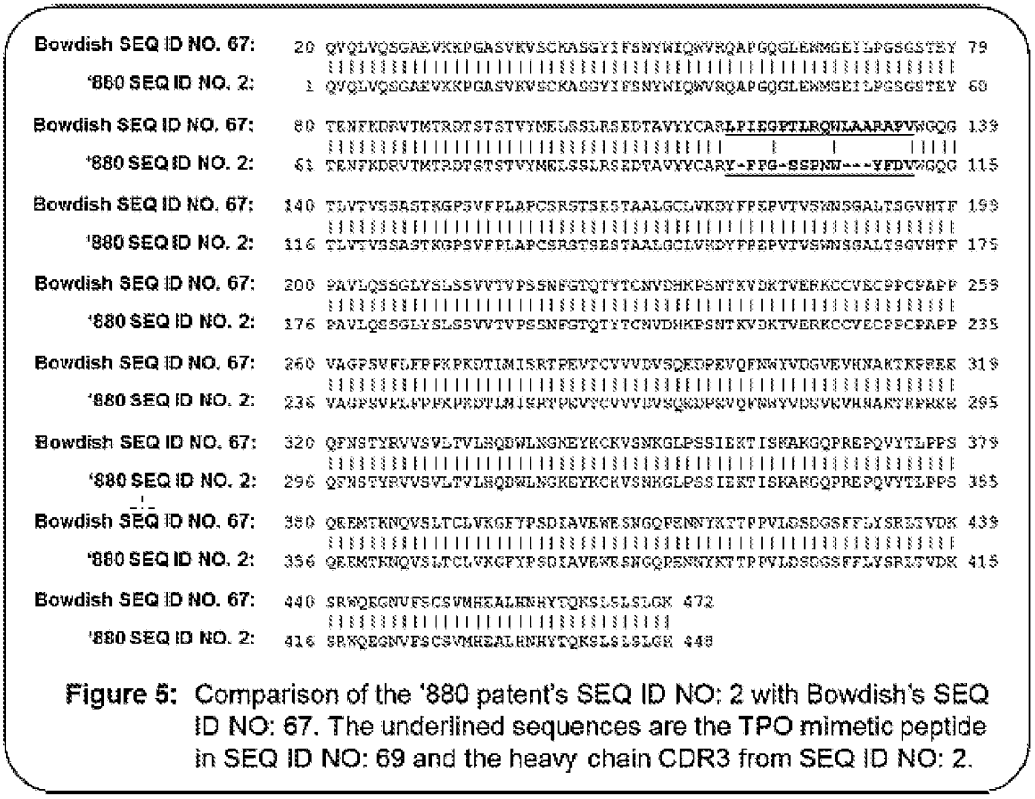


Figure 5: Comparison of the '880 patent's SEQ ID NO: 2 with Bowdish's SEQ ID NO: 67. The underlined sequences are the TPO mimetic peptide in SEQ ID NO: 69 and the heavy chain CDR3 from SEQ ID NO: 2.

Ex. 1002 ¶ 55. According to Dr. Balthasar, Figure 6 shows an alignment of SEQ ID NO: 2 of the '880 patent with the heavy chain CDRs identified in Evans underlined, including the YFFGSSPNWYFDV sequence of CDR3. *Id.* ¶¶ 55, 143.

Reproduced below is Figure 11 of Dr. Balthasar's declaration, relating to the relationship between the heavy chain CDR3 and Bowdish's TPO peptide.

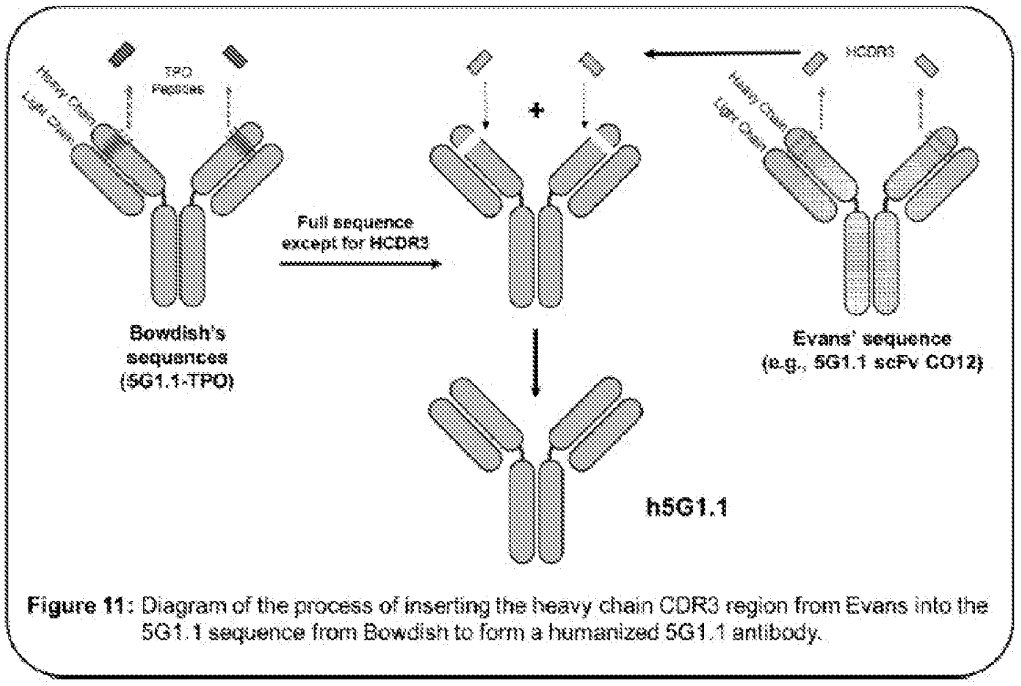


Figure 11: Diagram of the process of inserting the heavy chain CDR3 region from Evans into the 5G1.1 sequence from Bowdish to form a humanized 5G1.1 antibody.

Ex. 1002 ¶ 122. Figure 11 shows the original Bowdish scaffold antibody, including the location of eculizumab heavy chain CDR3; the use of Evans as a source of the HCDR3; and the replacement of Bowdish's TPO peptide with Evan's HCDR3. *Id.* According to Dr. Balthazar, Figure 11 "illustrate[s] how a POSA would have arrived at the claimed sequence (*i.e.*, eculizumab) by placing the heavy chain CDR3 disclosed in Evans into the 5G1.1 antibody sequence disclosed in Bowdish." *Id.*

With respect to reason to combine, Petitioner argues that, because the combination of Bell and Wang taught the use of eculizumab for the

treatment of PNH, wherein it was well known that eculizumab was also known in the art as humanized `5G1.1,' `h5G1.1,' or `h5G1.1-mAb' with a hybrid IgG2/IgG4 constant region, the skilled artisan would have looked to e.g., Bowdish and Evans to recreate the molecule used in those successful studies. *See* Pet. 55; Ex. 1002 ¶¶ 147–151. Moreover, with respect to the specific sequence of SEQ ID NO: 2, Petitioner asserts that, as of the filing date of the '880 patent, it was well known that antibodies with a hybrid IgG2/IgG4 constant region carried certain benefits, such as a reduced ability to elicit unwanted inflammatory events and lessened propensity to activate the complement system. Pet. 14 (citing Ex. 1032, 11, 19, 28; Ex. 1031, 451; Ex. 1002 ¶¶ 48, 56); *see* Ex. 1002 ¶¶ 24, 166. As noted by Dr. Balthasar, for example:

> A POSA would have been aware that the HuG2/G4 antibody design should prove useful in humanization of other antibodies intended for human use where elimination of FcR binding and C [*i.e.*, complement] activation may be desirable. AMG1031, 451; *see also*, AMG1034, 1280. Because the goal of using eculizumab in treating PNH is to reduce the level of complement activation, using a heavy chain constant region that avoids a counter-productive activation of complement by the therapeutic antibody aligns well with the desired outcome. AMG1005, ¶¶[0003], [0012].

Ex. 1002 ¶ 48.

Patent Owner argues that, absent impermissible hindsight, the skilled artisan would not have combined, or reasonably expected success in combining the asserted references. Prelim. Resp. 4–5, 57. Patent Owner argues that Bell, like Hillmen and Hill '05, taught eculizumab was the antibody of Thomas and nothing in the other references would point the

skilled artisan toward a different antibody, e.g., the IgG2/IgG4 hybrid covered by the claim. *Id.* Patent Owner also argues Thomas taught away from the claimed invention because Thomas described an "eculizumab" with an IgG4 constant region. *Id.* at 55; *see also id.* at 51–52 (arguing that Bell, Hillmen, and Hill '05 taught away from the IgG2/IgG4 version of eculizumab).

Patent Owner argues that even assuming one of ordinary skill did combine the cited references to obtain eculizumab having the claimed sequence, "a POSA would not have reasonably expected the resulting compound to work in a pharmaceutical composition for preventing C5 cleavage and safely and effectively treating PNH . . . . [because] even small changes to the amino acid sequence could have a substantial impact on the binding properties and the safety and efficacy of an antibody intended for human administration." *Id.* at 57–58 (citing *Novartis Pharm. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051 (Fed. Cir. 2019). Patent Owner thus contends that, in view of this complexity and unpredictability, the skilled artisan would not have ventured away from Thomas's known antibody; i.e., would not have looked to Bowdish and Evans for an isotype variant of that antibody. *Id.* at 40–41.

2. Analysis

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has carried its burden to show a reasonable likelihood that, at least, claim 2 of the '880 patent would have been obvious under Ground 5.

Regarding Patent Owner's argument that the combination of Bell, Bowdish, Evans, and Wang involves improper hindsight and that the combination fails to render the challenged claims obvious because Bell's disclosed antibody would necessarily be that of Thomas's disclosure, we are not convinced. As summarized in Section I(F)(3), above, Bell extols the virtues of eculizumab for the treatment of PNH, but does not identify its amino acid sequence. Bell does cite to and incorporate by reference Thomas, thus, Thomas's IgG4 isotype antibody would be one type of eculizumab contemplated by Bell. But, as discussed in section II(D)(2), one of ordinary skill in the art would have understood that "eculizumab" encompassed multiple isotypes, including one having the hybrid IgG2/IgG4 isotype noted in Tacken and Bowdish. Here, Bowdish discloses a substantial portion of the anti-C5 antibody 5G1.1 and points to Evans as evidencing the remaining amino acid sequence. And, with respect to Patent Owner's argument that neither Bowdish nor Evans uses the term "eculizumab" (Prelim. Resp. 58–59), on the present record, we accept from Dr. Balthasar's Declaration that one of ordinary skill in the art would have looked to those references for the structure of eculizumab, particularly given that Bowdish incorporates Evans for the construction of 5G1.1. *See*, *e.g.*, Ex. 1006 ¶ 191; Ex. 1002 ¶¶ 54, 78, 79, 89, 90, 140–148, 151. Accordingly, Petitioner's arguments rely on the disclosures of the prior art and no improper hindsight is necessarily invoked under Petitioner's rationale.

As for Patent Owner's contention that Thomas taught away from the claimed invention (or, somehow taught away from the prior art combination), we disagree. A "teaching away" requires a reference to

actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *Id.* at 1200 (citation and emphasis omitted). "The prior art's mere disclosure of more than one alternative does not constitute a teaching away from . . . alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *Id.* at 1201. Thomas does not criticize, discredit, or discourage the claimed invention or the prior art combination. Thomas, at most, teaches the original eculizumab construction, an alternative to the version as taught by Bowdish and Evans.

On the present record, we are also not persuaded by Patent Owner's argument that, "[e]ven if Bowdish and Evans were combined . . . , a POSA would not have reasonably expected the resulting compound to work in binding to C5 or safely and effectively treating PNH" because even small changes could substantially impact an antibody's binding properties, safety, and efficacy for human administration. *See* Prelim. Resp. 57.

As an initial matter, claims 2 and 3 are not directed to the treatment of any particular disease. And, although claim 1 recites "[a] pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH)," it is not clear whether claim 1 requires any showing of safety and efficacy as these are standards for FDA approval of new drugs rather than of patent law. *Helsinn Healthcare S.A. v. Teva*

Pharms. USA, Inc., 855 F.3d 1356, 1372–73 (Fed. Cir. 2017), *cert. granted*, 138 S. Ct. 2678 (2018), and *aff'd*, 139 S. Ct. 628 (2019) ("Approval of a new drug by FDA, however, is a more demanding standard than that involved in the patents-in-suit. The patents here make no reference to FDA standards and broadly claim a palonosetron formulation for reducing the likelihood of emesis and CINV.").

Further, Bell teaches that a variety of compounds containing the variable regions of a humanized 5G1.1 are useful to the treatment of PNH, stating: "In particularly useful embodiments, the compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb (eculizumab), h5G1.1-scFv (pexelizumab) and other functional fragments of h5Gl.l." Ex. 1005 ¶ 12. Moreover, Bell touts the benefits of "eculizumab" in a long term clinical trial, indicating that the treatment is suitable "for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH)," as set forth in claim 1. As noted above, one of ordinary skill in the art understood eculizumab to encompass a humanized 5G1.1 antibody having the IgG2/IgG4 isotype indicated in SEQ ID NO: 2.

Although we recognize Patent Owner's argument that "sequence changes outside of the antigen-binding site, *e.g.*, in the heavy chain constant region" may influence antibody affinity, specificity, and immunogenicity, this is counterbalanced by Petitioner's citation to eculizumab of the IgG2/IgG4 isotype and its reasoned argument that the skilled artisan would look to the hybrid sequence because it was known "that antibodies with a hybrid IgG2/IgG4 constant region carried certain benefits, such as a reduced ability to elicit unwanted inflammatory events and lessened propensity to

activate the complement system." *See* Prelim. Resp. 11; Pet. 14 (citing Ex. 1032, 11, 19, 28; Ex. 1031, 451; Ex. 1002 ¶¶ 48, 56).

On balance, the present record suggests that a person of ordinary skill in the art would have reasonably expected a version of eculizumab having a heavy chain consisting of SEQ ID NO: 2 to comprise and anti C5 antibody as required in claims 2 and 3, and to work for the purpose set forth in claim 1 ("treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH)"). The parties are invited to further address these points during trial.

We take note of Patent Owner's arguments relating to, and evidence of, objective indicia of non-obviousness, discussed in Section II(I), below. Although we note that there is some evidence to support Petitioner's contentions of commercial success, long-felt but unmet need, and industry praise, we also note some potential shortcomings in Patent Owner's presentation, including the rebuttability of the presumption of a nexus between their evidence and the claimed and novel subject matter. We expect this issue will be further developed at trial.

Again, to summarize, based on the evidence presented at this stage in the proceedings, it has been shown that there is reasonable likelihood that at least claim 2 of the '880 patent would have been obvious over Bell, Bowdish, and Evans under Ground 5.

H. Obviousness in view of Bell, Evans, Mueller, and Wang (Ground 6)

In Ground 6, Petitioner challenges claims 1–3 as obvious in view of Bell, Evans, Mueller, and Wang. Pet. 58–68. Patent Owner opposes. Prelim. Resp. 58–62; *see also id.* at 4–5, 32–39.

1. The Parties' Contentions

Referencing its arguments for Ground 4, Petitioner contends that, "Bell and Wang together taught all of the elements of claims 1–3 except for the claimed antibody sequences.' " Pet. 58. Petitioner then points to Evans and Mueller as teaching the amino acids of SEQ ID NOs: 2 and 4. *Id.* at 59–66. As stated by Petitioner in the context of Ground 1: "**Evans** disclosed the amino acid sequences of eculizumab's heavy and light chain variable domains, and **Mueller** disclosed the hybrid IgG2/IgG4 heavy chain and light chain constant domains of eculizumab." *Id.* at 28 (citing Ex. 1007, 44:4–13; Ex. 1008, 52–53, 58–61; Ex. 1002 ¶78); *see id.* at 59–66 (citing, e.g., Ex. 1002, ¶¶ 156, 165, 166, 170–175). Petitioner further argues:

> Knowing that chimeric IgG2/IgG4 constant regions that were known not to activate the complement system (AMG1008, 7:28-31, 8:23-26, 12:27-32), a POSA reading Bell and Evans also would have looked to Mueller for "h5G1.1" sequence information. AMG1002, ¶¶166, 173. Mueller taught methods for making "chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4 " (HuG2/G4 mAb)." AMG1008, 12:27-30; *see also, id.*, 8:23-26. In particular, Mueller described a control antibody "h5G1.1 CO12 HuG2/G4 mAb," which a POSA would have readily identified as a humanized anti-C5 antibody because of the "h5G1.1" nomenclature coupled with the hybrid IgG2/IgG4 constant region ("HuG2/G4"). AMG1008, 12:37, FIG. 15; AMG1005, ¶[0052]; AMG1034, 1279; AMG1049, 838-839; AMG1002, ¶166, 173–174.

Id. at 61–62.

Figure 14 from the Balthasar Declaration is reproduced below.

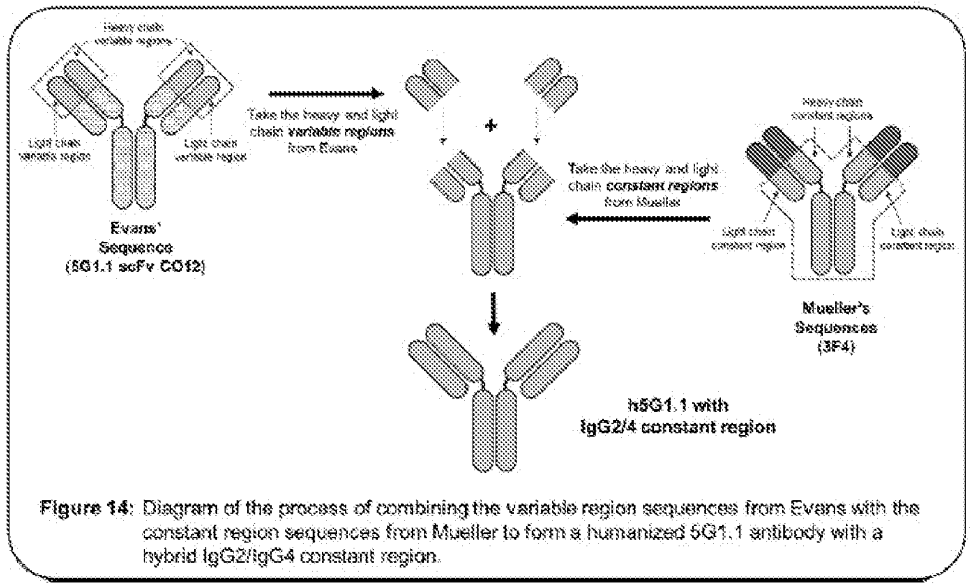


Figure 14: Diagram of the process of combining the variable region sequences from Evans with the constant region sequences from Mueller to form a humanized 5G1.1 antibody with a hybrid IgG2/IgG4 constant region.

Ex. 1002 ¶ 156. According to Petitioner, the above figure presents an overview of how one of ordinary skill in the art would have combined the teachings of Evans and Mueller to arrive at the complete eculizumab antibody sequence described in claim 1. *See* Pet. 60.

Relying on Dr. Balthasar's testimony, Petitioner argues that "Mueller disclosed the amino acid sequence of a hybrid IgG2/IgG4 heavy chain constant domain when Mueller disclosed the sequence of the chimeric anti-VCAM `3F4' antibody." Pet. 64 (citing Ex. 1002 ¶ 169, 173; Ex. 1008, 58-61). "Given that Mueller used this humanized anti-C5 antibody as an isotype control for 3F4 HuG2/G4, a POSA would have reasonably expected the disclosed heavy and light chain constant regions to be the same as those in the 3F4 HuG2/G4 chimeric antibody. AMG1002, ¶¶57, 166." *Id.* at 63. Accordingly Petitioner argues, one of ordinary skill in the art would have

aligned Mueller's chimeric 3F4 HuG2/G4 heavy chain and mature 3F4 heavy and light chain variable regions such that a skilled artisan aligning the two would identify the 3F4 variable regions (at Figure 9) as amino acids 20–137 of the 3F4 HuG2/G4 heavy chain and amino acids 20–131 of the 3F4 light chain. *Id.* at 62 (citing e.g., Ex. 1002 ¶ 173). Petitioner contends that the skilled artisan "would have immediately known that the remainder of the 3F4 HuG2/G4 heavy chain (amino acids 138-463 is the hybrid IgG2/IgG4 constant region of that antibody, and that the remainder of the 3F4 chain (amino acids 132–238) is the light chain constant region of that antibody." *Id.* at 63 (citations omitted). With this understanding of the heavy and light chain constant domain sequences in mind, Petitioner contends the skilled artisan would have looked to Evans to complete the whole antibody using Evans's variable regions identified from its SEQ ID NO: 20, particularly because Evans uses the same "CO12" nomenclature to refer to its 5G1.1 scFv as Mueller does in referring to h5G1.1. *Id.* at 63–65 (citing Ex. 1002 ¶¶ 156, 167–168, 172).

Petitioner's rationale for combining Mueller and Evans is that Mueller taught antibodies with lower immune response and identified an antibody as h5G1.1 CO12 HuG2/G4 mAb, which the skilled artisan would have known is eculizumab. Further, Petitioner argues, Evans taught the complementary parts of this anti-C5 antibody, so, by combining the elements of the two references, a complete antibody would have been created having the SEQ ID NO: 2 and SEQ ID NO: 4 of the claim. *Id.* at 66–67; *see also id.* at 67–68 (further discussing why one of ordinary skill in the art would have combined the cited references with a reasonable expectation of success).

Patent Owner argues "[a] POSA would have understood that Mueller could have used ***any*** antibody with an IgG4 or IgG2/G4 isotype as a `negative control' for its *in vitro* experiments, as long as it did not bind to VCAM," meaning, there would be no reason to incorporate the variable regions taught by Evans. *Id.* at 59. And, according to Patent Owner, without improper hindsight, the skilled artisan would not have sought to combine Mueller and Evans. *See, e.g.*, Prelim. Resp. 3–4. Patent Owner argues "[a] POSA as of March 15, 2007 considering the problem addressed by the '880 patent – designing anti-C5 antibody compositions to prevent cleavage of C5 and to treat PNH – would have had no reason to look at Mueller, which had nothing to do with that problem. *Id.* at 59. (citing *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013) ("While a prior art reference may support any finding apparent to a person of ordinary skill in the art, prior art references that address different problems may not, depending on the art and circumstances, support an inference that the skilled artisan would consult both of them simultaneously.")).

2. Analysis

In contrast to Ground 5, where Bowdish expressly incorporates Evans, thereby rendering the combination unquestionable, the references asserted in Ground 6 provide no express link between the teachings of Mueller and Evans. Although such a combination is possible, the mere fact that prior art can be combined does not establish that one of ordinary skill would have done so. *See, e.g.*, *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (The "mere fact that the prior art may be modified in the manner suggested . . .

does not make the modification obvious unless the prior art suggested the desirability of the modification.□).

Ground 6, thus, presents a close question on whether there would have been sufficient motivation to combine Mueller and Evans in the manner argued by Petitioner. Upon review of the Balthasar Declaration, it is apparent that Mueller's 3F4 heavy chain provides a match for part of the claimed SEQ ID NO: 2. *See* Ex. 1002 ¶ 58, Figure 8. Further, Mueller's 3F4 light chain provides a match for part of the claims SEQ ID NO: 4. *Id.* ¶ 59, Figure 9.

Figure 10 of the Balthasar Declaration, reproduced below, illustrates the extent that each of Evans and Mueller (and Bowdish, per Ground 5) discloses the claimed SEQ ID NOs: 2 and 4.

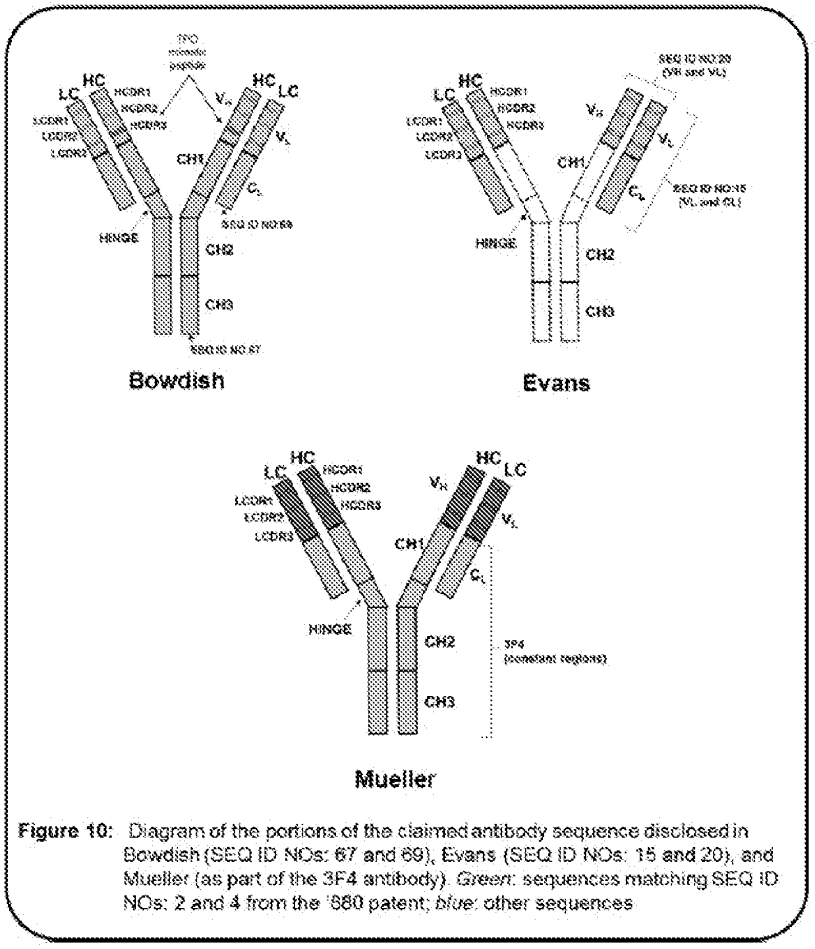


Figure 10: Diagram of the portions of the claimed antibody sequence disclosed in Bowdish (SEQ ID NOs: 67 and 69), Evans (SEQ ID NOs: 15 and 20), and Mueller (as part of the 3F4 antibody). *Green*: sequences matching SEQ ID NOs: 2 and 4 from the '880 patent; *blue*: other sequences

Ex. 1002 ¶ 60. Dr. Balthasar's Figure 10 shows three antibody structures: Bowdish top-left, Evans top-right, and Mueller bottom center. The Figure shows identity with SEQ ID NOs: 2 and 4 of the '880 patent in green and differences in blue.

Based on the above figure, Petitioner's rationale for combining the teachings of Mueller and Evans is somewhat tenuous. In particular, we are concerned with the reasons one of ordinary skill in the art would have paired Mueller with Evans with, choosing precisely those portions of Mueller's and Evan's constructs to create an antibody having exactly the sequences set forth SEQ ID NOs. 2 and 4. At this stage in the proceedings, based on the evidence before us, the answer is not entirely clear and Patent Owner's argument regarding improper hindsight makes some sense. True, Mueller discloses "a humanized antibody directed against human C5 (h5G1.1 CO12 HuG4 mAb)," but little else regarding its structure. *See* Ex. 1008, 12. It is not apparent that the skilled artisan, knowing of Evans, would have looked to Mueller, or vice versa.

Based on the evidence presented at this stage in the proceedings, Petitioner has not sufficiently demonstrated a reasonable likelihood that claims 1–3 of the '880 patent would have been obvious over the combination set forth in Ground 6.

I. Objective Evidence of Non-Obviousness

Factual considerations underlying the obviousness inquiry include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations. *See Graham*, 383 U.S. at 17–18. Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR*, 550 U.S. at 406, (2007). Although evidence pertaining to secondary considerations must be taken into account whenever present, it does not necessarily control the

obviousness conclusion. *See*, *e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

Petitioner contends no objective indicia of non-obviousness support patentability of the challenged claims. Pet. 38, 46, 58, 68–70. In particular, Petitioner notes that during the prosecution of the related '504 patent, Alexion argued that the claimed heavy chain of eculizumab, i.e., the hybrid IgG2/IgG4 constant domain, provided surprising and unpredictable results, such as decreased effector function, reduced immunogenicity, and increased half-life. Pet. 68–69 (citing Ex. 1014, 588, 593 (¶ 8)). However, Petitioner contends, because eculizumab's hybrid IgG2/IgG4 constant region was well known in the art (as evidenced by Tacken), the allegedly surprising and unpredictable features of the antibody have no nexus to the challenged claims. *Id.* at 69 (citing Ex. 1034, 1279).

Petitioner further contends that one of ordinary skill in the art would not have found surprising the alleged beneficial results of using the hybrid constant region of SEQ ID NO: 2 because, in view of Mueller II, antibodies with the claimed hybrid IgG2/IgG4 heavy chain were known not to bind FcR and to be less immunogenic, whereas it was well known that antibodies with this claimed hybrid heavy chain would have an increased half-life. *Id.* (citing Ex. 1031, 488, 451; Ex. 1032 ("Rother"), 5, 19[21]; Ex. 1002 ¶ 180–182); *see*, *e.g.*, Ex. 1032, 5–6 (disclosing that antibodies having "an engineered constant region that includes an IgG2-derived portion and an IgG4-derived portion . . . maintain the function of the non-Fc component

[21] Rother et al., WO 2005/007809 A2, published Jan. 27, 2005 (Ex. 1032).

and/or have increased half-life compared to the non-Fc component alone and/or lack unwanted antibody Fc-mediated cell activating and inflammatory properties including events resulting from Fc-receptor antibody engagement and complement activation").

Patent Owner contends that evidence of commercial success, long-felt, but unmet need, and industry praise support the non-obviousness of the challenged claim. Prelim. Resp. 61. Patent Owner argues that SOLIRIS, the product embodying the claimed antibody, is a commercial success, having produced annual net product sales in excess of $1 billion in 2018. *Id.* (citing Ex. 2018, 70). Patent Owner further contends that this commercial success "has a direct nexus to the patented features of the '880 patent, which claims pharmaceutical compositions of the uniquely-engineered, non-naturally occurring antibody responsible for the drug's clinical (and therefore commercial) success as a treatment for PNH, as well as the complement-mediated hemolytic condition aHUS." *Id.*

At this stage in the proceedings, based on the evidence presented by Patent Owner, it is apparent that SOLIRIS is a successful product. "[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). This "presumption of nexus is rebuttable: a patent challenger may respond by presenting evidence that shows the proffered objective evidence was `due to extraneous factors other than the patented invention.'" *Id.* Here, the parties appear to agree that the claim of the '149 patent is directed to the

commercial product SOLIRIS. However, commercial success "is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996).

Patent Owner argues that, because SOLIRIS is "the first FDA-approved treatment to reduce hemolysis in patents with PNH," there is evidence that the claimed antibody fulfilled a long-felt, unmet need in the market. Prelim. Resp. 61–62 (citing Ex. 2019, 1270).

At this stage in the proceeding, the available evidence supports that anti-C5 antibodies were considered potential therapeutic options for "many years" before 2007, and that Alexion's eculizumab product "is currently the only complement-specific antibody on the market" and is the "first and only approved therapy for PNH." Ex. 2019, 1270. Again, it may be presumed that there is a nexus between the claimed and novel elements of the SOLIRIS product and the meeting of the long-felt need. However, "[w]here the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Patent Owner also contends "SOLIRIS® also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade . . . ." Prelim. Resp. 62 (citing Ex. 2020; Ex. 2021).

As with the other two contended bases for indicia of non-obviousness, while it is apparent there was high praise for the SOLIRIS product from the

relevant industry, there is a rebuttable presumption that this praise has a nexus with the claimed subject matter. *Cf. In re Kao*, 639 F.3d at 1068.

Given the early stage of these proceedings, we decline to accord much weight to Patent Owner's substantially untested evidence of objective indicia of non-obviousness. The parties will have the opportunity to further develop these facts during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

J. The Board's Discretion to Deny Institution under 35 U.S.C. §§ 325(d) and 314(a)

1. The Parties' Positions

Patent Owner argues the Petition should also be denied institution under 35 U.S.C. §§ 325(d) and 314(a), because Amgen's Grounds rely on the `same or substantially the same prior art or arguments' previously presented to the PTO "[i]n the course of patent prosecution leading to issuance of the '880 patent, as well as prosecution of related U.S. Patent Nos. 9,719,880 (`the '880 patent') and 9,732,149 (`the '149 patent'). Prelim. Resp. 25, 62–63; *see id.* at 63 (asserting that the Examiner considered Hillmen, Evans, and Wang; and further reviewed Bell ("cumulative of Bowdish"), and Mueller II ("cumulative of Mueller"). Patent Owner argues that in the course of prosecution leading to the issuance of the '880 patent, the Examiner:

> "Expressly discussed Amgen's asserted references Hillmen 2004 (AMG1004), Evans (AMG1007), and Wang (AMG1028) as a basis for rejection, before ultimately finding the claims to be allowable over the art (*see, e.g.*, AMG1014 at 557-561, 623-628, 738-743);

- Considered Amgen's asserted reference Bell (AMG1005), which Alexion submitted to the PTO (*see, e.g.*, AMG1014 at 566);
- Considered U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen relies here (*see, e.g.*, AMG1016 at 154); and
- Considered the "Mueller II" article (AMG1031), which is cumulative of Amgen's asserted "Mueller" reference (AMG1008) because, as Amgen's declarant recognized, it "discloses the same antibodies" as Mueller. (*See, e.g.*, AMG1016 at 625; AMG1002 ¶ 119–110 & n.12.)

Prelim. Resp. 17–18.

Petitioner's position on this issue is that "[t]he arguments and evidence presented herein were not before the examiner during prosecution and, therefore, do not constitute `the same or substantially the same prior art or arguments' under 35 U.S.C. §325(d).' " Pet. 24. In particular, Petitioner argues that

> the examiner rejected Alexion's claims as obvious over combinations of Hillmen, Evans, Wang and Thomas during prosecution. Thomas was the only reference relied upon for eculizumab sequence information. AMG1016, 596-602. And, the examiner allowed the '880 patent claims mistakenly believing" because of Alexion's mischaracterization of the art" that the sequence and structure of eculizumab were not already known. *Id.*, 762-763.
>
> Though Hillmen, Evans, and Wang were referenced by the examiner during prosecution, this Petition presents them in a different light, along with new references" Bell, Bowdish, and Mueller" which teach the IgG2/IgG4 constant domain missing from the art combination raised during prosecution.

> Bell and a parent application to Bowdish (US 2003/0049683 A1) was cited but not relied upon during prosecution, and Mueller was not cited at all. Thus, the art combinations here, which were not raised by the examiner during prosecution, provide the complete sequence of eculizumab, thereby teaching the very thing the examiner mistakenly concluded was missing from the prior art. Consequently, this Petition is not the same/substantially the same as or cumulative of any previous arguments and § 325(d) does not preclude instituting this Petition.

Id. at 24–25.

2. Analysis

Regarding the Board's discretion under 35 U.S.C. § 325(d), in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, the Board enumerated non-exhaustive factors to be considered in exercising discretion under 35 U.S.C. § 325(d) on whether to institute *inter partes* review. Case IPR2017-01586, slip op. at 17–18 (PTAB Dec. 15, 2017) (Paper 8) (precedential as to § III.C.5, first paragraph). The non-exhaustive *Becton* factors are:

> 1. the similarities and material differences between the asserted art and the prior art involved during examination;
>
> 2. the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> 3. the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> 4. the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> 5. whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and

> 6. the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Id. (numbering added). The *Becton* factors are not dispositive, but are part of a balanced assessment of the relevant circumstances in a particular case and we do not simply default to a tally of each factor to determine whether or not an IPR should be instituted.

Here, Patent Owner has not clearly identified how its arguments fall under the above-noted factors, but has generally argued that the prior art before us now was considered by the prosecuting Examiner either directly or as being cumulative of references that were so considered, and has further argued that the unpatentability issues presented in the Petition are the same as those at issue before the Examiner. Upon review of this evidence, we note that the Examiner considered Hillmen in rejecting a claim for obviousness-type double patenting and for anticipation. *See* Ex. 1014, 482, 557–561. As discussed in section II(D)(2), above, at this stage in the proceedings, the anticipation Ground 1 over Hillmen, on its own, is not considered sufficient to institute IPR; therefore, Hillmen's consideration during prosecution is not determinative here. Rather, we focus on the Bell, Bowdish, Evans, and Wang— the references of Ground 5, upon which we base our institution decision.

As an initial matter, Alexion did address the substance of Evans during prosecution. *See* Ex. 1014, 588. But, according to Patent Owner, the Examiner "[c]onsidered" Bell and "U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen

relies here. Prelim. Resp. 18. Both of these citations, however, are to an Information Disclosure Statement signed by the Examiner. *See id.* (citing Ex. 1014, 565, 566). Patent Owner does not direct us to, nor do we discern, where either Bell or some version of Bowdish was substantively considered during prosecution. The Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution. *See, e.g.*, *Amneal Pharms. LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, slip op. at 40 (PTAB Nov. 7, 2018) (Paper 8) (declining to deny institution based on Section 325(d) where the reference was listed on the face of the patent, but Patent Owner provided no evidence about the extent to which the Examiner evaluated the reference during prosecution); *Digital Check Corp. d/b/a ST Imaging v. E-Imagedata Corp.*, IPR2017-00178, slip op. at 12 13 (PTAB Apr. 25, 2017) (Paper 6) (acknowledging that a prior art reference was cited in an IDS, but granting institution because there was no indication that the claims were rejected based on those references or that the Examiner substantively discussed those references during prosecution); *Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, slip op. at 7 9 (PTAB Apr. 3, 2017) (Paper 8) (refusing to deny institution based on Section 325(d) for grounds based on a prior art reference that was simply cited in an IDS and not considered at any length); *Praxair Distribution, Inc. v. INO Therapeutics LLC*, IPR2015-00893, slip op. at 8 (PTAB Sept. 22, 2015) (Paper 14) (granting institution even though the references were previously cited in an IDS because patent owner failed to identify with specificity where the references were considered); *HyperBranch Medical Technology, Inc. v.*

Confluent Surgical, Inc., IPR2018-01099, slip op. at 17 (PTAB Nov. 27, 2018) (Paper 14) (instituting IPR because, *inter alia*, "[t]he Examiner does not appear to have considered the combined teachings of Spero and Haber during examination of the '021 patent.").

We also note that the Examiner cited Wang in much the same context as argued here by Petitioner. *See* Ex. 1004, 560–561 (Examiner asserting that based on Wang, "the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg/ml solution of the antibody sterile, preservative free solution"). We do not discern, however, where Alexion addressed this issue on the merits, arguing instead that "Wang fails to teach any part of the sequence of eculizumab, let alone its unique heavy chain." *Id.* at 587.

Based on the evidence presented by Patent Owner, *Becton* factors 1–6 weigh in favor of not exercising our discretion not to institute here. Therefore, based on the evidence cited by Patent Owner and for the reasons above, we decline to exercise our discretion under section 325(d) to deny institution here.

Other than the heading of Section VI of the Preliminary Response and that section's first sentence invoking the statute, Patent Owner presents no arguments or evidence directed to the Board's discretion under 35 U.S.C. § 314(a). Therefore, we also decline to exercise our discretion under section 314(a) to deny institution.

II. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of prevailing on Ground 5 in showing that claim 2 of the '880 patent is obvious over the combination of Bell, Bowdish, and Evans. Given this determination, we institute trial on all challenged claims raised in the Petition.[22] *See PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (indicating that a decision whether to institute an *inter partes* review "require[s] a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

Our decision at this stage derives from our preliminary review of the challenged claims, the asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration. We emphasize that at this stage of the proceeding, we have not made a final determination as to the construction of any claim term or the patentability of the instituted claims. Our final decision will be based on the full record developed during trial.

[22] In view of the complexity of the art and arguments presented, the parties are, nevertheless, invited to negotiate an agreement to focus on some subset of the asserted claims and Grounds.

III. ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of claims 1□3 of U.S. Patent No. 9,718,880 B2, in accordance with each ground on which the challenge to each claim is based in the Petition, is hereby *instituted*; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of the '880 patent will commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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Paper No. 15
Entered: August 30, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN, INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS,
Patent Owner.

Case IPR2019-00741
Patent 9,732,149 B2

Before TINA E. HULSE, ROBERT A. POLLOCK, and RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314

Amgen Inc. ("Petitioner" or "Amgen") filed a Petition for an *inter partes* review of claim 1, the sole claim of U.S. Patent No. 9,732,149 B2 ("the '149 patent," Ex. 1001). Paper 2 ("Pet."). Alexion Pharmaceuticals ("Patent Owner" or "Alexion") timely filed a Preliminary Response. Paper 10 ("Prelim. Resp."). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 13 ("Reply"); Paper 14 ("Sur-reply").

Under 37 C.F.R. § 42.4(a), we have authority to determine whether to institute an *inter partes* review. We may institute an *inter partes* review if the information presented in the petition filed under 35 U.S.C. § 311, and any response filed under Section 313, shows that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314. After reviewing the parties' submissions, we conclude that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing the claim of the '149 patent is unpatentable under at least one ground. Therefore, we institute *inter partes* review of the aforementioned claim on all grounds raised in the petition, pursuant to 35 U.S.C. § 314. *See SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018); *see also* Guidance on the Impact of SAS on AIA Trial Proceedings (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial).

I. INTRODUCTION

A. *REAL PARTIES-IN-INTEREST*

Petitioner identifies itself, "Amgen Inc.," as the real party-in-interest. Pet. 58. Patent Owner also identifies itself, "Alexion Pharmaceuticals, Inc.," as the real party-in-interest. Paper 3, 2.

B. *RELATED MATTERS*

Petitioner has disclosed, "Amgen has concurrently filed petitions for IPR of U.S. Patent Nos. 9,718,880 ["the '880 patent] (IPR2019-00740) and 9,725,504 [the '504 patent] (IPR2019-00739), which are related to the '149 patent and also owned by Alexion." Pet. 58. Patent Owner identifies the same related *inter partes* reviews as Petitioner. Paper 3, 2.[1]

The '504, '880, and '149 patents are related as follows: the '149 patent issued from U.S. Patent Application No. 15,284,015, filed January 19, 2017, which is a continuation of U.S. Patent Application No. 15/260,888 (now the '504 Patent), filed on September 9, 2016, which is a continuation of U.S. Patent Application No. 15/148,839 (now the '880 Patent), filed on May 6, 2016, which is a continuation of U.S. Patent Application No. 13/426,973, filed on March 22, 2012, which is a continuation of U.S. Patent Application No. 12/225,040, filed as international application PCT/US2007/006606 on March 15, 2007. The parties appear to agree (they, at least, do not dispute) that this March 15, 2007 filing date is the priority date of the '149 patent.

[1] Patent Owner's Mandatory Notices begins listing its pages at page 4. This appears to be an error. We, therefore, cite to the document's pages by counting consecutively from the first page.

C. THE '149 PATENT

The invention of the '149 patent relates to the pharmaceutical antibody eculizumab, which is a humanized anti-C5 antibody. *See* Ex. 1001, Abstract. For reference, we reproduce Figure 1 from the Balthasar Declaration,[2] illustrating the basic structure of an antibody:

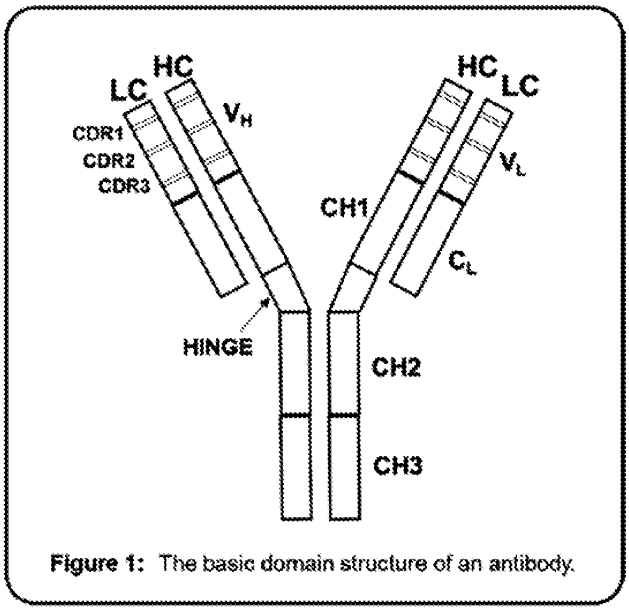


Figure 1: The basic domain structure of an antibody.

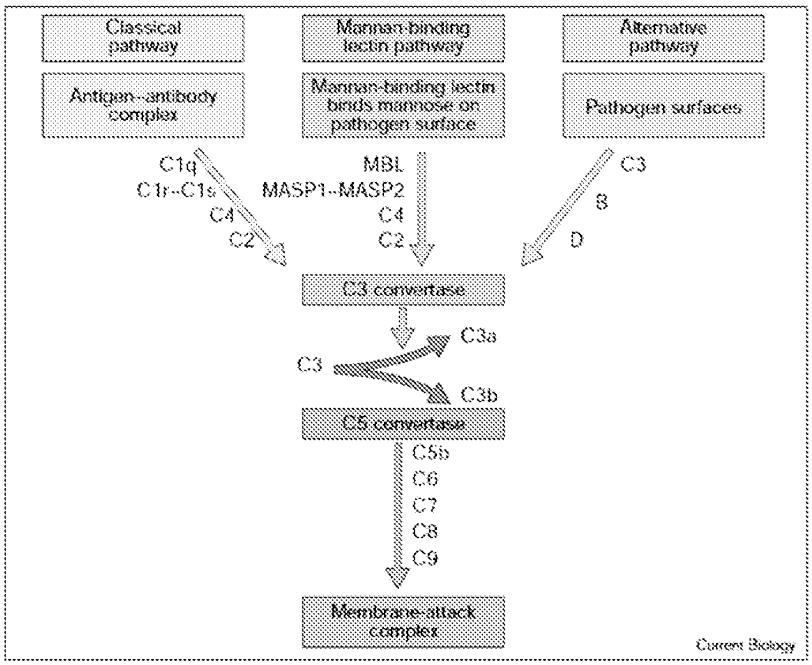
The figure above shows a basic antibody structure having hinged heavy chains (HC) and accompanying light chains (LC), each having constant regions (C_H and C_L) and variable regions (V_H and V_L), all arranged in a general "Y"-shaped structure, as the variable regions and portions of the constant heavy chain regions are hinged away from one another. Ex. 1002 ¶¶ 23–24. The variable regions of each chain also include three

[2] Declaration of Dr. Joseph P. Balthasar, Ph.D. (Ex. 1002, "Balthasar Declaration").

complementarity determining regions (CDR), which provide the antibody with antigen-binding specificity. *Id.*

The sole claim of the '149 patent is directed to a C5 binding antibody having specific amino acid sequences at the heavy and light chains (SEQ ID NO: 2 and SEQ ID NO: 4, respectively), where C5 refers to the complement protein C5 convertase. Ex. 1001, 39:1–5. Complement is a "system of plasma proteins . . . so-named because it complements the activity of antibody in the lysis of bacteria." Ex. 1022 R259; *see* Ex. 1001, 7:10–8:59. As part of the immune system, complement "has a central role in host defense against many micro-organisms and in the modulation of inflammatory reactions." *Id.*; *see* Ex. 1002 ¶ 27. The figure reproduced below shows "[t]he main pathways and components of the complement activation system." Ex. 1022, R259.

Figure 1



The above figure illustrates how various complement proteins are organized into three activation pathways. Ex. 1022, R259; *see* Ex. 1001, 7:19–30. All three pathways lead to the cleavage of C3 convertase and the resultant cleavage of C5 convertase (“C5”) into C5a and C5b. Ex. 1022, Fig. 1; *see* Ex. 1002 ¶ 28. As summarized in paragraph 28 of the Balthasar Declaration, cleavage of C5 initiates the terminal complement cascade.

According to the '149 patent's Specification,

> [s]uitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Pat. No. 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Pat. No. 5,660,825), U.S. Pat. No. 6,353,245 [Evans][3] teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

Ex. 1001, 10:65–11:6. The Specification further states,

> A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Pat. No. 6,355,245 [Evans]). These antibodies disclosed in U.S. Pat. No. 6,355,245 [Evans] include a preferred whole antibody (now named eculizumab).

Id. at 12:21–29. The Specification also states, “[e]culizumab is a humanized monoclonal antibody directed against the terminal complement protein C5,” and, thus, is intended to suppress the terminal activation cascade to prevent complement activation. Ex. 1001, Abstract, 1:63–64 (citing Thomas C.

[3] US 6,355,245 B1 (issued Mar. 12, 2002) (Ex. 1007, “Evans”).

Thomas et al., *Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single-Chain Fv*, 33(17) MOL. IMMUNOL. 1389–401 (1996) (Ex. 1023, "Thomas").

According to Patent Owner, eculizumab, the monoclonal antibody recited in claim 1 of the '149 patent, is the non-proprietary name for its SOLIRIS product, which was approved by the FDA "for treatment of patients with PNH [paroxysmal nocturnal hemoglobinuria] on March 16, 2007." Prelim. Resp. 1–2, 6–8 (citing Ex. 1033, 1256[4]; Ex. 2005, 1[5]; Pet. 2 (citing Ex. 1009, 2).[6] The '149 patent further identifies SEQ ID NO: 2 and SEQ ID NO: 4 as the "Eculizumab Heavy [C]hain" and "Eculizumab Light [C]hain," respectively. Ex. 1001 30:16–31, 30:39–46. SEQ ID NO: 2 encodes a hybrid IgG2/IgG4 heavy chain. *See, e.g.*, Pet. 3; Prelim. Resp. 14.

The claim of the '149 reads as follows:

> 1. An antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

Id. at 39:1–5. We reproduce SEQ ID NO: 2 and SEQ ID NO: 4 from the '149 patent Specification below:

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[4] Russell P. Rother et al., *Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria*, 25(11) NAT. BIOTECH. 1256–64 (2007) (Ex. 1033, "Rother").

[5] Alexion Pharmaceuticals, Inc., Soliris™ (eculizumab), Product Label (rev. 3/2007) (Ex. 2005).

[6] Alexion Application for Extension of Patent Term Under 35 U.S.C. § 156 and 37 C.F.R. § 1.740 for Evans patent, dated May 11, 2007 (Ex. 1009).

- Eculizumab Heavy chain

SEQ ID NO: 2

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMG[E]

ILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYF

FGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL

VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT

QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKD

TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST

YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY

TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD

SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

- Eculizumab Light chain

SEQ ID NO: 4

DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYG

ATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQ

GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV

DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG

LSSPVTKSFNRGEC

Ex. 1001, 30:16–31, 30:39–46. By way of a Certificate of Correction (dated May 15, 2018) the first line of SEQ ID NO: 2 was changed such that the final amino acid was changed from "A" to "E." *See id.* at final page.

D. PETITIONER'S ASSERTED GROUNDS FOR UNPATENTABILITY

Petitioner asserts five (5) grounds for unpatentability, three under 35 U.S.C. § 102(b) for anticipation and the remaining two under 35 U.S.C.

§ 103 for obviousness.[7] Pet. 21–22, 24–58. Petitioner's grounds are as follows:

Ground 1: Claim 1 is anticipated under 35 U.S.C. § 102(b) by Hillmen[8];

Ground 2: Claim 1 is anticipated under 35 U.S.C. § 102(b) by Hill '05[9];

Ground 3: Claim 1 is anticipated under 35 U.S.C. § 102(b) by Bowdish[10];

Ground 4: Claim 1 would have been obvious under 35 U.S.C. § 103 over Bell,[11] Bowdish, and Evans; and

Ground 5: Claim 1 would have been obvious under 35 U.S.C. § 103 over Evans and Mueller.[12]

Id. In support of these grounds for unpatentability, Petitioner submitted, *inter alia*, the Balthasar Declaration. Ex. 1002.

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[7] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '149 patent have an effective filing date before the effective date of the applicable AIA amendments, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103 throughout this Decision.

[8] Peter Hillmen, M.B., Ph.D., et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350(6) N. ENGL. J. MED. 552–59 (2004) (Ex. 1004, "Hillmen").

[9] Anita Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 BLOOD 2559–65 (2005) (Ex. 1047, "Hill '05").

[10] US 2003/0232972 A1 (published Dec. 18, 2003) (Ex. 1006, "Bowdish").

[11] US 2005/0191298 A1 (published Sept. 1, 2005) (Ex. 1005, "Bell").

[12] WO 97/11971 (published Apr. 3, 1997) (Ex. 1008, "Mueller").

II. DISCUSSION

A. ORDINARY LEVEL OF SKILL IN THE ART

Petitioner contends "A POSA [person of ordinary skill in the art] in the field of the '149 patent had knowledge of the scientific literature and ha[d] skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics before March 15, 2007," and "[a] POSA also had knowledge of laboratory techniques and strategies used in immunology research, including practical applications of the same," and "[t]ypically, a POSA would have had an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in the field," and "[a]lso, a POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others on the team, e.g., to solve a given problem; for example, a clinician and a formulation chemist may have been part of a team." Pet. 20–21 (citing Ex. 1002 ¶ 19) (emphasis omitted).

Patent Owner responds, "Amgen does not dispute that the '149 patent concerns an antibody `that binds C5,' defined by its specific amino acid sequence," and "Alexion does not dispute Amgen's POSA definition, except to clarify that the POSA would have ***at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry***." Prelim. Resp. 42.

The two proposed definitions of the skilled artisan are very similar, except that Patent Owner's description more-specifically defines the field of experience of the skilled artisan. However, Patent Owner concludes that

"[u]nder either description of a POSA, Amgen cannot prove unpatentability of claim 1 of the '149 patent under any of its five fatally flawed Grounds." *Id.*

At this stage in the proceedings, we accept and use Patent Owner's proposed definition of the skilled artisan, as being inclusive of Petitioner's definition, but being more specific as to what is meant by "experience in the field," taking into account the level of skill in the art reflected in the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)). Our decision whether to institute, however, does not turn on which party's definition of the skilled artisan is used, and our determinations would be unchanged if we applied Petitioner's definition. Further, we note that evidence may be presented as the case progresses to support some other proposed definition of the skilled artisan, which may influence our determination of this issue.

B. CLAIM CONSTRUCTION

Based on the filing date of the Petition (Feb. 28, 2019), the Board interprets claim terms in an *inter partes* review ("IPR") using the same claim construction standard that is used to construe claims in a civil action in federal district court. *See* 83 Fed. Reg. 51,340 (Nov. 13, 2018) (to be codified at 37 C.F.R. pt. 42).

In construing claims, district courts give claims their ordinary and customary meaning, which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Sources for claim interpretation include "the words of the claims themselves, the remainder of the specification, the prosecution history [i.e., the intrinsic evidence], and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "[T]he claims themselves [may] provide substantial guidance as to the meaning of particular claim terms." *Id.* However, the claims "do not stand alone," but are part of "a fully integrated written instrument,' consisting principally of a specification that concludes with the claims," and, therefore, the claims are "read in view of the specification." *Id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995)).

Petitioner proposes "[t]he meaning of all claim terms in the '149 patent are plain on their face and require no further construction." Pet. 21 (citing Ex. 1002 ¶ 61).

Patent Owner states, "[c]laim 1 of the '149 patent recites the complete amino acid sequence for SOLIRIS®, which was not known prior to the March 15, 2007 priority date: the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4," but does not contest Petitioner's claim construction position nor propose an alternative claim construction. *See generally* Prelim. Resp.; *see id.* at 15–16.

At this stage in the proceedings, and for the purposes of this decision, we find it unnecessary to construe the language of claim 1 because the claim language is readily understandable on its face, within the context of the claim, to the person of ordinary skill in the art. Should the evidence so-

demand as the case continues, we may determine that certain claim language should be interpreted.

C. LEGAL STANDARDS

BURDEN IN INTER PARTES REVIEW

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

ANTICIPATION

Regarding anticipation, our reviewing court has held:

> a patent is invalid [or unpatentable] as anticipated if "the [claimed] invention was described in" a patent or published application "before the invention by" the patentee. 35 U.S.C. § 102(e). In order to anticipate the claimed invention, a prior art reference must "disclose all elements of the claim within the four corners of the document," and it must "disclose those elements `arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). "However, a reference can anticipate a claim even if it `d[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would `at once envisage' the claimed arrangement or combination." *Kennametal[, Inc. v. Ingersoll Cutting Tool Co.]*, 780 F.3d [1376,] [ ] 1381 (alteration in original) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)); *see also Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1344 (Fed. Cir.

> 2016) ("[A] reference may still anticipate if that reference teaches that the disclosed components or functionalities may be combined and one of skill in the art would be able to implement the combination." (citing *Kennametal*, 780 F.3d at 1383)).

Microsoft Corp. v. Biscotti, Inc., 878 F.3d 1052, 1068 (Fed. Cir. 2017). Put another way, an anticipating reference must clearly and unequivocally disclose the claimed subject matter or direct those skilled in the art to the claimed subject matter without any need for picking, choosing, and combining various disclosures of the reference not directly related to each other by its teachings. *In re Arkley*, 455 F.2d 586, 587–88 (CCPA 1972).

Further, prior art cited as anticipating may incorporate other prior art by reference.

> Incorporation by reference provides a method for integrating material from various documents into a host document — a patent or printed publication in an anticipation determination — by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein.

Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1273, 1282 (Fed. Cir. 2000) (citations omitted). Also, "[a] single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014). However, "[i]nherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency." *Scaltech Inc. v. Retec/Tetra L.L.C.*, 178 F.3d 1378, 1384 (Fed. Cir. 1999) (citations omitted).

OBVIOUSNESS

Regarding obviousness, the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness as set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is reasonably likely to be unpatentable as obvious under 35 U.S.C. § 103(a) as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious, the answer depends on whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

With these standards in mind, we address Petitioner's challenges below.

D. GROUND 1 – ANTICIPATION BY HILLMEN

THE PARTIES' POSITIONS

Petitioner contends Hillmen anticipates the '149 patent's claim because "Hillmen expressly disclosed `an antibody that binds C5[']" because Hillmen disclosed administering eculizumab to patients, which was a known anti-C5 antibody. Pet. 24–25 (citing Ex. 1004, abstract; Ex. 1002 ¶¶ 71–73).

Petitioner contends "Hillmen's antibody necessarily `comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4' because Alexion admitted that Hillmen's eculizumab . . . necessarily possesses those very amino acid sequences." *Id.* at 25–27 (citing Ex. 1015, 738 (Boone Declaration ¶ 6)[13]; Ex. 1024, 109; Ex. 1025, 2 (these exhibits identify a trial "C02-001" as testing SOLIRIS). The Boone Declaration, cited by Petitioner, in relevant portion, states first that study C02-001 was a study of the effect of eculizumab (h5G1.1-mAb) on patients with PNH, that Dr. Boone had reviewed the eculizumab antibody used in that study and its amino acid sequence, and that Dr. Boone "concluded that the antibody (eculizumab) used in each of the studies . . . contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4." Ex. 1015, 735–38 (¶¶ 5–6). As noted in n.13 *supra*, the Boone Declaration is dated May 11, 2017.

Although Petitioner does not argue that Hillmen literally expressly disclosed the claimed antibody structure with SEQ ID NOs: 2 and 4 (which, we note, it does not), Petitioner's position is that, because Hillmen disclosed a trial of the SOLIRIS eculizumab antibody, and because Patent Owner conceded that eculizumab antibody to be the claimed anti-C5 antibody, that Hillmen inherently discloses the claimed sequences. Pet. 26–27 (citing *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004)).

Petitioner's inherency rationale, based on what Petitioner calls "the general knowledge in the relevant field" (*id.* at 30), is summarized as

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[13] Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone, dated May 11, 2017 (submitted during the prosecution of U.S. Application Ser. No. 15/148,839, which became the '149 patent) (Ex. 1015, 734–41, "Boone Declaration").

follows. Contemporaneously with Hillmen's disclosure, the skilled artisan would have known that Bowdish disclosed the entire amino acid sequence of eculizumab, but for a heavy chain CDR3 region, which Bowdish disclosed as substituted with a TPO (thrombopoietin) amino acid sequence; the skilled artisan, however, would have known that Evans disclosed the amino acid sequences of eculizumab's heavy and light chain variable domains, including this CDR3 region; alternatively, understanding the above regarding Evans, the skilled artisan would have also known Mueller disclosed the hybrid IgG2/IgG4 heavy chain and light chain constant domains of eculizumab; therefore, having all this knowledge, the skilled artisan would have known that Hillmen's disclosure of a trial of "eculizumab" was necessarily the claimed anti-C5 antibody with the claimed SEQ ID NOs: 2 and 4. Pet. 29–30 (citing Ex. 1006 ¶¶ 191–193, Figs. 13A, 13B; Ex 1007, 44:4–13; Ex. 1008, 52–53, 58–61; Ex. 1002 ¶¶ 58, 75–76).

Petitioner also relies on statements made by Patent Owner during the prosecution of related U.S. Patent Application Ser. No. 11/127,438 (expressly abandoned July 24, 2018), where, in arguing that disclosures upon which the applicant relied for priority were supportive of the then-pending claims, stated:

> Applicant respectfully disagrees and asserts that the priority applications provide ample written support for the claimed descriptions. For example, the priority documents each describe that "Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-scFv and functional fragments of h5G1.1 are *described in U.S. Patent No. 6,355,245* [Evans], the disclosures of which are incorporated herein in their entirely [*sic*] by this reference . . . Applicant submits that *h5G1.1* . . . [was] *well-known to one of ordinary skill in the art as eculizumab* . . . at the time of filing of priority applications.

See Pet. 12 (quoting Ex. 1049, 838–39 (emphasis Petitioner's)). Petitioner's point is that Patent Owner has taken a position that the antibody structure disclosed in Evans was well-known to the skilled artisan so that such a person of skill would have considered this structure to be the eculizumab in Hillmen, and the antibody was publically disclosed before the March 15, 2007 priority date of the '149 patent.

Patent Owner argues, "Prior to March 15, 2007, the priority date of the '149 patent, however, the unique amino acid sequence of SOLIRIS® was not publicly known or disclosed in the prior art." Prelim. Resp. 1. Patent Owner argues:

> If a POSA were searching for the sequence of "eculizumab" as described in the art, the literature as of March 15, 2007 identified an amino acid sequence and corresponding structure that is very different from what the '149 patent claims. In particular, publications describing the safety, efficacy, and clinically relevant biological activity of "eculizumab" consistently directed a POSA to the 1996 "Thomas" publication (AMG1023) for the structure and design of the antibody, which in turn described a humanized antibody constructed with a naturally-occurring "IgG4" heavy chain constant region. The claimed antibody of the '149 patent has a very different, uniquely engineered, non-naturally occurring constant region that was nowhere described in Thomas or the prior art literature showing the safety and efficacy of "eculizumab."

Id. at 2–3 (emphasis omitted).

It is Patent Owner's position that, reading Hillmen's disclosure of "eculizumab" and Hillmen's reference to Thomas, the skilled artisan would not have been directed to the version of eculizumab of the '149 patent's claim, but, as of the '149 patent's March 15, 2007 priority date, would have understood Hillmen to refer to Thomas's disclosed eculizumab, which is an IgG4 antibody, rather than a hybrid IgG2/IgG4 antibody with SEQ ID

NO: 2, as claimed. *Id.* at 3, 11–12 (referencing Ex. 1023). Patent Owner notes that Hillmen cites Thomas as *the* reference for eculizumab. *Id.* at 12 (citing Ex. 1004, 553 (which cites Ex. 1023 as reference "15")).

Patent Owner argues that:

> Thomas . . . described the design and testing of a humanized anti-C5 antibody (termed "humanized 5G1.1" or "h5G1.1") featuring an "IgG4" heavy chain constant region, which was selected because the IgG4 isotype was thought to avoid activating human complement. (AMG1023 at 1396, 1399.) Thomas reported data showing that the IgG4 humanized antibody had suitable affinity and specificity, and was as effective as the original mouse antibody (termed "murine 5G1.1" or "m5G1.1") in an *in vitro* assay showing activity blocking C5 cleavage and preventing lysis of blood cells due to complement activity. (AMG1023 at 1396.)

Id. at 12–13 (emphasis omitted).

Patent Owner states that "[t]oday, but not prior to the March 15, 2007 priority date for the '149 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in claim 1 of the '149 patent, namely, `a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'" *Id.* at 13–15 (emphasis omitted). Patent Owner argues that neither

> Hillmen [n]or Hill [could] have enabled a POSA to make and use the specific antibody recited in claim 1 without undue experimentation, because both Hillmen and Hill guided a POSA as of March 15, 2007 to make and use a very different antibody – the IgG4 isotype antibody of Thomas. *See, e.g., Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (for a reference to anticipate, "[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation").

Id. at 44 (emphasis omitted). Patent Owner further argues that

> [t]he mere naming of an investigational product (e.g., "eculizumab") in a prior art publication does not inherently

> anticipate later-filed patent claims detailing the specific structure or composition of that product (i.e., SEQ ID NOs: 2 and 4), if a POSA could not have necessarily determined the later claimed structure/composition from the information publicly available as of the priority date.

Id. at 46 (emphasis omitted) (citing *Endo Pharms. Solutions, Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378–83 (Fed. Cir. 2018)).

ANALYSIS

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has not carried its burden to show a reasonable likelihood of anticipation of the claim of the '149 patent under Ground 1.

Petitioner concedes Hillmen does not expressly disclose the claimed antibody, instead, Petitioner relies on the doctrine of inherency and a post-priority-date admission by Patent Owner that the pharmaceutical (eculizumab) referenced in Hillmen was actually the claimed antibody.

Hillmen states "[w]e tested the clinical efficacy of eculizumab, a humanized antibody that inhibits the activation of terminal complement components, in patients with PNH." Ex. 1004, 552. Hillmen further states, "[e]culizumab is a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components.[14,15] It binds specifically to the terminal complement protein C5 . . . ." *Id.* at 553. Citation "14" of Hillmen refers to Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 NATURE 323–27 (1988), which does not mention eculizumab; this reference is not an exhibit in this IPR. Citation "15" of Hillmen refers to Thomas (Ex. 1023), which discloses a monoclonal antibody (5G1.1) that recognizes the human complement protein C5, which was shown to effectively block C5 cleavage. *See* Ex. 1023, 1389. The parties appear to agree that Thomas does not disclose the claimed antibody.

Thomas discloses the process of developing a humanized antibody (h5G1.1 HuG4) for human C5:

> *Construction of a humanized h5G1.1 antibody*
>
> Having demonstrated the effective humanization of the 5G1.1 variable regions, an intact humanized antibody (IgG4 isotype) was constructed and produced in 293-EBNA cells. The avidity of this humanized antibody (h5G1.1 HuG4) for human C5, was compared to the murine 5G1.1 mAb by determining the ability of each to compete binding of biotinylated 5G1.1 mAb to CS (Fig. 9). The humanized h5G1.1 mAb had a two-fold lower avidity than the murine antibody. However, the humanized h5G1.1 HuG4 antibody was equipotent with the murine antibody at protecting PAEC from lysis by human serum, with a 0.5-fold molar ratio of antibody to C5 (1:1 ratio of antibody binding sites to C5) completely inhibiting lysis of the PAEC (Fig. 10).

Id. at 1396. This paragraph was the culmination of Thomas's described development of a humanized anti-C5 antibody.[14] We find nothing in Thomas that expressly discloses or alludes to a hybrid IgG2/IgG4 antibody. *See generally* Ex. 1023.

In view of the above, even with the understanding that, as argued by Petitioner, Bowdish and Evans disclosed an anti-C5 antibody or an anti-C5 antibody fragment (scFab) that taught or suggested eculizumab could be the hybrid IgG2/IgG4 antibody of the claim, we conclude that Thomas also disclosed that eculizumab was an IgG4 isotype antibody. This means that

[14] We note, Patent Owner argues that as of the '149 patent's priority date, many other references cited Thomas when referring to eculizumab. *See* Prelim. Resp. 23–25 (Table 1). Without going into detail, we find Patent Owner has accurately shown how other contemporaneous prior art references (e.g., Hill '05 (Ex. 1047) and Bell (Ex. 1005)) cited Thomas for this purpose.

"eculizumab" referred to and refers to a class or category of anti-C5 antibodies, also called 5G1.1 or h5G1.1 mAbs.

This is also supported by the portion of the prosecution history of related U.S. Patent Application Ser. No. 11/127,438 (Ex. 1049), cited by Petitioners and discussed above. Petitioner points us to the Remarks section of an Office Action Response dated August 2, 2011. In the relevant pages, Alexion states, "the priority documents each describe that `Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-scFv and functional fragments of h5G1.1 are described in U.S. Patent No. 6,355,245 [Evans] and `Inhibition of Complement Activity by Humanized Anti-C5 antibody and Single Chain Fv', Thomas et al., *Molecular Immunology*, Vol. 33, No. 17/18, pages 1389-1401, 1996, the disclosures of which are incorporated herein in their entirely by this reference." Ex. 1049, 838. This same portion also states, "Applicant submits that h5G1.1 and h5G1.1-scFv were well-known to one of ordinary skill in the art as eculizumab and pexelizumab, respectively, at the time of filing of priority applications." *Id.* This same portion further states,

> ***Applicant further submits that eculizumab was first constructed in the IgG4 isotype***, ***see***, e.g., the bridging paragraph of the left and right columns of page 1396 of ***Thomas*** et al. (1996), *Id.*, a copy of which is submitted herewith as Exhibit C, ***and then into the G2/G4 format, see Mueller*** et al. (1997) *Molecular Immunology*, Vol. 34, No. 6, pages 441-452, a copy of which is submitted herewith as Exhibit D, while ***in either form the h5G1.1 antibody was well known*** to be incapable to activate human complement . . .

and it was Alexion's ultimate point that "it was well-known to one of ordinary skill in the art at the time of filing of priority applications that eculizumab has a G2/G4 Fe portion, i.e., a mutated Fe portion, "which

would have arguably supported the then-pending claim(s). *Id.* at 838–39 (emphasis added). Therefore, the statements above support that "eculizumab" referred to and refers to a category of antibodies, not a single antibody structure as argued by Petitioner, and also supports that Thomas's disclosure of eculizumab disclosed the first construction of eculizumab, as urged by Patent Owner here.

Upon considering the facts here in view of Petitioner's reliance on *Crish*, 393 F.3d 1253, and Patent Owner's citation to *Endo Pharms.*, 894 F.3d 1374, we find the latter case analogous to the facts here. In *Crish*, the Federal Circuit found that a claim to the specific sequence of a promoter region of the hINV gene was inherently disclosed by the prior art's disclosure of this gene, but not its promoter's sequence, and disclosure of a plasmid used to produce the gene because "[t]he starting material plasmid necessarily contain[ed] the gene of interest, including the promoter region." *Crish*, 393 F.3d at 1257–59 (also holding that evidence of use of this prior art plasmid to produce un-claimed promoters was "irrelevant"). Thus, in *Crish*, the Federal Circuit held that there could be only one necessary (correct) result from the prior art's disclosure, which was the claimed promoter sequence; hence, it was inherently disclosed and the claim anticipated. Further, in *Crish*, the Federal Circuit found that the claim to the nucleotide sequence of the hINV gene promoter region was inherently disclosed by prior art that "specifically identified [the promoter region] by size and location" because "[t]he starting material plasmid necessarily contain[ed] the gene of interest, including the promoter region." *Id.* at 1257–59. Here, however, Hillmen does not "specifically identify" an

eculizumab antibody containing the sequence of SEQ ID NO: 2, as required by claim 1.

Endo Pharms. compels a different result under the facts here. In *Endo Pharms.*, the issue was again inherency (in the context of obviousness) where prior art scientific articles described clinical trials for a drug, which was later claimed as a formulation having a specific mixture of castor oil and benzyl benzoate; however, the scientific articles did not mention this mixture, but only the active component testosterone undecanoate. *Endo Pharms.*, 894 F.3d at 1278. It was later confirmed that the composition of the clinical trials described in the prior art scientific articles did, indeed, have the claimed mixture of castor oil and benzyl benzoate. *Id.* The Federal Circuit held that because it was not demonstrated that a skilled artisan could extrapolate the vehicle formulation (mixture of castor oil and benzyl benzoate) used in the prior art scientific articles based on the performance data (pharmacokinetics) reported, i.e., such performance could not have only been attributed to the claimed formulation, the generic disclosure of the pharmaceutical formulation in the prior art did not inherently disclose the claimed formulation. *Id.* at 1281–83. Furthermore, *Endo Pharms.* distinguished *Crish* because that case was about the inherent properties of a known prior art product, rather than a product that was named, but not known or determinable based on the prior art disclosure of its performance characteristics. *Id.* at 1383.

Here, the prior art reference, Hillmen, discloses a clinical trial of "eculizumab." Ex. 1004, 552, 553. However, Hillmen does not explicitly identify the structure of the antibody tested, other than calling it "eculizumab" and referencing Thomas. *Id.* at 553 (citing Ex. 1023).

Thomas discloses a version of eculizumab different from that claimed (an IgG4 isotype rather than a hybrid IgG2/IgG4 antibody). Even accepting that it was possible the skilled artisan would have known of a hybrid IgG2/IgG4 antibody, as claimed (*see, e.g.*, Ex. 1002 ¶ 13), Hillmen's mere reference to "eculizumab" would have at least invoked the Thomas IgG4 isotype eculizumab, too. Thus, Hillmen's disclosure of "eculizumab" would not have necessarily led the skilled artisan to the claimed antibody with "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." Therefore, under *Endo Pharms.*, there is no inherent anticipation of claim 1 over Hillmen.

Moreover, although Hillmen cites Thomas and thereby invokes Thomas's disclosed eculizumab antibody, Bowdish, Evans, and/or Mueller are not cited in Hillmen. *See* Ex. 1004, 559. Therefore, Petitioner's discussion of Hillmen in view of Bowdish and Evans or in view of Evans and Mueller (*see* Pet. 29–30) is not relevant under an anticipation ground for unpatentability. We also disagree with Petitioner's position that such references' teaching, even if considered "general knowledge," would have somehow overridden Hillmen's direct invocation of Thomas's disclosure of eculizumab so as to point the skilled artisan to some alternative antibody structure.

Again, to summarize, based on the evidence presented at this stage in the proceedings, Petitioner has not shown that there is reasonable likelihood that the '149 patent's claim 1 is anticipated by Hillmen under Ground 1.

E. GROUND 2 – ANTICIPATION BY HILL '05

THE PARTIES' POSITIONS

We note at the outset that Petitioner's Ground 2 is, as is Hill '05's disclosure with respect to Hillmen's, an extension of Ground 1 and relies on substantially the same or similar facts and bases in law. *See* Pet. 31–34. Petitioner argues "[a]s in Ground 1, the law also compels finding anticipation in Ground 2." *Id.* at 34 (again citing, *inter alia*, *Crish*, 393 F.3d at 1258).

Petitioner contends, "Hill '05 is an Alexion publication describing results from a one-year extension study involving the same 11 patients enrolled in the Hillmen Phase 2 Pilot Study." Pet. 31 (citing Ex. 1047, 2559–60). Petitioner argues Hill '05, like Hillmen, is directed to and discloses administering "eculizumab" to such patients. *Id.* (citing Ex. 1047, 2565). Petitioner's rationale for Hill '05's anticipation of the '149 patent's claim is essentially the same as discussed above for Hillmen, only replacing Hillmen's generic disclosure for "eculizumab" with Hill '05's generic disclosure for "eculizumab," paired with the same identified admissions by Patent Owner during prosecution and the same contentions that Bowdish, Evans, and Mueller, rather than Thomas, would be the skilled artisan's basis for the structure of eculizumab. *See* Pet. 31–34 (citing Ex. 1015, 736, 783; Ex. 1047, abstract, 2559–60; Ex. 1002 ¶¶ 42–58, 79–86; Ex. 1004, abstract, 554; Ex. 1042, Abstract; Ex. 1011, abstract; Ex. 1005 ¶¶ 81–96; Ex. 1012, abstract, 1235; Ex. 1013, abstract; Ex. 1006 ¶¶ 191–193, Figs. 13A, 13B; Ex. 1007, 44:4–13; Ex. 1008, 52–53, 58–61).

Patent Owner argued Grounds 1 and 2 together and, thus, makes essentially the same arguments over Ground 2 as discussed above regarding Ground 1. *See* Prelim. Resp. 42–49.

ANALYSIS

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has not carried its burden to show a reasonable likelihood of anticipation of the claim of the '149 patent under Ground 2.

Upon reviewing Hill '05, we find its disclosure to be no more specific as to the structure of eculizumab than that of Hillmen. *See generally* Ex. 1047. Hill '05 states, "[w]e previously reported the outcome of an open-label study of eculizumab in patients with PNH.[2]" Ex. 1047, 2559 (reference "2" is Hillmen (Ex. 1004)). Hill '05 further states, "[e]culizumab is a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage.[9]" *Id.* (reference "9" is Thomas (Ex. 1023)). Thus, Hill '05, like Hillmen, invokes Thomas as a reference for eculizumab.

For the same reasons discussed above regarding Ground 1, based on the evidence presented at this stage in the proceedings, Petitioner has not shown that there is reasonable likelihood that the '149 patent's claim 1 is anticipated by Hill '05 under Ground 2.

F. GROUND 3 – ANTICIPATION BY BOWDISH

THE PARTIES' POSITIONS

It is Petitioner's position that Bowdish, which incorporates Evans by reference, discloses the entirety of the claimed anti-C5 antibody as a starter scaffold antibody.

Petitioner contends that Bowdish disclosed "a 5G1.1 antibody as the starter `scaffold' antibody sequence for creating a recombinant TPO-mimetic+h5G1.1 antibody." Pet. 35 (citing Ex. 1006 ¶ 191). Petitioner argues Bowdish disclosed "the full 5G1.1 antibody amino acid sequence [i.e., an anti-C5 antibody, as claimed,] except for the heavy chain CDR3 (HCDR3) sequence, which Bowdish replaced with the TPO-mimetic peptide sequence, LPIEGPTLRQWLAARAPV." *Id.* (citing Ex. 1006 ¶¶ 191–193, Figs. 13A (SEQ ID NO: 67; "5G1.1 –TPO Heavy Chain (Bold Denotes TPO mimetic) Amino acid sequence"), 13B (SEQ ID NO: 69; "5G1.1 Light Chain Amino Acid Sequence")).

Petitioner argues:

> A POSA would have understood that the only portion of the "scaffold" 5G1.1 antibody sequence not expressly disclosed in Bowdish is the HCDR3 sequence because Bowdish taught that "[t]he TPO mimetic peptide graft in Fab clone X4b has been *transplanted into the heavy chain CDR3* of another antibody framework, *5G1.1* . . . The sequence was *cloned into 5G1.1* in such a fashion as to *replace the native CDR3*."

Pet. 37–38 (citing Ex. 1006 ¶ 191; Ex. 1002 ¶¶ 91–93). Petitioner also argues, "Bowdish disclosed that the starter scaffold antibody 5G1.1 was produced according to Evans, stating that `[c]onstruction of 5G1.1 is described in [Evans], incorporated herein by reference.'" *Id.* at 38 (citing Ex. 1006 ¶ 191). Thus, it is Petitioner's contention that "a POSA would have known that the heavy chain of Bowdish's 5G1.1 starter antibody contained the YFFGSSPNWYFDV CDR3 sequence [of Evans], regardless of which `version' of Evans' humanized 5G1.1 the POSA considered." *Id.* at 38–39 (citing Ex. 1002 ¶ 95).

Petitioner points to the Balthasar Declaration (¶¶ 49–54, 58, 88–103) as support for and for an explanation as to how Bowdish discloses the claimed antibody. Pet. 35–41. The Balthasar Declaration states, "[a] POSA would have understood that Bowdish's `5G1.1' antibody is an anti-C5 antibody based on Bowdish's citation to Evans" which describes the anti-C5 antibody 5G1.1 "for information about `[c]onstruction of 5G1.1' . . . [and], Bowdish's `5G1.1' antibody necessarily comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." Ex. 1002 ¶ 89. The Balthasar Declaration states, "a POSA would have known that the only portion of the sequence disclosed in Bowdish's Figures 13A-13B that is different from the original h5G1.1 `scaffold' antibody disclosed in Bowdish is the portion of [its] SEQ ID NO: 67 that corresponds to the TPO peptide." *Id.* ¶ 92. The Balthasar Declaration explains, at length, how and why the Bowdish anti-C5 antibody starter scaffold and the Evans 5G1.1 antibody or antibody fragment with CDR3 amino acid sequence fit together (*see, e.g.*, Ex. 1002 ¶¶ 91–102), however, the combination and its relevance to the claimed antibody is perhaps best illustrated by the Balthasar Declaration's Figures 4, 5, 6, 7, and 13, which show Bowdish's SEQ ID NO: 67 as compared to the claimed SEQ ID NO: 2, Bowdish's SEQ ID NO: 69 as compared to the claimed SEQ ID NO: 4, Evans exemplary SEQ ID NO: 20 as compared to the claimed SEQ ID NOs: 2 and 4, and Bowdish's SEQ ID NO: 67 with Evan's heavy chain CDR3 sequence replacing the TPO peptide sequence as compared to the claimed SEQ ID NO: 2. We reproduce these figures below:

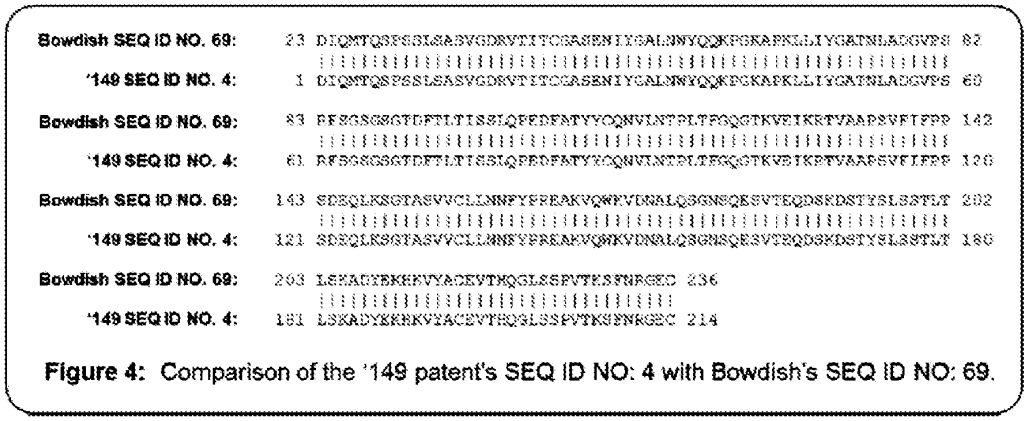


Figure 4: Comparison of the '149 patent's SEQ ID NO: 4 with Bowdish's SEQ ID NO: 69.

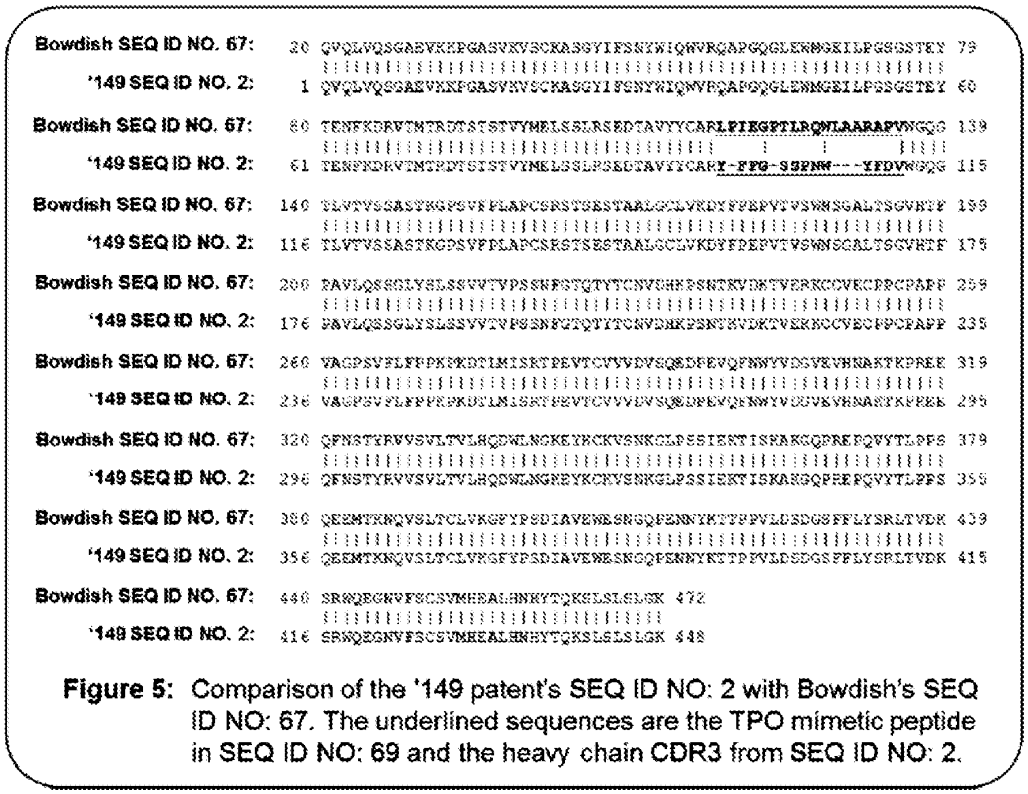


Figure 5: Comparison of the '149 patent's SEQ ID NO: 2 with Bowdish's SEQ ID NO: 67. The underlined sequences are the TPO mimetic peptide in SEQ ID NO: 69 and the heavy chain CDR3 from SEQ ID NO: 2.

Balthasar Declaration Figure 4 (above-top) shows that Bowdish's disclosed antibody amino acid sequence SEQ ID NO: 69 (minus leader sequences, which would be cleaved off as part of the maturation of the antibody) matches with the claimed antibody amino acid sequence SEQ ID NO: 4. Ex.

1002 ¶ 51. Balthasar Declaration Figure 5 (above-bottom) shows that Bowdish's disclosed antibody amino acid sequence SEQ ID NO: 67 (minus leader sequences) matches with the claimed antibody amino acid sequence SEQ ID NO: 2, except for the portion including the TPO mimetic amino acid sequence (underlined). *Id.*

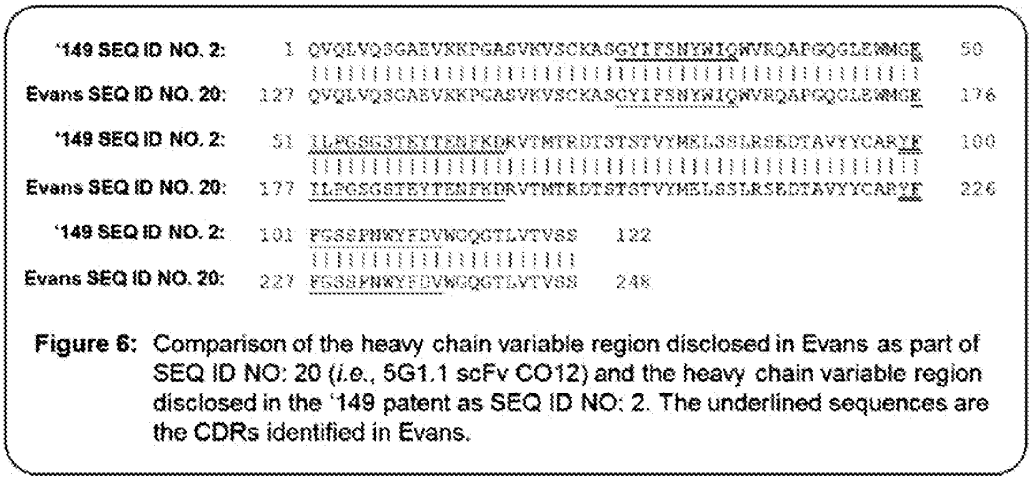


Figure 6: Comparison of the heavy chain variable region disclosed in Evans as part of SEQ ID NO: 20 (*i.e.*, 5G1.1 scFv CO12) and the heavy chain variable region disclosed in the '149 patent as SEQ ID NO: 2. The underlined sequences are the CDRs identified in Evans.

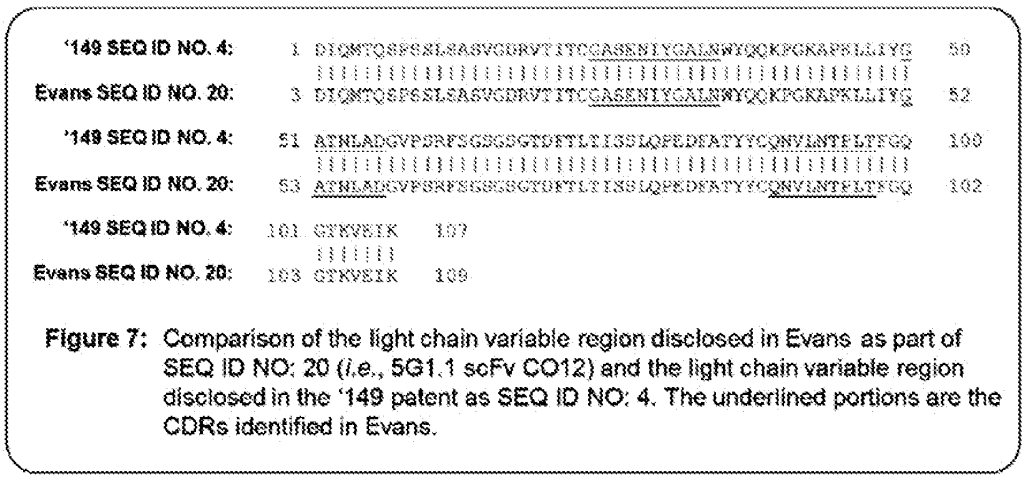


Figure 7: Comparison of the light chain variable region disclosed in Evans as part of SEQ ID NO: 20 (*i.e.*, 5G1.1 scFv CO12) and the light chain variable region disclosed in the '149 patent as SEQ ID NO: 4. The underlined portions are the CDRs identified in Evans.

Balthasar Declaration Figure 6 (above-top) shows that Evans's disclosed antibody amino acid heavy chain variable region sequence SEQ ID NO: 20 matches with the claimed antibody amino acid sequence SEQ ID NO: 2. Ex.

1002 ¶ 53. The underlined sequences are the CDRs identified in Evans. Balthasar Figure 7 (above-bottom) shows that Evans' disclosed antibody amino acid light chain variable region sequence SEQ ID NO: 20 (i.e., 5G1.1 scFv CO12) matches with the claimed antibody amino acid sequence SEQ ID NO: 4. *Id.* Again, the underlined portions being Evans' s CDRs.

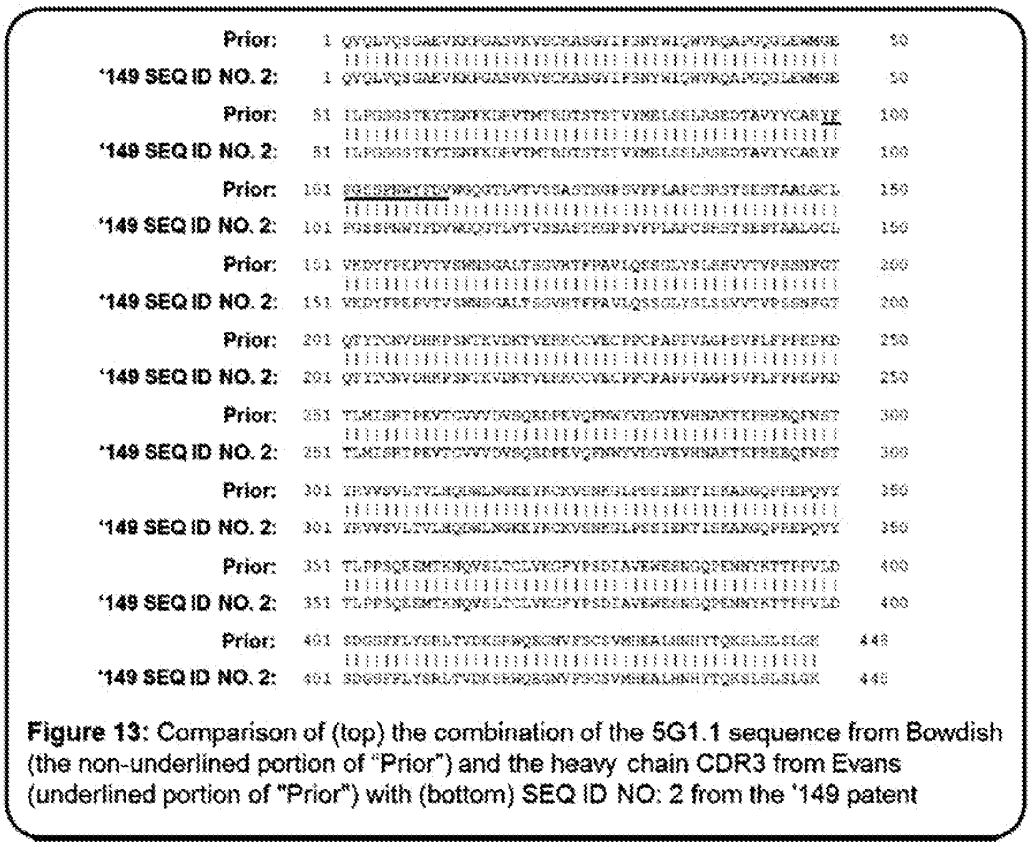


Figure 13: Comparison of (top) the combination of the 5G1.1 sequence from Bowdish (the non-underlined portion of "Prior") and the heavy chain CDR3 from Evans (underlined portion of "Prior") with (bottom) SEQ ID NO: 2 from the '149 patent

Balthasar Declaration Figure 13 (above) shows how, once Evans' s disclosed antibody amino acid heavy chain variable region sequence (underlined) is provided in Bowdish' s anti-C5 antibody scaffold structure, as it would have been before its replacement with the TPO sequence, the antibody sequence matches with the claimed antibody amino acid sequence SEQ ID NO: 2. Ex.

1002 ¶ 53. Having already shown in the Balthasar Declaration Figure 4, above, that Bowdish's SEQ ID NO: 69 matches the claimed SEQ ID NO: 4, Balthasar Declaration's Figure 13, above, accounts for the remainder of the claimed antibody.

Further to the above, the Balthasar Declaration further illustrates how the Bowdish, and its incorporated-by-reference Evans, antibody amino acid sequences fit together as the Bowdish starting 5G1.1, anti-C5 antibody scaffold at Figure 12, reproduced below:

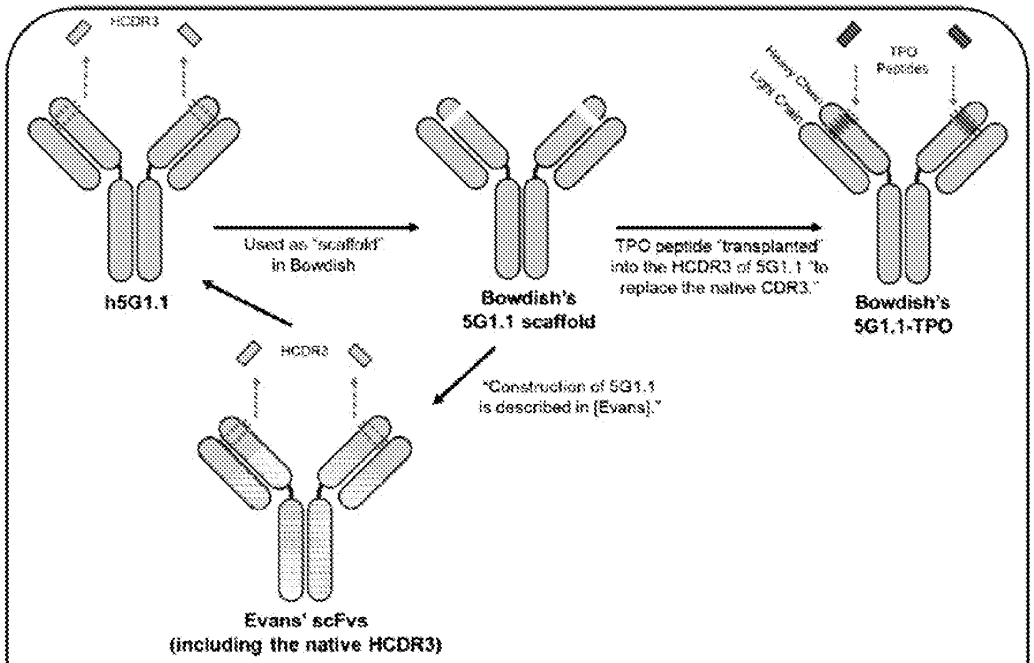


Figure 12: Diagram showing how the 5G1.1 sequence in Bowdish was used as a scaffold into which a TPO mimetic peptide was inserted to generate the 5G1.1-TPO construct (top row). The diagram also shows how the original 5G1.1 sequence could have been generated by inserting the heavy chain CDR3 region from Evans' svFvs into the 5G1.1 scaffold sequence (bottom row)

Balthasar Declaration Figure 12 (above) shows the original Bowdish scaffold antibody, the portion of that antibody removed and replaced with the TPO amino acid sequence, and how Evans's HCDR3-portion amino acid

sequence was that original amino acid portion replaced by the TPO amino acid sequence. Ex. 1002 ¶ 96.

The Balthasar Declaration states, "[a] POSA would have known that Bowdish explicitly disclosed the entire amino acid sequence of 5G1.1 with the exception of the heavy chain CDR3 region, and that the incorporated reference Evans provided the sequence of that missing heavy chain CDR3 region—and that "[c]onstructing the sequence of the source 5G1.1 antibody—which aligns perfectly with the [ ] claimed antibody—would have required only standard molecular and cellular biology methods that were well known in the art to provide predictable results." *Id.* ¶ 102 (citing Ex. 1006 ¶¶ 191–93, Figs. 13A, 13B; Ex. 1007, 21:4–24:61, 44:4–13; Ex. 1008, 37:37–39). Furthermore, although the Balthasar Declaration focuses on Evans's SEQ ID NO: 20 as evidence that its CDR3 sequence would be found in the original Bowdish antibody, the Balthasar Declaration states:

> a POSA would have seen that all of the 5G1.1 heavy chains in Evans contain the same CDR3 sequence: YFFGSSPNWYFDV. AMG1007, e.g., Fig. 19, 43:13-14, 43:26-27, 43:33-34, 43:60-61, 44:2-3, 44:12-13, 44:21-22, 44:30-31, 44:39-40, 44:49-50, 44:59-60, 45:3-4. A POSA therefore would have understood that Bowdish (via its incorporation of Evans) teaches that YFFGSSPNWYFDV is the sequence of the 5G1.1 heavy chain CDR3 (i.e., the heavy chain CDR3 of eculizumab).

Ex. 1002 ¶ 95 (emphasis omitted).

Patent Owner argues Bowdish is "a non-analogous reference" and "would not have disclosed or enabled the uniquely-engineered anti-C5 antibody of claim 1." Prelim. Resp. 3, 49. Patent Owner argues, at various points in its Preliminary Response, that neither Bowdish nor Evans uses the term "eculizumab." *Id.* at 4, 29.

Patent Owner also argues that,

> neither Bowdish's reference to using "5G1.1" as a scaffold for a TPO-mimetic peptide (AMG1006 ¶ [0066], [0191]), nor Bowdish's citation to Evans (*id.* ¶ [0191]), would have explained to a POSA how Bowdish's TPO-mimetic construct relates to the structure of "eculizumab," including the structure of its heavy chain constant region.

Prelim. Resp. 33–34. Patent Owner's point being that the skilled artisan would not read Bowdish, which incorporates Evans by reference, as disclosing the starting antibody structure that ultimately resulted in the TPO-mimetic construct.

Patent Owner also argues Bowdish does not expressly disclose "an antibody `comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'" Prelim. Resp. 49. Patent Owner argues that it is error to look to Evans's disclosure as it relates to Bowdish for anticipation because "the law makes clear that anticipation cannot be shown by combining portions of the claimed invention from multiple references." *Id.* at 50 (citing *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002).

Patent Owner also argues that, even considering Bowdish and Evans together, "Amgen fails to show how Bowdish and Evans together would have disclosed `[a]n antibody that binds C5' comprising the specific, uniquely-engineered amino acid sequence of claim 1 of the '149 patent." Prelim. Resp. 50. Patent Owner's argument is that Bowdish is focused on its TPO-mimetic construct and has nothing to do with C5 binding. Patent Owner contends that Bowdish's use of the term "5G1.1" in reference to its antibody scaffold would not have taught an anti-C5 antibody. *Id.* at 51. Patent Owner also argues that Evans would not have taught the skilled

artisan that an antibody with its variable region sequences would be an anti-C5 antibody. *Id.*

ANALYSIS

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has carried its burden to show a reasonable likelihood of anticipation of the claim of the '149 patent under Ground 3.

We are satisfied on the record before us, as discussed above, that Bowdish, which incorporates Evans, discloses a 5G1.1 antibody with a structure as disclosed by Bowdish's Figures 13A and 13B, but, rather than having a TPO mimetic peptide grafted therein at the heavy chain CDR3 portion, having the CDR3 amino acid sequence disclosed by Evans. *See* Ex. 1006 ¶ 191, Figs. 13A, 13B; Ex. 1007, 7:62–63, 10:9–10, 42:55–45:33, 121–123 (SEQ ID NO: 20), Figs. 18, 19; *see also* Ex. 1002 ¶¶ 49–54, 58, 88–103, Figs. 4, 5, 6, 7, 12, 13 (Balthasar Declaration explaining Bowdish's disclosure). On this record, Bowdish's disclosed starting 5G1.1 antibody is disclosed to be identical to the claimed anti-C5 antibody (Evans confirms that its 5G1.1 antibody, referenced by Bowdish, is anti-C5).

Furthermore, the Balthasar Declaration supports that only standard, well-known, molecular and cellular biology methods would have be required to both identify the starting 5G1.1 antibody structure of Bowdish (based on Evans) and that the skilled artisan would have been able to make such an anti-C5 antibody with the claimed amino acid sequences based on this disclosure. Ex. 1002 ¶¶ 102–103. This conclusion is bolstered by Bowdish's disclosure, which states "[t]hose of ordinary skill in the art using known techniques would be able to synthesize antibodies." Ex. 1006 ¶ 131.

Regarding Patent Owner's opening volley that Bowdish is not analogous art,

> [T]he question whether a reference is analogous art is irrelevant to whether that reference anticipates. A reference may be from an entirely different field of endeavor than that of the claimed invention or may be directed to an entirely different problem from the one addressed by the inventor, yet the reference will still anticipate if it explicitly or inherently discloses every limitation recited in the claims.

In re Schreiber, 128 F.3d 1473, 1478 (Fed. Cir. 1997). Further, although Patent Owner is correct that the word "eculizumab" does not appear in the disclosures of Bowdish or Evans, neither does it appear in the claim of the '149 patent, and Bowdish and Evans clearly disclose anti-C5 antibodies and/or fragments thereof, i.e., 5G1.1 mAb, 5G1.1 scFv CO12. *See, e.g.*, Ex. 1006 ¶ 191 (antibody framework 5G1.1, as constructed by Evans); Ex. 1007, 7:62–63 (5G1.1 is most preferred anti-C5 antibody), 44:4–13. In any event, even though the ultimate objectives of Bowdish are not to produce a therapeutic anti-C5 antibody, as is the focus of the '149 patent (and Evans), Bowdish is nonetheless directed, in part, to such an antibody and requires it as a starting point for other uses (as a scaffold), and Bowdish expressly integrates the disclosure of Evans, which *is* directed to such therapeutic anti-C5 antibodies. Thus, Bowdish "is from the same field of endeavor, regardless of the problem addressed" or "is reasonably pertinent to the particular problem with which the inventor is involved," even if it is not within the inventor's field of endeavor. *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000–01 (Fed. Cir. 2016) (quoting *In re Clay*, 966 F.2d 656, 658–59 (Fed. Cir. 1992)).

As for Patent Owner's contention that Bowdish does not expressly disclose the claimed amino acid sequences, Bowdish incorporates Evans by reference (Ex. 1006 ¶ 191), which means that Evans's disclosure, in particular that portion describing the construction of a 5G1.1 antibody, is integrated from Evans into the Bowdish host document; Bowdish makes clear that Evans is effectively part of Bowdish as if it were explicitly contained therein. *See Advanced Display Sys.*, 212 F.3d at 1282. Petitioner is not "combining" Bowdish and Evans. Bowdish has already combined the two as an integrated document.

Regarding Patent Owner's argument that Bowdish has nothing to do with an anti-C5 antibody and its use of the term "5G1.1" would not refer to such, we disagree. Bowdish is clear that its starting antibody is the antibody with a structure as shown in its Figures 13A and 13B, but constructed as Evans taught to construct a 5G1.1 antibody, which Evans confirmed is an anti-C5 antibody. *See* Ex. 1006 ¶ 191; Ex. 1007, cols. 7–8.

Again, to summarize, based on the evidence presented at this stage in the proceedings, it has been shown that there is reasonable likelihood that the '149 patent's claim 1 is anticipated by Bowdish, which incorporates Evans by reference, under Ground 3.

G. OBJECTIVE EVIDENCE INDICATING NON-OBVIOUSNESS

Factual considerations that underlie the obviousness inquiry include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations, or objective indicia, evidencing non-obviousness. *See Graham*, 383 U.S. at 17–18. Relevant secondary considerations include commercial success, long-felt but unsolved needs,

Samsung Bioepis Exhibit No. 1002
Page 13027

failure of others, and unexpected results. *KSR*, 550 U.S. at 406, (2007). Although evidence pertaining to secondary considerations must be taken into account whenever present, it does not necessarily control the obviousness conclusion. *See*, *e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

Before moving on to Petitioner's grounds based on obviousness, we address Petitioner's contention that "[t]here are no objective indicia of nonobviousness." Pet. 41, 47, 48, 57–58. In particular, Petitioner notes that during the prosecution of the '149 patent's parent application (the '504 patent), Alexion argued that the claimed heavy chain of eculizumab, i.e., the hybrid IgG2/IgG4 constant domain, provided surprising and unpredictable results, such as decreased effect or function, reduced immunogenicity, and increased half-life. Pet. 57 (citing Ex. 1014, 588, 593 (¶ 8)). Petitioner contends the claimed sequence of eculizumab was well-known in the art and that the alleged surprising and unpredictable features of the antibody were not shown to have a nexus with the claim limitations. *Id.* (citing Ex. 1034, 1279). Petitioner further contends that, in view of Mueller II, antibodies with the claimed hybrid IgG2/IgG4 heavy chain were known not to bind FcR and to be less immunogenic, and that it would have been known that antibodies with this claimed hybrid heavy chain would have an increased half-life. *Id.* at 57–58 (citing Ex. 1031, 488, 451; Ex. 1032, 5, 19; Ex. 1002 ¶ 140).

Patent Owner contends that evidence of commercial success, long-felt, but unmet need, and industry praise supports the non-obviousness of the challenged claim. Prelim. Resp. 60.

Patent Owner argues that SOLIRIS, the product embodying the claimed antibody, is a commercial success, having produced annual net product sales in excess of $1 billion in 2018. *Id.* (citing Ex. 2018, 70). Patent Owner contends that this commercial success "has a direct nexus to the patented features of the '149 patent, which claims the uniquely-engineered, non-naturally occurring antibody responsible for the drug's clinical (and therefore commercial) success as a treatment for PNH, as well as the complement-mediated hemolytic condition aHUS." *Id.* at 61.

At this stage in the proceedings, based on the evidence presented by Patent Owner, it is apparent that SOLIRIS is a successful product. "[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). This "presumption of nexus is rebuttable: a patent challenger may respond by presenting evidence that shows the proffered objective evidence was `due to extraneous factors other than the patented invention.'" *Id.* Here, the parties appear to agree that the claim of the '149 patent is directed to the commercial product SOLIRIS. However, commercial success "is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention 'as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter.'" *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996).

Patent Owner argues that because SOLIRIS is "the first FDA-approved treatment to reduce hemolysis in patents with PNH, 'there is

evidence that the claimed antibody fulfilled a long-felt, unmet need in the market. Prelim. Resp. 61 (citing Ex. 2019, 1270).

At this stage in the proceeding, the available evidence supports that anti-C5 antibodies were considered potential therapeutic options for many years before 2007, and that Alexion's eculizumab product is currently the only complement-specific antibody on the market and is the first and only approved therapy for PNH. Ex. 2019, 1270. Again, it may be presumed that there is a nexus between the claimed and novel elements of the SOLIRIS product and the meeting of the long-felt need. However, "[w]here the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Patent Owner also contends "SOLIRIS® also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade . . . ." Prelim. Resp. 61 (citing Ex. 2020; Ex. 2021).

As with the other two contended bases for indicia of non-obviousness, although it is apparent there was high praise for the SOLIRIS product from the relevant industry, there is a rebuttable presumption that this praise has a nexus with the claimed subject matter. *Cf. In re Kao*, 639 F.3d at 1068.

With the above-discussed arguments and evidence in mind when considering obviousness, we consider Petitioner's grounds for unpatentability below. However, given the early stage of these proceedings, we decline to accord much weight to Patent Owner's substantially untested evidence of objective indicia of non-obviousness. The parties will have the

opportunity to further develop the relevant facts during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

H. Ground 4 – Obviousness Over Bell, Bowdish, and Evans

The Parties' Positions

Petitioner's Ground 4, although based in obviousness, is substantially similar in many respects to the anticipation Ground 3, discussed above. Ground 4, like Ground 3, cites Bowdish and Evans, but combines their relevant disclosure with the Bell reference. Petitioner's arguments on Ground 4 also echo those of Ground 3 to the extent they discuss Bowdish and Evans. *See* Pet. 41–44. Thus, the discussion above for Ground 3 also applies here to Ground 4 and we supplement this discussion as needed to identify and address the parties' additional arguments unique to this ground.

Petitioner additionally contends:

> Bell taught that targeting complement protein C5 with eculizumab (h5G1.1) is safe and effective for treating PNH patients, providing ample reason for a POSA to make a humanized anti-C5 antibody such as eculizumab. AMG1005, ¶¶[0083]-[0096]. Because Bell does not expressly provide the amino acid sequence of its anti-C5 antibody, a POSA would have looked to other known teachings in the art pertaining to eculizumab (5G1.1), like Bowdish and Evans.

Pet. 45. Petitioner argues that this would have led the skilled artisan to combine Bowdish and Evans with Bell. *Id.* Petitioner's premise is that, having Bell in hand and knowing an anti-C5 antibody (eculizumab) was a desirable product, the skilled artisan would have consulted Bowdish and Evans, each of which refers to its antibody as 5G1.1, in order to identify the structure (amino acid sequence) of eculizumab. *See* Ex. 1005 ¶¶ 12, 52 ("Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other

functional fragments of h5G1.1 are described in U.S. Pat. No. 6,355,245 [Evans] and . . . Thomas et al., . . . the disclosures of which are incorporated herein in their entirety by this reference.□), ¶¶ 81□96 (discussing eculizumab as the anti-C5 antibody h5G1.1-mAb); Ex. 1006 ¶ 191 (identifying a 5G1.1 antibody constructed as in Evans); Ex. 1007 cols. 7□8 (discussing antibodies to human complement component C5, i.e., anti-C5 antibodies, as 5G1.1); *see also* Ex. 1002 ¶ 107 (□Bell discloses `an antibody that binds C5' as required by claim 1 in its disclosure of eculizumab, and provides a reason to make that antibody.□).

Petitioner cites the Balthasar Declaration (¶¶ 101□119) as explaining how and why the skilled artisan would have combined Bell, Bowdish, and Evans so as to achieve the claimed anti-C5 antibody (the Declaration's rationale for obviousness is, as expected, very similar to the rationale set forth for anticipation under Ground 3). The Balthasar Declaration states:

> a POSA would have had reason to combine the disclosures of Bell, Bowdish and Evans to arrive at the antibody of claim 1, and would have had a reasonable expectation of doing so because these three references provide complementary information relating to an anti-C5 antibody that would have required only routine techniques to combine.

Ex. 1002 ¶ 106. The Balthasar Declaration states that □Bell concluded that `[p]atients in the two year study experienced a reduction in adverse symptoms associated with PNH' □and □Bell's report of successfully treating PNH with eculizumab would have provided reason for a POSA to make eculizumab for the same purposes.□ *Id.* ¶ 107 (quoting Ex. 1005 ¶ 96). The Balthasar Declaration notes that Bell identifies that the anti-C5 antibody eculizumab is useful, but does not expressly disclose its structure, in particular the heavy chain with SEQ ID NO: 2 and the light chain with SEQ

ID NO: 4, but the Declaration indicates that Bowdish and Evans disclose as much and that Bowdish and Evans would be referenced by the skilled artisan wanting to obtain this antibody. Ex. 1002 ¶¶ 108–117. As such, Petitioner's rationale for motivation to combine these references is supported.

Petitioner argues that the skilled artisan would have had a reasonable expectation of successfully combining the cited prior art to achieve an anti-C5 antibody as claimed because, as with Ground 3, "only basic molecular biology techniques" were required. Pet. 47 (citing Ex. 1002 ¶ 118 ("A POSA would have had a reasonable expectation of success in making the antibody of claim 1 from the disclosures of Bell, Bowdish, and Evans because doing so would have required only basic molecular and cellular biology techniques.")). As further support for this, as already noted above, Bowdish expresses that "[t]hose of ordinary skill in the art using known techniques would be able to synthesize antibodies" and Evans describes such techniques for producing an anti-C5 antibody as a pharmaceutical agent for humans. Ex. 1006 ¶ 131; Ex. 1007, 7:6–13, 19:46–67, 21:4–24:64, 37:35–45:33; 121–123 (SEQ ID NO: 20).

Patent Owner argues that, absent impermissible hindsight, the skilled artisan would not have combined, or reasonably expected success in combining, Bowdish, Evans, and Bell. Prelim. Resp. 5, 52–55. Patent Owner argues that Bell, like Hillmen, taught eculizumab was the antibody of Thomas, i.e., an IgG4 constant-region-antibody, and nothing in the other references would point the skilled artisan toward a different antibody, e.g., the antibody covered by the claim. *Id.* As a tertiary part of this hindsight argument, Patent Owner also argues Thomas taught away from the claimed

invention because Thomas described an "eculizumab" with an IgG4 constant region. *Id.* at 53.

Patent Owner argues that Petitioner has overlooked "the complexity and unpredictability involved in designing monoclonal antibodies for human clinical therapy, where even small changes to the amino acid sequence (including in the "constant" regions) could significantly impact the antigen-binding affinity and specificity of the antibody, as well as the antibody's clinical efficacy and safety." Prelim. Resp. 39 (citing Ex. 2015, 506, 508; Ex. 2017, 961–62). Patent Owner's contention is that, in view of this complexity and unpredictability, the skilled artisan would not have ventured away from Thomas's known antibody; i.e., would not have looked to Bowdish and Evans (or Mueller) to teach such an antibody. *Id.* at 41.

Patent Owner also argues that "[e]ven if Bowdish and Evans were combined as per Amgen's hindsight-driven theory, a POSA would not have reasonably expected the resulting compound to work in binding to C5 or safely and effectively treating conditions such as PNH." *Id.* at 56. Patent Owner's rationale is that even small changes could substantially impact an antibody's binding properties, safety, and efficacy for human administration. *Id.* Patent Owner also argues that Bell, in citing Thomas for preparation of h5G1.1-mAb, taught away from the prior art combination or changing the antibody to be the claimed structure. *Id.* at 56–57.

ANALYSIS

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has carried its burden to show a reasonable likelihood of that the claim of the '149 patent would have been obvious under Ground 4.

"It is well settled that `anticipation is the epitome of obviousness.' " *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)); accord *Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008). Here, on the facts before us, there is no reason to depart from this well-settled principle of law. As we have noted above in this and the preceding section, we have found on the record before us at this preliminary stage that there is a reasonable likelihood that claim 1 is anticipated by Bowdish, which incorporates, i.e., is necessarily combined with, Evans. Thus, likewise, there is a reasonable likelihood that the claim would have been obvious over these references for the same reasons under the legal standards for obviousness set forth above. Adding the disclosure of Bell to the combination of Bowdish and Evans serves to reinforce the proposition that a 5G1.1 antibody as taught by Bowdish and Evans would be desirable to the skilled artisan.[15]

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[15] Patent Owner at one point notes that "Amgen suggests that `eculizumab' was somehow disclosed or claimed by the Evans patent (AMG1007) (e.g., Petition 2, 46, 49-50) "but it is undisputed that Evans neither used the term `eculizumab,' nor disclosed the heavy chain constant region or full sequence of the claimed antibody of the '149 patent." Prelim. Resp. 29"30 (footnote and emphasis omitted). Patent Owner accurately identifies that Evans does not expressly disclose the term eculizumab, this heavy chain constant region, or full antibody sequence; however, as noted above, Bowdish both discloses the antibody structure and expressly invokes its own combination with Evans for the express purpose of constructing a 5G.1.1 antibody. This provides further support that Bowdish and Evans would have been combined with Bell by the skilled artisan for the purpose of identifying eculizumab's (5G1.1) structure.

Regarding Patent Owner's argument that Bowdish, Evans, and Bell's combination would require improper hindsight and that Bell's disclosed antibody would necessarily be that of Thomas's disclosure, we are not convinced. As noted above, Bell extols the virtues of the anti-C5 antibody, eculizumab, but does not identify its structure. Bell does cite to and incorporates by reference Thomas, thus, Thomas's IgG4 isotype antibody would be one type of eculizumab contemplated by Bell. However, Bell *also* cites to and incorporates by reference Evans, which is cited by and incorporated by referenced by Bowdish. As discussed above regarding Ground 3, Bowdish discloses and requires the anti-C5 antibody 5G1.1 and points to Evans for to how to make it. Thus, Petitioner's arguments rely on the disclosures of the prior art and no improper hindsight is necessarily invoked under Petitioner's rationale.

As for Patent Owner's contention that Thomas taught away from the claimed invention (or, somehow taught away from the prior art combination), we disagree. A "teaching away" requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *Id.* at 1200 (citation and emphasis omitted). Thomas does not criticize, discredit, or discourage the claimed invention or the prior art combination. Thomas, at worst, teaches the original eculizumab construction, an alternative to the version as taught by Bowdish and Evans. Teaching an alternative, however,

is not sufficient to show a reference teaches away from the claimed invention. *See id.* at 1201 ("The prior art's mere disclosure of more than one alternative does not constitute a teaching away from . . . alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.").

Regarding Patent Owner's argument that the complexity and unpredictability of antibody engineering for clinical therapy would mean that only Thomas's antibody would have been used in the prior art, we find the evidence of record does not support this. First, the claim of the '149 patent does not recite using the anti-C5 antibody for a clinical therapy. Second Petitioner has argued and this argument is supported by the evidence, as noted above, that the antibody could be prepared using the skill and techniques known in the art.

Regarding Patent Owner's argument that "[e]ven if Bowdish and Evans were combined . . . , a POSA would not have reasonably expected the resulting compound to work in binding to C5 or safely and effectively treating conditions such as PNH "because even small changes could substantially impact an antibody's binding properties, safety, and efficacy for human administration, we disagree. Prelim. Resp. 56. As noted above, the claim of the '149 patent covers only the antibody, and does not recite any particular use thereof (other than functionally being anti-C5). Thus, whether a therapeutic use of the claimed or prior-art-disclosed antibody would or would not be safe or effective is not material here. Further, Regarding Patent Owner's related argument that Bell taught away from the claim and combination with Bowdish and Evans, we also disagree. Bell does, indeed, cite Thomas as disclosing "[m]ethods for the preparation of h5G1.1-mAb,

h5G1.1-scFv and other functional fragments of h5G1.1, but it also cites Evans in the very same sentence. *See* Ex. 1005 ¶ 52. Thus, Thomas and Evans each teaches a version of Bell's antibody and how to make it.

We take note of Patent Owner's arguments relating to and evidence of objective indicia of non-obviousness, discussed above at Section II.G. Although we noted that there was some evidence to support Patent Owner's contentions of commercial success, long-felt but unmet need, and industry praise, we also noted that the relevant facts are likely not fully developed and Patent Owner's contentions may be rebutted. Therefore, at this stage in the proceedings, we find that Petitioner should be given the opportunity to rebut Patent Owner's evidence during trial where the parties can develop the record further.

Again, to summarize, based on the evidence presented at this stage in the proceedings, it has been shown that there is reasonable likelihood that the '149 patent's claim 1 would have been obvious over Bell, Bowdish, and Evans under Ground 4.

I. GROUND 5 – OBVIOUSNESS OVER EVANS AND MUELLER

THE PARTIES' POSITIONS

Petitioner contends, "[c]laim 1 also would have been obvious in view of Evans and Mueller and 'a POSA would have had a reason to combine these references with a reasonable expectation of successfully making the claimed antibody.'" Pet. 48 (citing Ex. 1002 ¶¶ 120–137). Petitioner argues that "Mueller disclosed the amino acid sequence of an anti-C5 antibody's light chain constant domain and the hybrid IgG2/IgG4 heavy chain constant domain" and "Evans disclosed the complete amino acid sequences of the heavy and light chain variable domains of anti-C5 antibodies" and

described combining the antibody variable regions with constant domains including hybrid IgG constant domains to make a complete anti-C5 antibody. Pet. 48–50 (citing Ex. 1007, 44:4–13, 45:24–33, SEQ ID NO: 20; Ex. 1008, 58-61; Ex. 1002 ¶¶ 121, 123–125, 129–133, Fig. 16).

Petitioner argues:

> In looking for a constant domain to pair with Evans' variable regions, a POSA would have looked to Mueller because Mueller taught antibody constant regions designed with a lower propensity to activate the immune system (and complement) a desirable feature for a complement inhibiting antibody. AMG1008, 7:28-31, 8:23-26, 12:27-30; AMG1002, ¶¶125-128. A POSA reading Evans also would have looked to Mueller for h5G1.1 sequence information because Mueller disclosed a 5G1.1 antibody with a hybrid IgG2/IgG4 constant domain. AMG1002, ¶¶125-128.

Pet. 50. Petitioner notes, Dr. Balthasar explains, Mueller disclosed the amino acid sequence of a hybrid IgG2/IgG4 heavy chain constant domain when Mueller disclosed the sequence of the chimeric anti-VCAM `3F4' antibody. *Id.* at 51 (citing Ex. 1002 ¶¶ 129, 132; Ex. 1008, 58–61).

Petitioner' s rationale for combining Mueller and Evans is that Mueller disclosed chimeric 3F4 HuG2/G4 heavy chain, and mature 3F4 heavy and light chain variable regions such that, a skilled artisan aligning the two would identify the 3F4 variable regions (at Figure 9) as amino acids 20–137 of the 3F4 HuG2/G4 heavy chain and amino acids 20–131 of the 3F4 light chain. Pet. 51 (citing Ex. 1008, 51–53, 58–61, Fig. 9). Petitioner contends that, seeing this, a skilled artisan would have immediately known that the remainder of the 3F4 HuG2/G4 heavy chain (amino acids 138-463 is the hybrid IgG2/IgG4 constant region of that antibody, and that the remainder of the 3F4 light chain (amino acids 132–238) is the light chain constant region

of that antibody." *Id.* at 51–52 (citing Ex. 1002 ¶ 132, Fig. 15; Ex. 1008, 52–53, 56–57). With this understanding of the heavy and light chain constant domain sequences in mind, Petitioner contends, the skilled artisan would look to Evans to complete the whole antibody using Evans's variable regions identified from its SEQ ID NO: 20, particularly because Evans uses the same "CO12" nomenclature to refer to its 5G1.1 scFv as Mueller does in referring to h5G1.1. *Id.* at 52–53.

Petitioner's argued rationale for combining Mueller and Evans is that Mueller taught antibodies with lower immune response and identified an antibody as h5G1.1 CO12 HuG2/G4 mAb, which the skilled artisan would have known is eculizumab. Further, Petitioner argued, Evans taught the complementary parts of this anti-C5 antibody, so, by combining the elements of the two references a complete antibody would be created having the SEQ ID NO: 2 and SEQ ID NO: 4 of the claim. *Id.* at 55–56.

Patent Owner argues that, without improper hindsight, Mueller and Evans would not have been combined by the skilled artisan. Prelim. Resp. 58. Patent Owner argues "[a] POSA as of March 15, 2007 considering the problem addressed by the '149 patent "designing an anti-C5 antibody that would be safe and effective to treat conditions such as PNH "would have had no reason to look at Mueller, which had nothing to do with that problem." *Id.* (citing *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013) ("While a prior art reference may support any finding apparent to a person of ordinary skill in the art, prior art references that address different problems may not, depending on the art and circumstances, support an inference that the skilled artisan would consult both of them simultaneously.").

Patent Owner argues "[a] POSA would have understood that Mueller could have used ***any*** antibody with an IgG4 or IgG2/G4 isotype as a `negative control' for its *in vitro* experiments, as long as it did not bind to VCAM," meaning, there would be no reason to incorporate the variable regions taught by Evans. *Id.* at 59.

ANALYSIS

Unlike the case with Bowdish and Evans, here, Mueller and Evans do not reference one another. Would their combination be impossible? Certainly not. However, the mere fact that prior art can be combined does not establish that one of ordinary skill would have done so. *See, e.g.*, *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (The "mere fact that the prior art may be modified in the manner suggested . . . does not make the modification obvious unless the prior art suggested the desirability of the modification.").

Ground 5 presents a close question on whether there would have been motivation to combine Mueller and Evans in the manner argued by Petitioner. Upon review of the Balthasar Declaration, it is apparent that Mueller's 3F4 heavy chain provides a match for part of the claimed SEQ ID NO: 2. *See* Ex. 1002 ¶ 56, Fig. 8. Further, Mueller's 3F4 light chain provides a match for part of the claims SEQ ID NO: 4. *Id.* ¶ 57, Fig. 9.

The Balthasar Declaration provides an illustration as its Figure 10 showing the extent each of Evans and Mueller (and Bowdish) disclose the claimed SEQ ID NOs: 2 and 4; this figure is reproduced below:

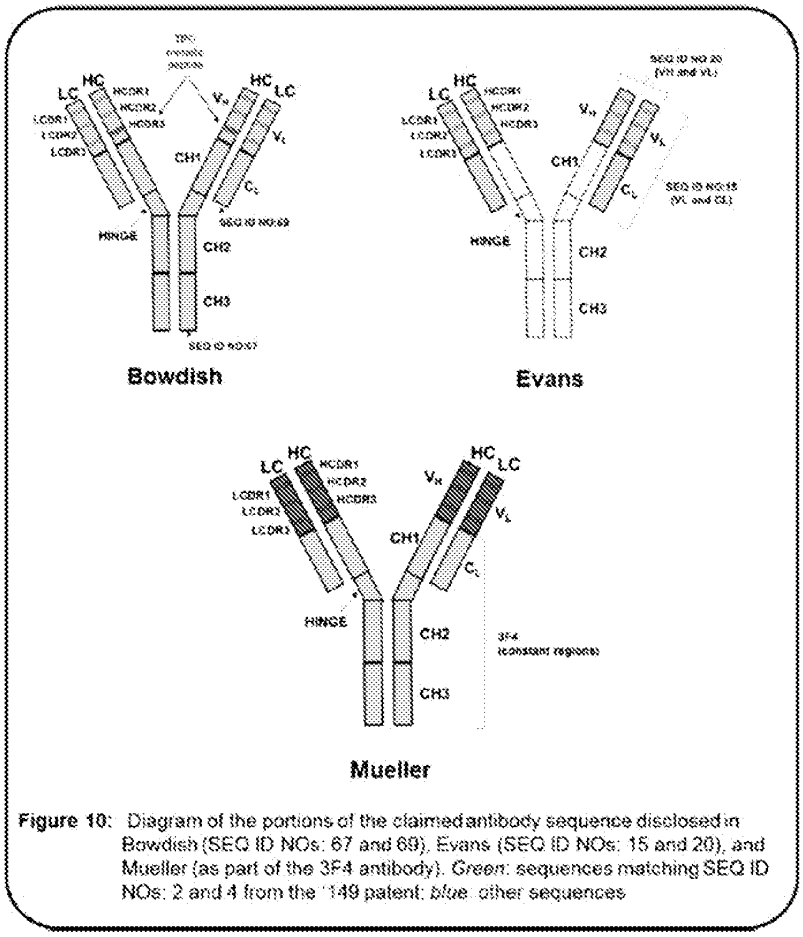


Figure 10: Diagram of the portions of the claimed antibody sequence disclosed in Bowdish (SEQ ID NOs: 67 and 69), Evans (SEQ ID NOs: 15 and 20), and Mueller (as part of the 3F4 antibody). *Green*: sequences matching SEQ ID NOs: 2 and 4 from the '149 patent; *blue*: other sequences

Ex. 1002 ¶ 58. The Balthasar Declaration's Figure 10 shows three antibody structures: Bowdish top-left, Evans top-right, and Mueller bottom; with the sequence portions disclosed by each matching the claimed sequences in green and their other sequence portions in blue.

Based, in part, on this figure, it appears that Petitioner's rationale for combining Mueller and Evans is somewhat tenuous. We are left asking why

would the skilled artisan pair Evans with Mueller, and then chose precisely the portions of Evans's and Mueller's disclosed amino acid sequences to use and which to discard so as to arrive at a final antibody that perfectly matched the claimed antibody? At this stage in the proceedings, based on the evidence before us, the answer is not entirely clear.

In view of this, Patent Owner's argument regarding improper hindsight makes some sense. True, Mueller mentions "a humanized antibody directed against human C5 (h5G1.1 CO12 HuG4 mAb)," but beyond mentioning it, Mueller does not provide much other disclosure. *See* Ex. 1008, 12. It is not apparent that the skilled artisan, knowing of Evans, would look to Mueller, or vice versa.

Based on the evidence presented at this stage in the proceedings, it has not been shown that there is reasonable likelihood that the '149 patent's claim 1 would have been obvious over Mueller and Evans under Ground 5.

J. BOARD'S DISCRETION TO DENY INSTITUTION UNDER 35 U.S.C. §§ 325(D) AND 314(A)

THE PARTIES' POSITIONS

Patent Owner argues that the "Petition should also be denied institution under 35 U.S.C. §§ 325(d) and 314(a), because Amgen's Grounds rely on the `same or substantially the same prior art or arguments' previously presented to the PTO." Prelim. Resp. 61. Patent Owner argues that during prosecution the Examiner "extensively considered" Hillmen (Ex. 1004) (which is cumulative of Hill '05 (Ex. 1047)), Evans (Ex. 1007), Bell (Ex. 1005), U.S. Patent 7,482,435 cumulative of Bowdish (Ex. 1006), and Mueller II (Ex. 1031) cumulative of Mueller (Ex. 1008), as well as having considered the arguments presented thereover as Grounds 1–5. Prelim. Resp. 62–63.

Patent Owner contends "[i]n the course of patent prosecution leading to issuance of the '149 patent, as well as prosecution of related U.S. Patent Nos. 9,725,504 (`the '504 patent') and 9,719,880 (`the '880 patent'), the Examiner considered the same, or substantially the same, prior art that Amgen now asserts in its Petition." Prelim. Resp. 16. Patent Owner states:

> For example, in finding claim 1 of the '149 patent to be novel and nonobvious, the Examiner:
>
> - Expressly discussed Amgen's asserted references Hillmen 2004 (AMG1004), Evans (AMG1007), and Wang (AMG1028) as a basis for rejection, before ultimately finding claim 1 to be allowable over the art (*see, e.g.*, AMG1015 at 486-487, 596-598);
> - Considered Amgen's asserted references Hill 2005 (AMG1047) and Bell (AMG1005), which Alexion submitted to the PTO (*see, e.g.*, AMG1015 at 490, 497, 504);
> - Considered U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen relies here (*see, e.g.*, AMG1015 at 489); and
> - Considered the "Mueller II" article (AMG1031), which is cumulative of Amgen's asserted "Mueller" reference (AMG1008) because, as Amgen's declarant recognized in connection with Amgen's Petition regarding the related '880 patent, Mueller II "discloses the same antibodies" as Mueller. (*See, e.g.*, AMG1015 at 506; IPR2019-00740, AMG1002 ¶ 169 & n.12.)

Prelim. Resp. 17.

Petitioner's position on this issue is that:

> The arguments and evidence presented herein were not before the examiner during prosecution and, therefore, do not

> constitute the same or substantially the same prior art or arguments under 35 U.S.C. §325(d).
>
> During prosecution, the examiner rejected Alexion's claims as (i) anticipated by Hillmen in view of Thomas; (ii) anticipated by Appel; and (iii) anticipated by Wang. AMG1015, 598-600. Those rejections rested solely on disclosures in Thomas and Evans for eculizumab sequence information. *Id.* The examiner later allowed the '149 patent claims mistakenly believing – because of Alexion's mischaracterization of the art – that the sequence and structure of eculizumab were not already known.
>
> Though Hillmen was referenced by the examiner during prosecution, this Petition presents it in a different light, along with new references – Bell, Bowdish, and Mueller, which teach the IgG2/IgG4 constant domain missing from the art raised during prosecution.
>
> Bell and a parent application to Bowdish (US 2003/0049683 A1) was cited but not relied upon during prosecution, and Mueller was not cited at all. Thus, this Petition presents important information that the examiner failed to appreciate or consider, including information never even presented to the examiner. Consequently, this Petition is not the same as, substantially the same as, or cumulative of any previous arguments. Rather, the art combinations here, which were not raised by the examiner during prosecution, provide the complete sequence of eculizumab, thereby teaching the very thing the examiner mistakenly concluded was missing from the prior art.

Pet. 23–24.

ANALYSIS

Regarding the Board's discretion under 35 U.S.C. § 325(d), in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, the Board enumerated non-exhaustive factors to be considered in exercising discretion under 35 U.S.C. § 325(d) on whether to institute *inter partes* review. Case IPR2017-01586,

slip op. at 17–18 (PTAB Dec. 15, 2017) (Paper 8) (precedential as to § III.C.5, first paragraph). The non-exhaustive *Becton* factors are:

> 1. the similarities and material differences between the asserted art and the prior art involved during examination;
>
> 2. the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> 3. the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> 4. the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> 5. whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> 6. the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Id. (numbers added). The *Becton* factors are not dispositive, but are part of a balanced assessment of the relevant circumstances in a particular case and we do not simply default to a tally of each factor to determine whether or not an IPR should be instituted.

Here, Patent Owner has not clearly identified how its arguments fall under the above-noted factors, but Patent Owner has, generally, argued that the prior art before us now was considered by the prosecuting Examiner either directly or as being cumulative of references that were so considered, and has further argued that the unpatentability issues presented in the Petition are the same as those at issue before the Examiner.

Patent Owner has specifically cited the prosecution history of the '149 patent (application ser. no. 15/284,015) in support of its arguments under section 325(d). Prelim. Resp. 17 (citing Ex. 1015, 486–87, 489, 490, 497,

504, 506, 596–98)); *see also id.* at 62–63. Upon review of this evidence, what we find is that the Examiner actually considered Hillmen in rejecting the claim for obviousness-type double patenting and for anticipation. *See* Ex. 1015, 488, 596. As discussed above, at this stage in the proceedings, the anticipation Ground 1 over Hillmen, on its own, is not considered sufficient to institute IPR; therefore, Hillmen's consideration during prosecution is not determinative here.

However, the other identified references were listed in Information Disclosure Statements signed by the Examiner, but we are not pointed to evidence that they were expressly considered during prosecution; we cannot draw any particular inference from the mere inclusion of the reference on an Information Disclosure Statement. The Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution. *See, e.g.*, *Amneal Pharmaceuticals LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, Paper 8 at 40 (PTAB Nov. 7, 2018) (declining to deny institution based on Section 325(d) where the reference was listed on the face of the patent, but Patent Owner provided no evidence "about the extent to which the Examiner evaluated" the reference during prosecution); *Digital Check Corp. d/b/a ST Imaging v. E-Imagedata Corp.*, IPR2017-00178, Paper 6 at 12–13 (PTAB Apr. 25, 2017) (acknowledging that a prior art reference was cited in an IDS, but granting institution because there was no indication that the claims were rejected based on those references or that the Examiner substantively discussed those references during prosecution); *Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, Paper 8 at 7–9 (PTAB Apr. 3, 2017) (refusing to deny institution based on

Section 325(d) for grounds based on a prior art reference that was simply cited in an IDS and not considered at any length); *Praxair Distribution, Inc. v. INO Therapeutics, LLC*, IPR2015-00893, Paper 14 at 8 (PTAB Sept. 22, 2015) (granting institution even though the references were previously cited in an IDS because patent owner failed to identify with specificity where the references were considered); *HyperBranch Medical Technology, Inc. v. Confluent Surgical, Inc.*, IPR2018-01099, Paper 14 at 17 (PTAB Nov. 27, 2018) (instituting IPR because, *inter alia*, "[t]he Examiner does not appear to have considered the combined teachings of Spero and Haber during examination of the '021 patent.").

Based on the evidence presented by Patent Owner, *Becton* factors 1–6 weigh in favor of not exercising our discretion not to institute here. Therefore, based on the evidence cited by Patent Owner and for the reasons above, we decline to exercise our discretion under Section 325(d) to deny institution here.

Other than the heading of Section VI of the Preliminary Response and that section's first sentence invoking the statute, Patent Owner presents no arguments or evidence directed to the Board's discretion under 35 U.S.C. § 314(a). *See* Prelim. Resp. 61–63. Therefore, we also decline to exercise our discretion under Section 314(a) to deny institution.

III. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of prevailing on Grounds 3 and 4 in showing that claim 1 of the '149 patent is either anticipated by Bowdish or would have been obvious over Bell, Bowdish, and Evans. Our decision at this stage derives from our preliminary review of the challenged claims, the

asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration.

In accordance with the Court's decision in *SAS Institute, Inc.*, 138 S. Ct. at 1359–60 and Office guidance,[16] we institute an *inter partes* review of the challenged claim of the '149 patent on all grounds alleged by Petitioner.[17] Nevertheless, this decision does not reflect a final determination on the patentability of the claim. We further note that the burden remains on Petitioner to prove unpatentability of each challenged claim. *Dynamic Drinkware*, 800 F.3d at 1378.

ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of claim 1 of the '149 patent, in accordance with each ground on which the challenge to each claim is based in the Petition, is hereby *instituted*; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of the '149 patent will commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

---

[16] Guidance on the Impact of SAS on AIA trial proceedings (Apr. 26, 2018), accessible at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial (last accessed Oct. 2, 2018) ("At this time, if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition," and "for pending trials . . . , the panel may issue an order supplementing the institution decision to institute on all challenges raised in the petition.").

[17] In view of the complexity of the art and arguments presented, the parties are, nevertheless, invited to negotiate an agreement to focus on some subset of the asserted Grounds.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00739
Patent: 9,725,504

DECLARATION OF ARTURO CASADEVALL, M.D., PH.D.

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TABLE OF CONTENTS

I. Introduction 1

II. Experience and Qualifications 4

III. Bases of Opinions and List of Documents Considered 8

IV. Summary of Opinions 9

V. Legal Standards 11

A. Standards for Anticipation 11

B. Standards for Obviousness 14

VI. Background 16

A. Overview of the '504 Patent 16

B. SOLIRIS® and its Use for Treatment of Paroxysmal Nocturnal Hemoglobinuria ("PNH") 20

C. Mechanism of Action for SOLIRIS® in Treating PNH 21

D. State of the Art Regarding Humanized Monoclonal Antibodies of March 15, 2007 23

1. General Antibody Structure 23

2. Design and Development of Humanized Monoclonal Antibodies for Human Therapeutic Use 26

3. Nomenclature and Naming for Humanized Monoclonal Antibodies 40

4. Changes to Amino Acid Sequence, Including in the Constant Region, Can Significantly Impact the Binding, Safety, and Efficacy of Therapeutic Antibodies 45

5. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" To Be an IgG4-Isotype Humanized Antibody 55

Samsung Bioepis Exhibit No. 1002
Page 13052

E. The Novel, Uniquely-Engineered Amino Acid Sequence of SOLIRIS® Was Not Known to a POSA as of March 15, 2007.....68

VII. Opinions.....70

A. Dr. Balthasar's Opinions Misread the Prior Art and Rely on Hindsight Analysis.....70

1. A POSA Before March 15, 2007 Would Not Have Understood "Eculizumab" To Contain the Uniquely-Engineered Heavy Chain Constant Region Reflected in SEQ ID NO: 2 of the '504 Patent.....70

2. The Antibody Sequence Recited in the '504 Patent, and Methods of Treatment and Pharmaceutical Compositions of an Antibody Comprising the Sequence Recited in the '504 Patent, Were Not Publicly Known Before March 15, 2007.....79

B. Claims 1-3 and 7-10 of the '504 Patent Were Not Anticipated by Hillmen '04 (Ground 1).....91

C. Claims 4 and 5 of the '504 Patent Would Not Have Been Obvious In View Of Hillmen Combined with Bell (AMG1005) (Ground 2), and Claim 6 Would Not Have Been Obvious in View of Hillmen, Bell, and Wang (AMG1028) (Ground 3).....95

D. Claims 1-5 and 7-10 of the '504 Patent Would Not Have Been Obvious Over Bell, Bowdish, and Evans (Ground 4), and Claim 6 Would Not Have Been Obvious Over Bell, Wang, Bowdish and Evans (Ground 5).....98

1. Bell (and Wang) Did Not Disclose the Specific Sequence of Claims 1-10, and Would Not Have Motivated a POSA to Make An Antibody With the Claimed Sequence.....99

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Combine Bell and Wang with Bowdish and Evans.....103

Samsung Bioepis Exhibit No. 1002
Page 13053

3. A POSA Would Not Have Been Motivated Make the Specific Claimed Antibody that Dr. Balthasar Assembles in Hindsight from Bowdish and Evans 108

4. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Make, and Would Not Have Reasonably Expected Success in Making, the Claimed Pharmaceutical Compositions for Treatment of PNH from Bell, Bowdish and Evans (or Wang for Claim 6) 119

E. Claims 1-5 and 7-10 of the '504 Patent Would Not Have Been Obvious Over Bell, Evans, and Mueller (Ground 6), and Claim 6 Would Not Have Been Obvious Over Bell, Wang, Evans and Mueller (Ground 7).....126

1. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Combine Bell (and Wang) with Evans and Mueller, or to Make the Specific Claimed Antibody of the '504 Patent.....127

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Make, and Would Not Have Reasonably Expected Success in Making, the Claimed Pharmaceutical Compositions for Treatment of PNH Conditions from Bell, Wang, Mueller and Evans.....136

F. Objective Indicia Support the Nonobviousness of Claims 1-10 of the '504 Patent.....139

1. SOLIRIS® is the Commercial Embodiment of the '504 Patent.....140

2. SOLIRIS® Fulfilled a Long-Felt, Unmet Need for a Treatment of PNH, Which Others Failed to Satisfy.....142

3. SOLIRIS® Is A Commercial Success 146

4. Industry Praise 147

5. Copying 147

VIII. Conclusion 149

Samsung Bioepis Exhibit No. 1002
Page 13054

I, Arturo Casadevall, hereby declare and say as follows:

I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I have been retained by Alexion Pharmaceuticals, Inc. ("Alexion") as an independent expert consultant in this proceeding before the United States Patent and Trademark Office. Although I am being compensated at my normal consulting rate of $ 500/hr for the time I spend on this matter, no part of my compensation is dependent on the outcome of this proceeding, and I have no other interest in this proceeding.[1]

3. I understand the Patent Trial and Appeal Board ("PTAB") issued an Institution Decision (Paper No. 15) granting Amgen Inc.'s ("Amgen") Petition to institute this *Inter Partes* Review ("IPR") regarding claims 1-10 of United States Patent No. 9,725,504 ("the '504 patent") on seven "Grounds" alleging that claims 1-10 of the '504 patent are unpatentable as anticipated or obvious. I understand that the PTAB's Institution Decision regarding the '504 patent (Paper No. 15) is not a final decision, and is based on the PTAB's "preliminary review of the

[1] All opinions expressed and implied in this Declaration are solely my own and do not represent or reflect the views of my employer, the Johns Hopkins University.

challenged claims, the asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration." (Institution Decision, Paper No. 15, at 64.)

4. I have reviewed and considered Amgen's Petition regarding the '504 patent (Paper No. 2) ("Amgen's Petition"), the Declaration of Dr. Joseph P. Balthasar regarding the '504 patent (AMG1002) ("Balthasar Declaration"), the Institution Decision regarding the '504 patent (Paper No. 15) ("Institution Decision"), and the other documents cited throughout this Declaration. For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claims 1-10 of the '504 patent are anticipated or obvious in view of any of Amgen's seven "Grounds."

5. As stated in the Institution Decision, the PTAB found based on its "preliminary review" that Amgen had demonstrated a "reasonable likelihood" that it would prevail on at least one claim under one Ground: alleged obviousness of claims 1 in view of Bell (AMG1005), Bowdish (AMG1006), and Evans (AMG1007) ("Ground 4").[2] (Paper No. 15 at 37-48.) For the reasons I explain in

[2] I understand that Amgen's Ground 4 is directed to claims 1-5 and 7-10 of the '504 patent – but, for in its decision to institute this IPR in view of Ground 4, the Board "focus[ed] on claim 1," and noted that Alexion had "non-trivial

this Declaration, it is my opinion that Amgen has failed to show that claims 1-5 or 7-10 of the '504 patent are unpatentable under this Ground, or that claim 6 is unpatentable under the combination of Bell, Wang (AMG1028), Bowdish, and Evans ("Ground 5").

6. In its Institution Decision, the PTAB also stated that Amgen had ***not*** demonstrated a reasonable likelihood that it would prevail in showing the challenged claims were unpatentable with respect to five other Grounds: (1) alleged anticipation of claims 1-3 and 7-10 by Hillmen '04 (AMG1004) ("Ground 1"), (2) alleged obviousness of claims 4 and 5 in view of Hillmen '04 in combination with Bell ("Ground 2"), (3) alleged obviousness of claim 6 in view of Hillmen '04 in combination with Bell and Wang ("Ground 3"); (4) alleged obviousness of claims 1-5 and 7-10 in view of Bell, Evans, and Mueller (AMG1008) ("Ground 6"); and (5) alleged obviousness of claim 6 in view of Bell, Evans, Mueller (AMG1008) and Wang ("Ground 7"). (Paper No. 15 at 28-36, 52-54.) For the reasons I explain in this Declaration, it is my opinion that Amgen has failed to show that claims 1-10 of the '504 patent are unpatentable under any of these Grounds.

---

arguments" regarding the nonobviousness of claim 5 under Ground 4 and claim 6 under Ground 5. (Paper No. 15 at 37, 48 & n.20.)

II. EXPERIENCE AND QUALIFICATIONS

7. I am currently a Bloomberg Distinguished Professor of Molecular Microbiology & Immunology and Infectious Diseases at the Johns Hopkins Bloomberg School of Public Health, and the Alfred and Jill Sommer Professor and Chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health.

8. My educational background includes a B.A. in Chemistry, which I received from Queens College, City University of New York, in 1979. In 1983 and 1984, I received my M.S. and Ph.D. in Biochemistry, respectively, both from New York University. I also received my M.D. from New York University in 1985.

9. After I earned my M.D., I went on to complete an internship and residency in internal medicine at Bellevue Hospital from 1985-1988. From 1988-1989, I completed a fellowship in infectious diseases at the Montefiore Medical Center. Under the guidance of Matthew D. Scharff, I completed a postdoctoral fellowship in cell biology at the Albert Einstein College of Medicine from 1989-1991.

10. I became an Assistant Professor of Medicine and Microbiology & Immunology at the Albert Einstein College of Medicine in 1992, and I was promoted to Associate Professor in 1996 and Professor in 2001. I became the

Samsung Bioepis Exhibit No. 1002
Page 13058

Director of the Division of Infectious Diseases at Montefiore Medical Center in 2000.

11. Between 2002 and 2015, I assumed a number of additional roles at the Albert Einstein College of Medicine. I was named the Selma and Jacques Mitrani Professor in Biomedical Research in 2002. In 2006, I became the Chair of the Department of Microbiology & Immunology, and was named the Leo and Julia Forchheimer Professor of Microbiology & Immunology. In 2013, I became the Director of the Center for Immunological Sciences.

12. In 2015, I accepted my current position at the Johns Hopkins Bloomberg School of Public Health. I was also named a Bloomberg Distinguished Professor.

13. I am a member of multiple scientific societies, including the American Academy of Arts and Sciences and the American Association of Immunologists. I currently serve as the Elected Chair of the Board of Governors of the American Academy of Microbiology.

14. I also serve on the editorial boards of multiple scientific journals, including the Journal of Infectious Diseases and the Journal of Experimental Medicine. I am the Founding Editor and Editor-in-Chief of mBio, the first open access general journal of the American Society for Microbiology. I am also Deputy Editor of the Journal of Clinical Investigation.

Samsung Bioepis Exhibit No. 1002
Page 13059

15. During my career, I have served and continue to serve on scientific advisory committees. These include the CDC Advisory Panel on Anthrax Immune Globulin, on which I served in 2004; the Scientific Advisory Board for the NIAID Immune Epitope Database, on which I served from 2004-2006; the Abbott Laboratories Award in Clinical and Diagnostic Immunology Selection Committee, on which I served from 2004 to 2007; and the National Science Advisory Board for Biosecurity, on which I served from 2005-2014.

16. My work has been recognized with a number of awards and distinctions, including a Merit Award from the National Institutes of Health, which I was awarded in 2007. I have been elected to the National Academy of Medicine and the American Academy of Arts and Sciences.

17. Over the course of my career, I have authored over 800 publications, books, book chapters, and monographs. I am also an inventor on multiple issued patents and pending patent applications.

18. I have over 25 years' experience in the fields of immunology and microbiology, including therapeutic antibody design. In particular, I have worked extensively for over 15 years to research the effect of antibody constant regions on antibody binding and specificity. I first started working on this issue in 1992. In 2002, my laboratory published our first significant paper on the subject, McLean *et*

al., Isotype can affect the specificity of an antibody for a polysaccharide antigen, J IMMUNOL., 169:1379-86 (2002) (ALXN 2013), which I co-authored.

19. Following McLean 2002, my laboratory continued to publish research related to the impact of antibody constant regions on antibody binding and specificity. For example, I co-authored Torres *et al.*, Variable region identical antibodies differing in isotype demonstrate differences in fine specificity and isotype, J. IMMUNOL., 174:2132-2142 (2005), and Torres *et al.*, The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917-27 (2007) (ALXN2009). I also co-authored a major review article, Janda *et al.*, Ig Constant Region Effects on Variable Region Structure and Function, FRONT. MICROBIOL., 7(22): 1-10 (2016) (ALXN 2010) in 2016. In total, I have published 15 publications related to the effect of antibody constant regions on antibody binding and specificity.

20. In addition to my academic research work, I have also been directly involved in the development of two monoclonal antibodies for therapeutic treatment. The first was an antibody for treatment of cryptococcal meningitis, which was developed in my lab and tested in clinical trials in 2001. The second was an antibody to treat melanoma, which was developed in my lab in partnership

with Pain Therapeutics, and tested in clinical trials in 2007. I also served on Pfizer's advisory board for therapeutic antibodies from 2011 to 2014.

21. My additional research interests include fungal and bacterial pathogenesis. Research from my lab has led to development of an antibody to fungal melanin that is currently in evaluation for the treatment of melanoma. We are also currently working to develop antibody-based countermeasures to protect against anthrax.

22. I am board certified in Infectious Diseases and in Internal Medicine until 2023.

23. As reflected by my education and experienced discussed above, and further reflected in my curriculum vitae, I am an expert in the design, development, evaluation, and testing (including biological and physicochemical analysis) of monoclonal antibodies for use in human clinical therapy, including humanized monoclonal antibodies. I was also an expert in these fields prior to March 15, 2007. A copy of my curriculum vitae is attached to this Declaration as **Appendix A** (ALXN2023.)

III. BASES OF OPINIONS AND LIST OF DOCUMENTS CONSIDERED

24. The opinions contained in this declaration are based on the documents I reviewed and my knowledge and professional judgment. In forming the opinions expressed in this declaration, I reviewed the documents discussed

Samsung Bioepis Exhibit No. 1002
Page 13062

throughout in this declaration, as well as the documents listed in **Appendix B**. My opinions are further based on background, education, and my over 25 years of experience and knowledge of therapeutic antibody design, including both academic research and development work for monoclonal antibody therapeutics.

25. In forming my opinions, I have also considered the perspective of a person of ordinary skill in the art ("POSA") as of March 15, 2007, including the knowledge available to a POSA as of that date, and how a POSA would have read and understood the literature pertinent to the invention claimed in the '504 patent.

26. I understand that, in its Institution Decision, the Board accepted that a POSA in the field of the '504 patent would typically have "an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline," who would have "at least two years of experience engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry." (Paper 15 at 20-21.) I agree with this definition of a POSA, and provide my opinions in this Declaration from the perspective of a POSA as of March 15, 2007.

IV. SUMMARY OF OPINIONS

27. I have considered the opinions of Dr. Joseph P. Balthasar, as set forth in his February 27, 2019 declaration ("Balthasar Declaration") (AMG1002), and

the documents therein. I submit this Declaration in order to respond to opinions offered by Dr. Balthasar.

28. It is my opinion that claims 1-10 of the '504 patent are not anticipated by, or obvious in view of, any of the alleged prior art or combinations of prior art at issue in Amgen's seven "Grounds" in this proceeding.

29. I disagree with Dr. Balthasar's conclusions that claims 1-3 and 7-10 of the '504 patent was anticipated by Hillmen '04 (AMG1004) (as alleged in "Ground 1"). In my opinion, Hillmen '04 did not disclose each and every element recited in claim 2 as arranged in the claim, whether expressly or inherently.

30. I further disagree with Dr. Balthasar's conclusions that (1) claims 4 and 5 were obvious in view of the combination of Hillmen and Bell (AMG1005) ("Ground 2"); (2) that claims 1-5 and 7-10 were obvious in view of the combinations of Bell, Bowdish (AMG1006) and Evans (AMG1007) ("Ground 4") or the combination of Bell, Evans, and Mueller (AMG1008) ("Ground 5"), or (3) that claim 6 was obvious in view of the combinations of Hillmen '04, Bell, and Wang (AMG1028) ("Ground 3"), the combination of Bell, Bowdish, Evans, and Wang ("Ground 5"), or the combination of Bell, Evans, Mueller, and Wang ("Ground 7"). In my opinion, a POSA without the benefit of hindsight, and with the benefit of the full scope of prior art available as of March 15, 2007, would not have found the claimed invention obvious; and to the contrary, the art would have

led a POSA in a direction divergent to the path taken by the claimed invention. It is also my opinion that a POSA without the benefit of hindsight would not have been motivated to combine the teachings of any of these references because there was no teaching, motivation, suggestion, or other reason to do so, and that a POSA would not have had a reasonable expectation of success with respect to the claimed invention.

31. It is also my opinion that "objective indicia" further support the non-obviousness of the invention recited in claims 1-10 of the '504 patent, including at least the fulfillment of a long-felt, unmet need; commercial success; failure of others; copying; and industry praise.

V. LEGAL STANDARDS

32. I have been advised by counsel of the following legal principles, which I have considered and applied in forming my opinions set forth in this Declaration.

33. I understand the burden of proving unpatentability of the '504 patent rests with Amgen in this proceeding.

A. Standards for Anticipation

34. I have been informed by counsel that, to establish anticipation, Amgen must show that a single prior art reference discloses each and every

element of the claimed invention, within the four corners of the document, arranged as in the claim.

35. I understand that a document may "incorporate by reference" the disclosure of another document. I understand that a document may be incorporated by a reference in its entirety, or only with respect to certain information, depending on the language setting out the incorporation by reference. To the extent a document is incorporated by reference, I understand that its disclosures should be considered as part of the incorporating document.

36. I have been informed by counsel that a prior art document may anticipate either expressly or inherently. I understand a document does not anticipate just because it refers to a molecule or formulation that is later revealed to be the one claimed. Counsel has explained that, for a prior art document to inherently anticipate a patent claim, elements that are not disclosed expressly in the reference must be necessarily present in the document. I understand that a document is not anticipatory if any elements are only probably or possibly present.

37. I have been informed that, to anticipate, it is not enough that the prior art document discloses part of the claimed invention, which a POSA might supplement to make the whole. I also understand from counsel that, to anticipate, it is not enough that the prior art includes multiple, distinct teachings that a POSA might somehow combine to achieve the claimed invention.

Samsung Bioepis Exhibit No. 1002
Page 13066

38. I have been informed by counsel that, to anticipate, a document must provide every element of the claimed invention arranged or combined as in the claim, or permit a POSA reading the document to "at once envisage" the claimed invention. In other words, I understand that a reference does not anticipate a claimed invention if, on reading it, a POSA would not be able to immediately understand that the claim elements disclosed in the document should be arranged or combined in the manner recited in the claim.

39. Counsel has further informed me that, to anticipate, a single document must describe the claimed invention with sufficient precision and detail to establish that the subject matter existed in the prior art, and that ambiguous references do not anticipate a claim.

40. I have also been informed by counsel that, to anticipate a claimed invention, a prior art reference must be "enabled," such that a POSA could make and use the claimed invention without undue experimentation. I understand that the PTAB will consider the following factors in assessing whether a disclosure requires undue experimentation: (1) the quantity of experimentation necessary, (2) the amount or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Samsung Bioepis Exhibit No. 1002
Page 13067

B. Standards for Obviousness

41. I have been informed by counsel that, to establish obviousness, Amgen must show that the claimed invention as a whole would have been obvious to a POSA prior to the date on which the claimed invention was invented, without the benefit of hindsight knowledge. I have been informed that, for purposes of these proceedings, the relevant date of invention, or "priority date," is March 15, 2007, the earliest filing date for the '504 patent.

42. I have been informed by counsel that the Board will consider the following factors in determining whether Amgen has met its burden to establish invalidity based on obviousness: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness.

43. Counsel has explained that objective indicia supporting nonobviousness can include: that the invention satisfied a long-felt but unmet need that existed at the time of the invention; commercial success of products embodying the claimed invention; failure of others to solve the problem addressed by the claimed invention; copying of the invention; and industry praise.

44. I understand from counsel that, in assessing obviousness, it is improper to use hindsight knowledge of the invention claimed and described in the

'504 patent, or other documents or information that would not have been available to a POSA prior to March 15, 2007.

45. I further understand from counsel that, in the obviousness analysis, that the full scope and content of the prior art available to a POSA must be considered, and it is improper to use hindsight in selecting documents from the prior art for use in an obviousness analysis. I also understand it would be improper to assume obviousness by following the path that led the inventors to the claimed invention, and instead prior art must be viewed from the perspective of a POSA without the benefit of knowing how the inventors successfully achieved the claimed invention.

46. I understand from counsel that, in assessing obviousness, I must consider a prior art reference as a whole, for all that it teaches, including any portions that would have discouraged or pointed away from the claimed invention.

47. I have been informed that, to establish obviousness, Amgen must also show that, for a particular combination of prior art references, a POSA without the benefit of hindsight would have had a motivation or reason to combine those prior art references. I also understand from counsel that Amgen must show that a POSA, without the benefit of hindsight, would have had a reasonable expectation of success with respect to the claimed invention. I understand that hindsight bias

must be avoided in assessing whether a particular combination of references would have been obvious prior to the date of invention.

VI. BACKGROUND

A. Overview of the '504 Patent

48. In forming my opinions, I have reviewed the '504 patent, titled "Treatment of Paroxysmal Nocturnal Hemoglobinuria Patients by an Inhibitor of Complement."

49. I understand from counsel that the '504 patent claims priority back to U.S. Application No. 12/225,040, filed as PCT/US2007/006606 on March 15, 2007. I have been informed is the earliest priority date for the '504 patent.

50. I understand that the '504 patent reflects the work of Alexion scientists in developing SOLIRIS® as a safe and effective treatment for paroxysmal nocturnal hemoglobinuria ("PNH"). The '504 patent has ten claims directed to methods of treating a patient suffering from PNH by administering a pharmaceutical composition, as follows:

> **1.** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

2. The method of claim **1**, wherein the pharmaceutical composition is administered by intravenous infusion.

3. The method of claim **1**, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

4. The method of claim **1**, wherein the pharmaceutical composition is in a single unit dosage form.

5. The method of claim **4**, wherein the single unit dosage form is a 300 mg single unit dosage form.

6. The method of claim **1**, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.

7. The method of claim **1**, wherein the patient is anemic.

8. The method of claim **1**, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7±1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7±1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14±2 days.

9. The method of claim **1**, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

10. The method of claim **9**, wherein the immediate decrease occurs within one week of administration of the antibody.

Samsung Bioepis Exhibit No. 1002
Page 13071

(AMG1001 at 39:1-32.)

51. Claims 1-10 of the '504 patent recite the complete amino acid sequence for the active compound in SOLIRIS® (eculizumab): the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4. (AMG1001 at cols. 31-33, 35.) As I discuss below, a POSA prior to March 15, 2007 would ***not*** have known that eculizumab had the specific sequence recited in claims 1-10, and would not have known of any other monoclonal antibody having that specific sequence.

52. The '504 patent also provides data from the Phase III, placebo-controlled "TRIUMPH" clinical study, confirming that the claimed antibody is safe and effective for treating PNH, and identifying the safe and effective dosing regimen for that use. (AMG1001 at abstract, 19:50-28:35.) One of the efficacy parameters assessed in the TRIUMPH study as reported in the '504 patent was mean levels of lactate dehydrogenase ("LDH") – which the '504 patent describes as "a biochemical marker of hemolysis in PNH." As reported in the '504 patent, patients receiving the claimed antibody (which the '504 patent identified as eculizumab) showed an "immediate (one week) and sustained decrease in mean levels of LDH." (AMG1001 at 22:23-26; *see also* AMG1001 at 27:1-6 ("Lactate dehydrogenase, a biochemical marker of hemolysis in PNH, was immediately and consistently decreased in all eculizumab-treated patients.").) The '504 patent

Samsung Bioepis Exhibit No. 1002
Page 13072

points to Figure 1A as illustrating the "immediate and sustained decrease" in mean levels of LDH achieved by the specific claimed antibody of the '504 patent:

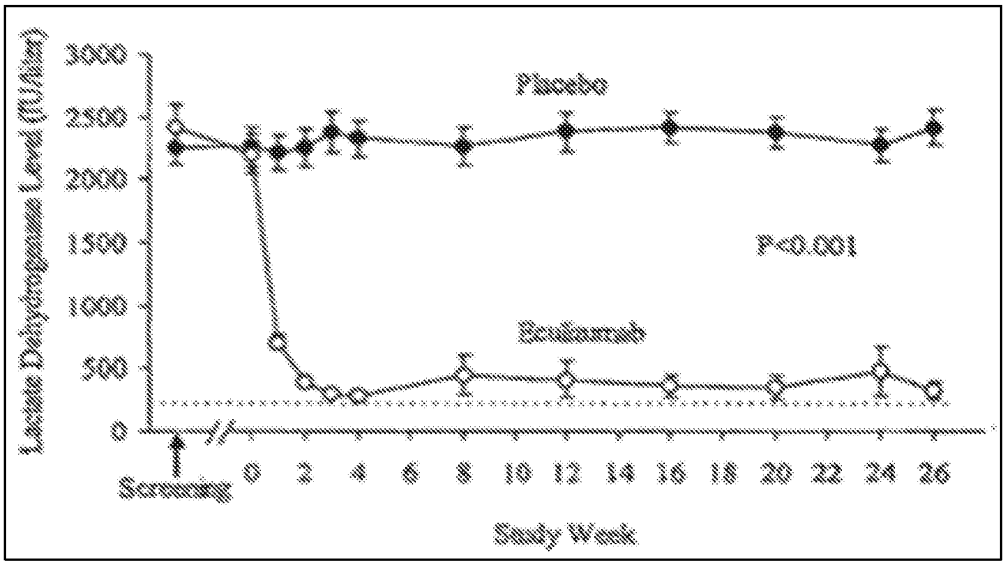


Figure 1: Figure 1A from the '504 patent (AMG1001)

53. The '504 patent also describes use of eculizumab in pharmaceutical compositions, including a "300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." (AMG1001 at 4:21-24, 5:21-25, 16:30-33.).)

54. Claims 1-10 of the '504 patent reflect the purpose of the '504 patent's invention: the development of a humanized monoclonal antibody, and pharmaceutical compositions of that antibody, that can block cleavage of C5 and be used as a safe and effective therapy for patients with PNH.

B. SOLIRIS® and its Use for Treatment of Paroxysmal Nocturnal Hemoglobinuria ("PNH")

55. PNH is a rare, life-threatening blood disorder characterized by chronic destruction of red blood cells ("hemolysis"), with periodic acute exacerbations of hemolysis ("paroxysms") that result in dark urine ("hemoglobinuria"). (AMG1047 at 2559.) Patients afflicted with PNH have symptoms including chronic and potentially disabling fatigue, dysphagia (difficulty swallowing), and recurrent pain, resulting in an impaired quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.) PNH patients also often suffer from severe anemia requiring frequent blood transfusions for survival, and can be susceptible to life-threatening blood clots ("thrombosis"). (AMG1047 at 2559.)

56. Prior to FDA approval of SOLIRIS®, there was a substantial need for a safe and effective therapy for the treatment of PNH. As stated in the pivotal Phase III clinical trial report for SOLIRIS® published in the New England Journal of Medicine, "there [was] ***no therapy*** that effectively reduce[d] intravascular hemolysis or improves the symptoms in patients with PNH" prior to SOLIRIS®. (AMG1012 at 1234; *see also* AMG1047 at 2559 ("There is ***no effective treatment*** for the ongoing hemolysis in PNH.").) Before the availability of SOLIRIS®, PNH patients were often "transfusion-dependent," meaning that their survival depended on receiving frequent blood transfusions. (AMG1004 at 557; AMG1047 at 2559.)

Samsung Bioepis Exhibit No. 1002
Page 13074

57. In clinical trials of SOLIRIS®, PNH patients showed reduced hemolysis and substantial improvements in outcomes, including reduced or eliminated need for blood transfusions, lessened anemia and fatigue, and improved quality of life. (AMG1033 at 1261.) Those trials also confirmed the safety of SOLIRIS® for long-term administration. (AMG1047 at 2564.)

58. SOLIRIS® received accelerated approval (under the "Priority Review" program for groundbreaking therapies) by the U.S. Food & Drug Administration ("FDA") on March 16, 2007. (ALXN2006 at 993; ALXN2030 at 1.) SOLIRIS® was the first therapy approved by the FDA for treatment of PNH. (ALXN2030 at 1.) By improving efficacy outcomes while reducing the need for more invasive therapies, SOLIRIS® represented a significant advance in PNH treatment.

C. Mechanism of Action for SOLIRIS® in Treating PNH

59. The active ingredient in SOLIRIS® is eculizumab, a humanized monoclonal antibody. SOLIRIS® works by binding with high "affinity" (*i.e.*, tightness) and "specificity" (*i.e.*, directed to a single target or "antigen") to the human protein "C5," a key component of the body's "complement" pathway.

60. PNH is caused by a genetic mutation resulting in abnormal blood cells that are unprotected from the body's "complement" system. (AMG1004 at 553; AMG1047 at 2559; AMG1012 at 1234.) The complement system is a component

Samsung Bioepis Exhibit No. 1002
Page 13075

of the human immune system that normally protects the body against invading infectious cells (*e.g.*, pathogenic bacteria), by forming a "membrane-attack complex" that causes invading cells to burst ("lysis"). (ALXN2019 at 1265-66.) If unimpeded, the complement system also has the potential to attack the body's own cells, causing dangerous disease conditions. (ALXN2019 at 1266-68.)

61. In PNH patients, the red blood cells of PNH patients are constantly under attack by the complement system ("chronic intravascular hemolysis"). (AMG1012 at 1239-1240.) Normally, red blood cells are protected against such attack from the complement system by membrane-bound proteins such as "CD59," which blocks the formation of the cell-lysing "membrane attack complex" on the cell surface. (AMG1012 at 1234.) In PNH patients, however, a genetic mutation in the "*PIG-A*" gene results in the absence of CD59 on red blood cells, leaving them chronically susceptible to destruction by the complement system. (AMG1012 at 1234.)

62. Without SOLIRIS® treatment, the body naturally cleaves C5 into two components, "C5a" and "C5b," which lead to the various downstream effects of the complement pathway, including hemolysis in PNH patients. When SOLIRIS® is administered, however, it binds to a critical location ("epitope") on C5 with sufficient affinity, specificity, and "fine specificity" (*i.e.*, binding to the right spot) to prevent cleavage of C5 into C5a and C5b. (AMG1004 at 2; AMG1047 at 2559;

Samsung Bioepis Exhibit No. 1002
Page 13076

AMG1012 at 1233.) By binding to C5 and blocking its cleavage, SOLIRIS® blocks the downstream effects of the complement pathway, and spares PNH patients' red blood cells from destruction. (*Id.*)

D. State of the Art Regarding Humanized Monoclonal Antibodies of March 15, 2007

1. General Antibody Structure

63. As of March 15, 2007, antibodies were known to be complex three-dimensional proteins characterized by one or more flexible, Y-shaped structures each formed from four polypeptide chains – two identical "heavy chains" and two identical "light chains." (ALXN2007 at 104-05; AMG1018 at 4.)

64. Each heavy and light chain polypeptide can be divided into a "variable" region, where the antigen binds, and a "constant" region, which may interact with other components of the immune system. (ALXN2007 at 105-106.) As discussed below in Section VI.D.4, however, a POSA as of March 15, 2007 would have been aware that antibodies are complex three-dimensional molecules, and that the structure of the constant region could potentially impact the antibody-antigen interactions of the variable region, even if the constant region is not directly in contact with the antigen.

65. The variable region of each of the two heavy chains and two light chains includes three "complementarity-determining regions" ("CDRs"), which together directly interact with a single epitope on a specific antigen. (AMG1018 at

Samsung Bioepis Exhibit No. 1002
Page 13077

9.) Portions of the variable region flanking the CDRs are termed "framework" regions. (AMG1029 at 6.)

66. Antibodies are divided into classes, or "isotypes," based on their constant regions. (ALXN2007 at 105; AMG1018 at 4; AMG1029 at 5.) There are five different naturally-occurring isotypes – IgA, IgD, IgE, IgG, and IgM – which determine the functional activity of the antibody. (ALXN2007 at 105; AMG1018 at 4-7; AMG1029 at 5.) These isotypes differ structurally in the amino acid sequences of their heavy chain constant regions, the number and location of their disulfide bonds, and the lengths of their "hinge" regions. (*See, e.g.*, ALXN2008 at 172; *see also* ALXN2009 at 13924; AMG1029 at 5.) The IgG isotype is the most abundant in humans and, as of March 15, 2007, was the most common class used for human therapy. (ALXN2007 at 105; AMG1018 at 4; AMG1029 at 2-5.)

67. IgG antibodies contain a single Y-shaped structure. IgG constant regions can be subdivided into different parts, with the light chain including a variable region ("VL") and a constant region "CL," and the heavy chain including a variable region ("VH") followed by constant region domains known as "CH1," the "hinge" region, "CH2," and "CH3." (ALXN2007 at 106.)

68. Antibody domains were also sometimes referred to in the art by the fragments that would be produced from proteolytic degradation. For example, the "CH2" and "CH3" domains together form what was known as the "Fc" region

Samsung Bioepis Exhibit No. 1002
Page 13078

("fragment crystallizable"), and the light chain associated with a truncated heavy chain containing only VH and CH1 form what was known as the "Fab" region ("fragment antigen binding"). (ALXN2007 at 106; AMG1018 at 8.)

69. Figure 1 (adopted from Amgen's Petition) depicts the basic structure of a full-length, intact IgG antibody in a simplified, 2-dimensional diagram. This type of diagram is useful for simple illustrations of antibody structure – but as I discuss further below in Section VI.D.4, a POSA as of March 15, 2007 would have understood that these diagrams do not reflect the complexity of the three-dimensional structures of antibodies that are integral to the nature of their antibody-antigen interactions, including binding affinity and specificity (including fine specificity).

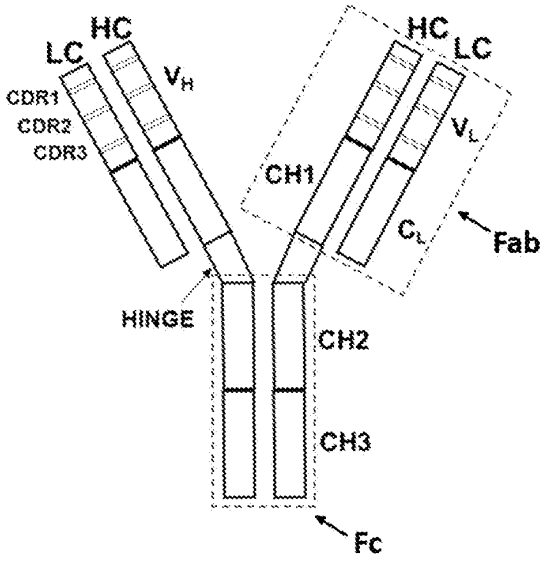


Figure 2: Basic structure of an IgG antibody (simplified 2-dimensional depiction)

Samsung Bioepis Exhibit No. 1002
Page 13079

2. Design and Development of Humanized Monoclonal Antibodies for Human Therapeutic Use

70. As of March 15, 2007, it was known that antibodies produced in an animal's natural immune response to an antigen are "polyclonal," meaning that they include a set of different antibodies having a mixture of different affinities and specificities. (ALXN2031 at 696; ALXN2032 at 210:18-211:12.) A set of polyclonal antibodies produced in a natural immune response will thus include multiple distinct antibodies, each with their own unique "primary amino acid sequence" for their heavy and light chain polypeptides. (*See* ALXN2031 at 696; AMG1018 at 11-17.)

71. By contrast, a POSA as of March 15, 2007 would have understood a "monoclonal antibody" was a single, unique antibody with one specific, defined structure. (ALXN2031 at 697; ALXN2032 at 10:9-22, 11:10-17.) In contrast to a set of polyclonal antibodies, a POSA would have understood that a monoclonal antibody has a single unique primary amino acid sequence for the entire antibody, including for both the variable region and constant region. (ALXN2031 at 697; ALXN2032 at 10:9-22, 11:10-17.) And associated with that unique sequence and structure, a POSA would have understood that each monoclonal antibody has its own specific binding properties (affinity and specificity) for the antigen against which it is directed. (ALXN2031 at 697; *see* ALXN2032 at 10:9-22, 11:10-17.)

Samsung Bioepis Exhibit No. 1002
Page 13080

72. As of March 15, 2007, technology existed to produce, isolate and characterize new monoclonal antibodies by laboratory means. Such new monoclonal antibodies were typically developed and discovered using hybrid antibody-forming cells called "hybridomas." (ALXN2031 at 697.) To generate monoclonal antibodies this way, first a mouse would be immunized with a target antigen. (ALXN2031 at 697.) Antibody-producing B cells from the immunized mouse would then be fused with immortalized cells from a mouse myeloma, a type of tumor. (ALXN2031. at 697.) The resulting unique hybrid cell lines cloned from individual antibody-producing cells ("hybridomas") could each make a unique, monoclonal mouse (murine) antibody directed to the target antigen. (ALXN2031 at 697.) Because the cells used to create hybridomas were of mouse origin, hybridomas made using this particular technology would only produce mouse antibodies. (ALXN2031 at 697.)

73. As of March 15, 2007, it was conventional to name a mouse monoclonal antibody after the hybridoma from which it was derived. For example, as I discuss further below, the anti-C5 mouse monoclonal antibody that Alexion obtained from the "5G1.1" hybridoma was referred to in the literature as "the 5G1.1 antibody" or "the 5G1.1 mAb." (AMG1007 at 38:43-67; AMG1023 at 1390, 1393, 1395; ALXN2032 at 10:9-22; 97:23-99:8; 165:11-21.)

Samsung Bioepis Exhibit No. 1002
Page 13081

74. Hybridomas generated in this process would then need to be screened for those producing mouse monoclonal antibodies with appropriate specificity. (ALXN2031 at 697.) Additional tests would need to be performed to further characterize promising candidates, including assays to assess binding affinity and appropriate biological activity. For example, with respect to the "5G1.1" mouse antibody, Evans states that the researchers (1) identified the "5G1.1" antibody by screening for C5 binding and activity in inhibiting complement-mediated hemolysis; (2) determined the specific binding affinity of "5G1.1" antibody for its antigen target C5, (3) further studied the "5G1.1" antibody in various *in vitro* assays showing that it blocked the cleavage of C5 and protected blood cells from lysis. (AMG1007 at 38:43-39:16; 39:36-40:29; ALXN2032 at 165:11-169:23; *see also* ALXN2029 at 12 (requiring characterization of antibody specificity, cross-reactivity, affinity, avidity, and immunoreactivity prior to human clinical trials).)

75. Finally, after a mouse monoclonal antibody with suitable properties was identified, its amino acid sequence could be determined using sequencing techniques, and the obtained sequence could be used as a basis to make more of the mouse monoclonal antibody, or fragments or derivatives of it. For example, in Evans, after identification and initial characterization, researchers sequenced and cloned the variable light chain and variable heavy chain regions of the "5G1.1" antibody. (AMG1007 at 40:36-42:54; ALXN2032 at 165:11-169:23.)

Samsung Bioepis Exhibit No. 1002
Page 13082

76. As of March 15, 2007, it was generally understood that, while mouse antibodies may be useful as laboratory research agents, they were generally not desirable for ***therapeutic*** use in humans. Specifically, a POSA understood that mouse antibodies can elicit immune reactions in human patients ("HAMA"), which could cause the mouse antibody to be ineffective or even harmful to human patients, particularly upon repeated administration. (ALXN2023 at 18; ALXN2034 at 3-4.) Such immune reactions were particularly undesirable in the context of treating chronic inflammatory or immune conditions requiring prolonged treatment. (*See* AMG1023 at 1390.)

77. For that reason, a POSA would have known of technologies for developing therapeutic antibodies that were intended to reduce immune reactions to non-human sequences, by designing new antibody structures that combines the mouse-derived sequences associated with antigen binding with human-derived antibody sequences. One such approach involved creating "chimeric" antibodies, where the sequences for variable regions of a mouse-derived antibody were combined with the constant region sequences (CL, CH1, hinge, CH2 and CH3) from a human IgG antibody. (ALXN2033 at 18; ALXN2034 at 3; AMG1029 at 8.) To further reduce the non-human character of therapeutic antibodies for human use, "humanization" technology was developed, whereby mouse sequences thought to be directly involved in antigen binding (including the "CDRs") would

Samsung Bioepis Exhibit No. 1002
Page 13083

be integrated into the sequence of an otherwise fully human antibody or fragment. (ALXN2033 at 18; ALXN2034 at 3; AMG1029 at 8.)

78. While the general concepts of making chimeric and humanized antibodies were known well before March 15, 2007, it was still true at that date that designing antibodies for human therapeutic use was an unpredictable art that required extensive experimentation and testing. (*See, e.g.*, ALXN2035 at 58-59; ALXN2036 at 141.) With humanization technology specifically, a POSA would have understood that there were many choices to make in the process of attempting design an antibody that could potentially be suitable for therapeutic use. Further, a POSA would not have been able to reasonably predict the impact that these various design choices would have upon the safety or efficacy of a newly-designed, unstudied antibody without conducting at least some human clinical testing. (ALXN2036 at 141 ("Only favorable results from clinical studies can confirm the success of a humanization experiment."); *see also*; ALXN2037 at 1343-44 (discontinuing clinical trial of humanized monoclonal antibody due to development of human antihuman antibodies ("HAHA") in 73% of study patients); (ALXN2038 at 624 (as of 2008, success rate of humanized monoclonal antibodies entering clinical trials was 17%).)

79. First, a POSA would have had to make choices about, and then empirically test, different designs for the variable regions of the humanized

antibody. As of March 15, 2007, humanized antibodies were often constructed using a technique known as "CDR-grafting," also known as "re-shaping," which involved the transfer of mouse CDRs into human framework regions. (ALXN2035 at 58; ALXN2036 at 135-137.) It was known at the time, however, that insertion of the mouse CDRs into a human framework could have unpredictable effects. For example, a POSA would have understood that the simple transfer of mouse CDRs into corresponding positions of the human framework regions could significantly reduce antibody binding and specificity compared to the parent mouse antibody. (ALXN2035 at 58; ALXN2036 at 140; ALXN2033 at 19.)

80. To attempt to maintain the same specificity and binding of the parent mouse antibody, additional amino acids from the mouse framework regions may have had to be inserted into the framework regions of the humanized antibody, but this could increase the risk of an immunogenic effect. (ALXN2036 at 140.) Furthermore, each modification step carried a risk of losing existing activity since antibody engineering then was a largely empirical exercise. (ALXN2035 at 58-60; ALXN2036 at 140-41; ALXN2033 at 19; *see* AMG1023 at 1394.) Accordingly, a POSA designing a humanized variable region would have had to make various choices, including: (1) the extent of the mouse CDRs to be transferred, (2) the human framework regions to be used, and (3) whether additional amino acids from the parent mouse antibody would need to be inserted into the framework regions

Samsung Bioepis Exhibit No. 1002
Page 13085

(called "back mutation") to maintain the same antibody binding and specificity as the parent antibody. (ALXN2035 at 58; ALXN2036 at 137-141; ALXN2033 at 19.) Finally, the POSA would have to make decisions on what cell line to express the recombinant antibody molecule, a choice that could affect immunoglobulin glycosylation, and thus affect antibody functions.

81. Even if a humanized variable region fragment (scFv or Fab, as discussed below) was developed and shown to have the desired antigen-binding and biological properties, a POSA would have understood that further development would be required – and additional choices would have to be made – to design a full-length, intact chimeric or humanized IgG-class monoclonal antibody. For example, a POSA would have had to choose which human constant regions to use. In designing appropriate constant regions, as of March 15, 2007, a POSA would have understood that there were four naturally occurring subclasses or "isotypes" – IgG1, IgG2, IgG3, and IgG4, and that humanized monoclonal antibodies approved by the FDA were predominantly of the IgG1 or IgG4 isotypes. (ALXN2007 at 105; AMG1029 at 2-4 (Table 1), 5.) As of March 15, 2007, all of the full-length chimeric or humanized commercial antibodies used one of the naturally-occurring IgG constant regions. (AMG1029 at 2-4 (Table 1).)

82. As discussed in Section VI.D.4 below, a POSA would have understood that, while the antibody constant regions do not directly contact the

Samsung Bioepis Exhibit No. 1002
Page 13086

antigen, the choice of isotype for an intact humanized monoclonal antibody could potentially impact many different properties, including antigen binding affinity and specificity; immunogenicity and immune system responses; antibody pharmacokinetics; antibody stability and ultimately, safety and efficacy when administered to people. A POSA would not have reasonably expected that every possible full-length antibody made by combining sequences from a variable region fragment with desirable binding and biological activity and sequences from an intact human constant region or a full human antibody would retain the same properties, and would have understood that empirical testing would be required to assess the efficacy of any full-length humanized antibodies that were generated. (*See* AMG1023 at 1394; Section VI.D.4 below.)

83. Ultimately, a POSA as of March 15, 2007 would not have been able to predict from the primary amino acid sequence alone whether a particular newly-designed humanized antibody would bind to its target with appropriate affinity and specificity, at the appropriate epitope to provide the desired biological activity. These attributes would need to be tested empirically with *in vitro* studies, including assays of binding affinity and *in vitro* biological activity assays. (*See* ALXN2036 at 150-153; ALXN2035 at 59; AMG1023 at 1391-1393.) Even such *in vitro* testing would not reliably predict whether an antibody would ultimately succeed as

Samsung Bioepis Exhibit No. 1002
Page 13087

a therapeutic agent that was suitably safe to give to patients – it would only be the beginning of the analysis.

84. As my group wrote in one of our 2007 studies, "[t]here is extensive anecdotal and unpublished evidence that many attempts to generate humanized mAbs based on mouse V regions have failed to produce useful Abs because of loss of specificity or affinity." (ALXN2039 at 1310.) I have personally observed loss of binding affinity and specificity as a result of replacing the mouse constant region with a human constant region while working to develop melanin-binding monoclonal antibodies for the therapy of melanoma. I have also personally observed that exchanging murine and human constant regions alters the binding characteristics of antibodies to Cryptococcus neoformans polysaccharide. (ALXN2039 at 1-2, 3-4.) Finally, we have reported that the simple act of changing the constant region of antibody could potentially result in new properties such as "polyreactivity," or reactivity with multiple antigens, a phenomenon of particular concern with regards to therapeutic antibodies where it is desirable to avoid all reactivity with host tissues. (ALXN2009 at 13917, 13924-25; ALXN2039 at 4; *see also* ALXN2038 at 626.)

85. As discussed in Section II above, I oversaw development of a murine monoclonal antibody for treatment of cryptococcal meningitis, which began clinical trials in 2001, and in the mid-2000s, I was closely involved with the

Samsung Bioepis Exhibit No. 1002
Page 13088

development of a murine antibody to treat melanoma. In the case of the antibody for the treatment of cryptococcosis we observed that in creating mouse-human chimeric antibodies that these differed in fine specificity from the parent murine mAb. (ALXN2013 at 1379.) In fact, concerns about changing the fine specificity of the anti-cryptococcal antibody were a major consideration in our decision to eventually use the parental murine mAb in human trials.

86. Likewise, in the case of the IgM antibody to melanin that we developed for the therapy of melanoma, efforts to create a mouse-human chimeric antibody led to loss of binding, and the difficulty involved in antibody engineering led this effort to abandon the original murine mAb used in clinical trials in favor of isolating a new murine IgG that could be more amenable to humanization. These experiences illustrate the unpredictable outcome associated with modifying murine mAbs to create more desirable mouse-human chimeric antibodies.

87. Further, whether or not a POSA had data from *in vitro* or animal studies, a POSA as of March 15, 2007 would have not reasonably expected success with a newly-designed humanized monoclonal antibody without further conducting clinical testing to study the safety and efficacy of the antibody in a relevant patient population. (*See* 1997 FDA Points to Consider at 29-39 (outlining preclinical and clinical studies for approval of monoclonal antibodies).) A POSA would have understood that at least some human clinical testing was required to demonstrate

Samsung Bioepis Exhibit No. 1002
Page 13089

that the antibody produces the desired clinical effect in people, and that the antibody is otherwise sufficiently safe and suitable for human administration – including whether it results in any undesirable immunogenic effects that limits efficacy or creates potential safety issues. (ALXN2042 at 91; *see* ALXN2029 at 37-39.) For example, although it was generally humanization efforts were generally intended to reduce potential immunogenicity as compared to a fully mouse antibody, a POSA would have understood that humanized antibodies – and even fully human antibodies – could still produce unwanted immune reactions in patients, and that safety would need to be assessed in clinical trials. (*See* ALXN2033 at 22; ALXN2034 at 4.) Those concerns would be exacerbated if a POSA were to consider using a unique, non-naturally occurring constant region for which there were no published reports of clinical testing in people, such as a hybrid IgG2/IgG4 constant region.

88. Accordingly, if a humanized antibody appeared sufficiently promising based on *in vitro* testing, a POSA would have understood that the antibody would need to be further studied in clinical trials with human patients. In general, such clinical studies would include "Phase I" studies that primarily assess safety; Phase II studies that further assess safety and also study the desired biological effects in the relevant clinical population; and larger Phase III trials (typically placebo-

Samsung Bioepis Exhibit No. 1002
Page 13090

controlled) to fully establish the drug is safe and effective for human clinical use. (ALXN2042 at 82; *see also* ALXN2029 at 34-37.)

89. As of March 15, 2007, the clinical trials needed to show the safety and efficacy of a therapeutic monoclonal antibody were rigorous, and required substantial resources. Particularly for a rare disease such as PNH, even small clinical trials to test for early signs of therapeutic effect and study safety were challenging, including, among other things, finding a sufficient number of appropriate patients to recruit for the study, developing and manufacturing antibody (and pharmaceutical compositions of the antibody) in suitable quantities and of suitable quality to be used in a human clinical trial, and coordinating with investigators across multiple sites. But such clinical trials were necessary, because as of that date, there was no way to reasonably predict a monoclonal antibody's therapeutic effects or safety in humans without actually performing human administration in a controlled setting.

90. Even pior to the start of human clinical trials, the antibody would have to be tested in preclinical studies, including animal studies assessing cross-reactivity of the antibody with non-target tissues, toxicology, and pharmacokinetics. (ALXN2029 at 29-33.)

91. And, even for use in an experimental monoclonal antibody clinical trials, an appropriate pharmaceutical formulation would have to be developed.

Samsung Bioepis Exhibit No. 1002
Page 13091

This would include development of a stability testing program and multiple studies, including accelerated stability testing, to ensure the drug would retain its biological activity and not degrade in the formulation to be administered. (ALXN2029 at 23.) If a new antibody was not sufficiently stable to be developed into a suitable formulation that could be stored and used for testing, it the likely FDA would not even permit experimental human testing to go forward.

92. A POSA as of March 15, 2007 would have known that, in addition to full-length, intact humanized antibodies, as of March 15, 2007, humanized monoclonal antibody "fragments" could be created for use in laboratory exploration and potential therapeutic applications. While commonly referred to as "fragments," these compounds were typically created using recombinant DNA technology that expressed the protein segment of interest, rather than enzymatic digestion of an intact humanized monoclonal antibody. (*See* ALXN2043 at 456; ALXN2044 at 188.)

93. For example, genetic engineering could be used to produce an antibody portion known as a "single-chain variable fragment," or "scFv." (ALXN2007 at 107; ALXN2044 at 188-189.) An scFv consists of only the variable domain of a light chain (VL) and the variable domain of a heavy chain (VH), connected by a synthetic peptide "linker" sequence. (ALXN2007 at 107; ALXN2044 at 190.) An "Fab" fragment, containing the complete light chain, but

Samsung Bioepis Exhibit No. 1002
Page 13092

only the VH and CH1 domains from the heavy chain (also known as "Fd"), could also be made by recombinant means. (ALXN2007 at 106; ALXN2044 at 190; ALXN2043 at 456.) Figure 2 below presents the basic structure of an scFv and an Fab, in a simplified 2-dimensional diagram.

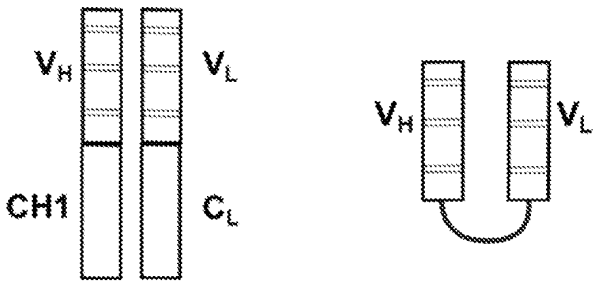


Figure 3: Left: Basic structure of an "Fab" (fragment antigen binding)

Right: Basic structure of an "scFv" (single-chain fragment, variable region)

94. A POSA as of March 15, 2007 would have understood that fragments such as scFv and Fab were structurally and functionally very different from a full-length, intact humanized antibody. Structurally, both the scFv and Fab fragments lack the complete, intact heavy chain constant region. For example, a POSA as of March 15, 2007 would have known that full-length, intact IgG antibodies have a prolonged plasma half-life relative to scFv and Fab fragments, due to their larger size and receptor interactions with the "Fc" region that is absent in the fragments. (AMG1023 at 1399; ALXN2044 at 188; ALXN2043 at 456.) A POSA would also

Samsung Bioepis Exhibit No. 1002
Page 13093

have known that the smaller scFv and Fab fragments have more rapid rates of tissue penetration relative to the larger, full-length IgG antibodies. (AMG1023 at 1390; AMG2007 at 107; ALXN2044 at 189; ALXN2043 at 456.) Further, as discussed in Section VI.D.4 below, a POSA would have understood that the constant regions of full-length antibodies could impact their binding affinity and specificity as well as immunogenicity and could also have other impacts on the immune system.

3. Nomenclature and Naming for Humanized Monoclonal Antibodies

95. A POSA as of March 15, 2007 would have known of various naming conventions for humanized antibodies used at different stages of development. Certain naming conventions used in early stages of development could be used to refer to groups or classes of related antibodies with different primary amino acid sequences, and consequently, different binding affinities, specificities, and potentially different profiles in terms of biologic activity, efficacy and safety. In contrast, a POSA would have understood that, in later stages of development, the use of specific, non-proprietary names and proprietary brand names would indicate the identification and development of a single, unique humanized monoclonal antibody with a single primary amino acid sequence and activity profile.

96. In early stages of humanized antibody design and development, it was a common (but informal) convention to refer to such antibodies by reference to the

Samsung Bioepis Exhibit No. 1002
Page 13094

original mouse hybridoma and mouse antibody from which they were developed. For example, Alexion identified the "5G1.1." hybridoma as producing the "5G1.1" mouse antibody, and often referred to the humanized antibodies and fragments derived from the "5G1.1" antibody as "humanized 5G1.1" or "h5G1.1." (*E.g.*, AMG1007 at 38:43-51; 47:28-32; AMG1023 at 1389, 1391; ALXN2032 at 97:22-99:20.)

97. I agree with Dr. Balthasar's deposition testimony that, without further context, the use of the terms such as "h5G1.1" would leave ambiguity as to exactly what particular antibody or set of antibodies are being referred to. (ALXN2032 at 98:2-99:8, 159:1-10, 202:24-203:14.) In fact, as Dr. Balthasar correctly testified, even the use of additional terminology indicating the isotype of a humanized antibody (*e.g.*, "h5G1.1 HuG4" or "h5G1.1 HuG2/G4") would leave ambiguity as to the exact structure and complete primary amino acid sequence of the antibody. (ALXN2032 at 241:23-242:12.)

98. Likewise, while a POSA would have had a good understanding of the naturally occurring human isotype constant regions (IgG1, IgG4, etc.), the use of terminology such as "IgG2/IgG4" to refer to a non-natural, engineered hybrid of constant region sequences would be unclear, and that terminology would not necessarily specify any one specific constant region structure or sequence.

Samsung Bioepis Exhibit No. 1002
Page 13095

99. In contrast to the informal naming conventions used by researchers in early development, the international and U.S. naming systems for therapeutic monoclonal antibodies as of March 15, 2007 account for the importance of an antibody's specific amino acid sequence to its activity. A POSA would have understood that, after a specific humanized monoclonal antibody with a single, unique sequence had progressed into clinical development, it may be assigned a "non-proprietary" name by authorities including INN and USAN (*e.g.*, "eculizumab"). (ALXN2045 at 1207; ALXN2046 at 10.) These unique, non-proprietary names were typically assigned around the time of clinical trials or entry into the clinical trial research stage, so that unique names would not be wasted on compounds with no clear potential to becoming a marketed product. (ALXN2045 at 11, 1207 (request should be filed after submission of Investigational New Drug (IND) application); *see also* ALXN2046 at 10.)

100. As explained by the 1997 INN Guidelines, "[a]n International Nonproprietary Name (INN) identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognized and is public property." (ALXN2046 at 1.) The purpose of assigning non-proprietary names to monoclonal antibodies, as for other drugs, is "to provide health professionals with a unique and universally identifiable name to identify each pharmaceutical substance." (*Id.*)

Samsung Bioepis Exhibit No. 1002
Page 13096

101. Under the non-proprietary naming system that existed in 2007, monoclonal antibodies all received the suffix "-mab," and humanized monoclonal antibodies in particular were given the suffix "-zumab." (ALXN2045 at 1210; ALXN2046 at 27.) Monoclonal antibodies modifying the body's immune response were given the additional naming element "li" before the suffix. (ALXN2045 at 1210; ALXN2046 at 28.) Accordingly, an immunomodulatory humanized monoclonal antibody would end with the suffix "-lizumab," with a unique, arbitrary prefix (*e.g.*., "ecu-"). (ALXN2045 at 1210; ALXN2046 at 27-28.) A POSA would have understood that these INN/USAN names with respect to humanized monoclonal antibodies would refer to one – and only one – specific antibody as defined by its unique primary amino acid sequence. (*See* ALXN2045 at 1210; ALXN2046 at 1.)

102. Accordingly, I agree with Dr. Balthasar's deposition testimony that a POSA as of March 15, 2007 would have understood that the term "eculizumab" referred to a single, unique antibody with a single defined structure and primary amino acid sequence – not a class or genus of antibodies. (ALXN2032 at 10:9-11:17, 98:19-99:8, 100:3-10; *see also* ALXN2045 at 304 (listing "eculizumab").) I disagree, however, with Dr. Balthasar's unsupported position that a POSA prior to March 15, 2007 would have understood that unique "eculizumab" monoclonal antibody to have a hybrid IgG2/IgG4 constant region, or the specific sequence

Samsung Bioepis Exhibit No. 1002
Page 13097

recited in SEQ ID NOS: 2 and 4 of the '504 patent. As I explain in Section VI.D.5 below, the prior art consistently instructed a POSA that the antibody named "eculizumab" was an ***IgG4*** isotype antibody with a different structure and amino acid sequence than the antibody of the pharmaceutical compositions recited in claims 1-10 of the '504 patent.

103. A POSA as of March 15, 2007 would have further understood that, when a humanized monoclonal antibody is in the very advanced stages of clinical testing and nearing submission for approval by FDA and other regulatory authorities, the research sponsor can select and propose a unique branded trade name (*e.g.*, "SOLIRIS®"). This is an arbitrary name associated with the specific unique antibody, subject to review by regulatory authorities to ensure no confusion with other brand-name products.

104. In my opinion, a POSA as of March 15, 2007 would have no doubt that a humanized monoclonal antibody assigned a non-proprietary "-zumab" suffix name (*e.g.*, "eculizumab), tested in Phase III clinical trials, and submitted to the U.S. FDA for approval under a proposed trade name (*e.g.*, "SOLIRIS®"), was a single, unique monoclonal antibody with a single, unique amino acid sequence.

Samsung Bioepis Exhibit No. 1002
Page 13098

4. Changes to Amino Acid Sequence, Including in the Constant Region, Can Significantly Impact the Binding, Safety, and Efficacy of Therapeutic Antibodies

105. As discussed in Section VI.D.2 above, a POSA as of March 15, 2007 would have understood that designing monoclonal antibodies for human clinical therapy was a complex and unpredictable process. One particular complicating factor was the inability to reasonably predict the *in vitro* and *in vivo* properties and effects of an untested monoclonal antibody based only on its primary amino acid sequence. A POSA as of March 15, 2007 would have understood that antibodies are not simply flat, two-dimensional "Y" structures, but are complex, three-dimensional molecules that can be sensitive to changes in primary amino acid sequence – such that even small changes to the amino acid sequence could significantly impact antigen-binding affinity and specificity, and clinical safety and efficacy. (*See, e.g.*, ALXN2015 at 506, 508; ALXN2017 at 961-62.)

106. The classical view was that an antibody's variable regions, and its CDRs in particular, were the determinants of antigen binding, since they contained the amino acid residues that most directly interact with the antigen through non-covalent bonding. (ALXN2013 at 1379; ALXN2009 at 13917.) But well before March 15, 2007, a POSA in the field of the '504 patent would have been attuned to an increasing body of scientific literature showing that antibody binding (including

Samsung Bioepis Exhibit No. 1002
Page 13099

affinity and specificity) could be impacted by amino acid changes ***outside*** the CDR regions.

107. For example, a POSA would have known that changes to "framework" amino acids within the variable regions, but outside the CDRs, could have a significant impact on antibody binding. (*See, e.g.*, ALXN2051 at 487; ALXN2052 at 253.) As discussed in Section IV.B.2 above, it was known that the transfer of murine CDRs into human framework regions would often reduce the specificity and affinity of a humanized variable antibody or fragment relative to a parent mouse antibody. (ALXN2035 at 58-60; ALXN2036 at 140-41; ALXN2033 at 19.) For that reason, in the context of designing humanized antibody variable regions, a POSA would have known that amino acid changes might be required to human sequences flanking the mouse-derived CDRs in order to achieve the desired binding properties. (*See* ALXN2035 at 58-60; ALXN2036 at 140-41.)

108. A POSA as of March 15, 2007 also would have known that changes related to the constant regions – whether combining constant region sequences, or portions thereof, with variable region sequences from other antibodies or truncated antibody derivatives (*e.g.*, "fragments" such as Fab or scFv), or switching the type of constant regions used in a full-length antibody – could impact antigen binding and other properties of the original antibody/fragment. For example, a POSA would have understood that "isotype switching" – changing an antibody's constant

Samsung Bioepis Exhibit No. 1002
Page 13100

region sequences while retaining sequences from the variable region – could impact critical properties such as an antibody's specificity and affinity, as well as other properties such as immunogenicity. (*See, e.g.*, ALXN2013 at 1379.) Prior to March 15, 2007, I personally was involved in research on this phenomenon, and published three articles prior to that date discussing my research. (ALXN2013; ALXN2040; ALXN2009.) As discussed below in this Section, there were several observations in the literature dating to the 1990s that the constant regions could affect the properties of the variable regions. Since that date, I have also published reviews discussing my work and the work of other groups establishing the impact of "isotype switching" on antigen binding, including research that was performed and published prior to March 15, 2007. (ALXN2010.)

109. My laboratory's first major publication on this subject was McLean (ALXN2013), published in 2002. In that article, we compared the binding specificity of chimeric antibodies containing the same mouse antibody variable regions but different human constant regions – specifically, IgA, IgG 1/2/3/4, and IgM constant regions. (ALXN2013 at 1379.) We performed a number of *in vitro* experiments to assess the specificity and affinity of the chimeric antibodies compared to the parent mouse antibody, including ELISAs and immunofluorescence and competition experiments. (ALXN2013 at 1380-82.) We observed that each of the chimeric antibodies had different binding characteristics

Samsung Bioepis Exhibit No. 1002
Page 13101

from each other, and the parent murine antibody. (*See* ALXN2013 at 1380-81 (Fig. 1).) In particular, we observed that the chimeric antibodies had differences in "fine specificity" from each other and the parent mouse antibody despite having identical variable region sequences – meaning that the antibodies could still bind the target antigen, but they appeared to bind ***different epitopes***, which can significantly impact their biological activity. (ALXN2013 at 1379, 1383-84.) As we described in our paper, "[g]iven that each [chimeric antibody] type had identical [variable] region sequence, we were surprised to find large differences in binding to [target antigens]." (ALXN2013 at 1379.) We concluded that "[o]ur observations add to the growing body of evidence that in certain circumstances, the [immunoglobulin constant] region can affect the fine specificity of an [antibody] molecule," and, further, that "it is critical that each [chimeric antibody] be carefully tested for specificity to insure the fidelity of the [antibody] engineering process." (ALXN2013 at 1385-86.)

110. Our findings in McClean were significant because they contributed to a growing body of work describing the impact of changes to antibody constant regions, including isotype-switching, on antibody binding. Prior to McClean, there were already a number of studies reporting that the constant regions could influence antibody binding. For example, in 1995, Greenspan and Cooper published an article describing how IgG3 monoclonal antibodies had been

Samsung Bioepis Exhibit No. 1002
Page 13102

observed to more effectively bind target antigens than IgG1 and IgG2b monoclonal antibodies or IgG3-derived Fab fragments with the same variable sequences. (ALXN2014 at 227.) As stated in Greenspan, "[t]hus, it was established that differences in the heavy chain constant (CH) domains, and in the Fc region in particular, substantially influence the apparent functional affinities (avidities) of these IgG mAbs." (ALXN2014 at 227.)

111. In 1996, Pritsch *et al.* published a study comparing the binding activity of two antibodies with identical variable regions sequences and either the IgG or IgA isotype. The authors found that, "in spite of sharing identical variable domain sequences, having identical light chain constant domains and recognizing overlapping epitopes on the [antigen], both [antibodies] significantly differed" in their affinity for the target antigen. (ALXN2011 at 2239.) The authors concluded that "changes in the [constant heavy] domains can affect the functional affinity and specificity of [antibodies], through a complex mechanism involving [antibody] flexibility and cooperative interactions in the case of [antibodies] bound to multivalent [antigens]." (ALXN2011 at 2242.)

112. A POSA would also have been aware of McCloskey (ALXN2008), also published in 1996. McCloskey taught that, despite having the same variable region sequences, "human antibodies of different IgG subclasses which bind the same antigen have been shown to differ in functional affinity." (ALXN2008 at

Samsung Bioepis Exhibit No. 1002
Page 13103

169.) The McCloskey publication used surface plasmon resonance (BIAcore) to assess the affinity and binding kinetics of chimeric antibodies made using the same mouse variable region sequences, but fused to different human IgG constant regions. (*Id.*) As illustrated by, *e.g.*, Figure 1, the authors found that each IgG subclass had different antibody binding characteristics. (ALXN2008 at 170-71.) The authors also found that, for IgG2 and IgG4, there was "a significant difference in the [binding] pattern obtained" with the full-length antibodies as compared to antibody fragments. (ALXN2008 at 171.) The authors concluded that, "[e]ngineered antibodies may differ in their functional affinity and hence in their function, depending upon their subclass. Such consideration may be of importance when considering the choice of antibodies for therapeutic use." (ALXN2008 at 172.)

113. Following McClean, in 2005 and 2007, my laboratory published additional studies on the impact of the constant regions on antibody binding and specificity (ALXN2040, ALXN2009, ALXN2039), which I also co-authored. In all of these papers, we observed that changes to the constant region could affect antibody binding and specificity. (ALXN2040 at 2132-33, 2135-38, 2140-41 (differences in fine specificity observed in two families of mouse isotype switch variants); ALXN2009 at 13917-18, 13924 (differences in antibody-antigen interactions observed in variable region identical mouse antibody isotype switch

variants); ALXN2039 at 1310-11 (mouse antibody and mouse-human chimeric with identical variable regions had different binding affinity).) In our 2005 study, we concluded that "[f]rom a practical perspective, the findings that isotype can influence the fine specificity should be an important consideration in the development of genetically engineered [antibodies] for therapeutic use because it is conceivable that humanization techniques or the synthesis of mouse-human chimeric Abs can alter the fine specificity of the original [antibody]." We also observed that antibodies with the same variable regions – but different constant regions – could exhibit polyreactive characteristics (i.e., could bind multiple antigens), and that this could have implications for self-reactivity. (ALXN2009 at 13924-25; ALXN2039 at 1310 ("[Observed polyreactivity] implies that mouse-human [chimeric antibody] construction may yield [immunoglobulins] with binding characteristics that are different from the parental murine mAb, including the possibility for unexpected self-reactivity.").)

114. Based on publications such as McClean, Greenspan, Pritsch 1996, and McCloskey, by March 15, 2007, a POSA would have understood that the constant regions of an antibody can have an impact on antibody binding. Mechanistically, a POSA would have been aware of publications describing how changes to the "CH1" and "hinge" portions of the heavy chain constant region could impact antibody binding, suggesting that these regions in particular modulated the

Samsung Bioepis Exhibit No. 1002
Page 13105

antibody-antigen interaction. (ALXN2012 at 3388; ALXN2009 at 13924.) For example, in 2000, in a follow-on study to their 1996 publication, Pritsch *et al.* assessed the impact of heavy chain regions on the antibody-antigen interaction, and concluded that their results provided "definitive evidence" both that "isotype can influence binding affinity to antigen" and that the CH1 domain can play an important role in the antigen-antibody interaction." (ALXN2012 at 3387-88.) In one of our 2007 studies, in which we used surface plasmon resonance (BIAcore) to further assess the impact of the constant heavy chain region on antibody binding, my group similarly concluded it was likely that "structural differences in the CH1 domain are responsible for the differences in affinity constants and, consequently, for variations in [antigen] binding." (ALXN2012 at 13924.)

115. More recently, in 2016, I co-authored a review article, Janda, summarizing the work of various groups related to the impact of the constant regions on antibody binding, including work that was published prior to March 15, 2007. As described in Janda, by the first decade of the twenty-first century, at least eight different groups had independently described changes to antibody specificity resulting from isotype-switching despite the conservation of variable region sequences. (ALXN2010 at 3-4.) These publications, including some of the studies I discussed above, were based on experiments involving a variety of techniques, including ELISA, ITC, and surface plasmon resonance (BIAcore). (*Id.*) Based on

the growing number of publications showing differences in antibody binding following isotype-switching, by March 15, 2007, a POSA would have been aware that changes to the constant region sequences of an antibody could impact antibody binding, even when leaving variable regions untouched.

116. In addition to potentially affecting binding, by March 15, 2007, a POSA would have understood that switching to a uniquely-engineered, non-naturally occurring (*i.e.*, "foreign") heavy chain constant region, such as a hybrid sequence constructed from portions of the IgG2 and IgG4 heavy chains, could also raise heightened immunogenicity concerns since it could have perceived by the immune system as antigenically "foreign." In particular, a POSA would have known that administering an antibody with a "foreign" heavy chain isotype to human patients could potentially result in harmful immunogenic reactions. (*See, e.g.*, ALXN2015 at 508 (describing how single amino acid substitution in an antibody drastically impacted how other antibodies ("anti-idiotype" antibodies) would bind to it); ALXN2036 at 141 ("[I]mmunogenicity is a complex issue; intrinsic factors such as protein sequence and structure are likely to be as important as extrinsic ones"); *see also* ALXN2037 at 1343-44; ALXN2038 at 624-26).)

117. Because of the unpredictability and complexity inherent in antibody design, a POSA as March 15, 2007 would not have been able to reasonably extrapolate the *in vitro* or clinical properties of one monoclonal antibody with a

unique amino acid sequence to a different antibody with a different sequence. A POSA would have understood that a monoclonal antibody's specific amino acid sequence was critical to its function, and that even small changes in an antibody's sequence could potentially affect its binding affinity and specificity, and thus, its safety and efficacy in humans.[3] (*See, e.g.*, ALXN2010 at 3; ALXN2011 at 2240-42; ALXN2008 at 171-72; ALXN2012 at 3391-92; ALXN2013 at 1384-86; ALXN2009 at 13924-26.)

118. In sum, as of March 15, 2007, a POSA would have known that antibody affinity and specificity could be substantially influenced even by sequence changes outside of the antigen-binding site, including changes in the heavy chain constant region. (*See, e.g.*, ALXN2013 at 1379; ALXN2014 at 226-27; ALXN2011 at 2239; ALXN2008 at 169; ALXN2012 at 3388; ALXN2009 at 13924; ALXN2010 at 3-4.) A POSA would have understood that such sequence changes could potentially result in harmful immune reactions following human

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[3] Furthermore, a POSA could not reliably predict that a hybrid IgG2/IgG4 would be expressed efficiently in cells in sufficient quantities for therapeutic antibody production since it was known that even point mutations in the constant region affected antibody secretion and here was an antibody with a very different and unnatural constant region. (ALXN2047 at 1111-12, 1117-18.)

administration, and that the immune consequences could not be reasonably predicted without human clinical testing. (*See, e.g.*, ALXN2015 at 508; ALXN2036 at 141 ("[I]mmunogenicity is a complex issue; intrinsic factors such as protein sequence and structure are likely to be as important as extrinsic ones"); *see also* ALXN2037 at 1343-44; ALXN2038 at 624-26.)

5. A POSA as of March 15, 2007 Would Have Understood "Eculizumab" To Be an IgG4-Isotype Humanized Antibody

119. In my opinion, a POSA as of March 15, 2007 would have understood that "eculizumab" was a single, unique humanized monoclonal antibody developed by Alexion, having a single, unique structure and primary amino acid sequence. I have reviewed the deposition transcript of Dr. Balthasar, and understand that he agrees with me fully on this point. (ALXN2032 at 10:9-11:17, 98:19-99:8, 100:3-10.)

120. I also have reviewed the Board's Institution Decision, which contained the statement that "'eculizumab' referred to and refers to a class or category of anti-C5 antibodies, also called 5G1.1 or h5G1.1 mAbs." (Paper No. 15 at 21-22.) I respectfully disagree with the Board on this point, and I understand Dr. Balthasar does as well.

121. While it is correct that, as I explain in Section VI.D.3 above, a POSA would have understood that the terms "5G1.1" or "h5G1.1" could potentially refer to multiple different antibody structures (when not further limited or clarified by

additional context), a POSA as of March 15, 2007 would have understood that the term "eculizumab" was a non-proprietary name referring to one unique antibody with a unique structure and primary amino acid sequence. And, for the reasons explained below, a POSA would have understood that structure and sequence to be consistent with the intact humanized ***IgG4*** isotype monoclonal antibody described in Thomas (AMG1023).

122. By March 15, 2007, a POSA would have understood that "eculizumab" was at a very late stage of development, with Alexion having published results of Phase II and Phase III human clinical trials showing that "eculizumab" was safe and effective for the treatment of PNH. (*See, e.g.*, AMG1012 at 1239, 1241-1242; AMG1004 at 552, 558; AMG1047 at 2559, 2564; AMG1005 ¶¶ [0081-0096].) A POSA would have further known that, as of September 2006, Alexion had applied for marketing approval of "eculizumab" from the U.S. FDA and European authorities based on the results of those human clinical trials, and had proposed the trade name "SOLIRIS®" for marketing the product following a future approval. (6/20/2006 Alexion Press Release; *see also* AMG1012 at 1239.) A POSA would have had no doubt that "eculizumab" and "SOLIRIS®," at that very late stage of development, was limited to a single humanized monoclonal antibody with a single structure and primary amino acid sequence.

123. If a POSA as of March 15, 2007 were to inquire further as to the specific structure of "eculizumab," they could have reached only one conclusion after considering the full scope of the literature: that "eculizumab" was an intact, humanized monoclonal antibody with the humanized variable region and ***IgG4*** isotype constant region as described in Thomas (AMG1023). That is because, as illustrated in Table 1 below, the literature concerning "eculizumab" and its clinical properties consistently and uniformly cited to Thomas (AMG1023) for the identify of "eculizumab." The only reasonable conclusion in view of the pre-March 15, 2007 literature's repeated reference to Thomas for the description of "eculizumab" was that Thomas in fact described "eculizumab."[4]

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[4] A POSA would not have understood these references as citing Thomas only for a general discussion of the "humanization" of "5G1.1," as Dr. Balthasar appeared to suggest at his deposition. (*See* ALXN2032 at 82:10-83:1, 86:6-23.) The references I discuss above cite Thomas for what "eculizumab" *is*, which a POSA would have understood as referring to a specific structure. And Dr. Balthasar does not dispute that Thomas disclosed a full-length, intact, IgG4 isotype humanized antibody derived from the "5G1.1" mouse antibody. (*See* AMG1002 ¶ 47; ALXN2032 at 242:21-243:4.)

Samsung Bioepis Exhibit No. 1002
Page 13111

Table 1: References to "Eculizumab" as Thomas's Humanized IgG4 Antibody

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hillmen 2004 (AMG1004) at 553, reporting on a Phase II clinical trial for PNH, and citing ***Thomas***, Ref. No. 15	"Eculizumab is a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components.[14, 15] It binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b. . . ."
Hill 2005 (AMG1047) at 2559, reporting on a Phase II clinical trial for PNH, and citing ***Thomas***, Ref. No. 9	Eculizumab is a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage.[9]"
Hillmen 2006 (AMG1012) at 1234, reporting on a pivotal Phase III clinical trial for PNH, and citing ***Thomas***, Ref. No. 13	Eculizumab (Soliris, Alexion Pharmaceuticals) is a humanized monoclonal antibody directed against the terminal complement protein C5."[13]
Hill 2007 (ALXN2028) at 31, reporting on successful treatment of PNH in a patient with aplastic anemia and citing ***Thomas***, Ref No. 6	"Eculizumab is a novel humanized monoclonal antibody directed against the complement protein C5.[6]"

Samsung Bioepis Exhibit No. 1002
Page 13112

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Bell (AMG1005) at [0052], in a patent application describing results of Phase II clinical trials for PNH, citing ***Thomas***	"Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in U.S. Pat. No. 6,355,245 and [*Thomas*], the disclosures of which are incorporated herein in their entirety by this reference. The antibody h5G1.1-mAb is currently undergoing clinical trials under the tradename eculizumab."
Kaplan (AMG1021) at 1018, in a review article discussing development of "eculizumab," citing ***Thomas***, Ref. No. [258884]	"Humanized 5G1.1, Fab and scFv molecules were produced by grafting the complementary determining regions of 5G1.1 on to human framework regions *[258884]*."
Brekke (AMG1019) at 56, in a review article discussing development of therapeutic antibodies, citing Kaplan (AMG1021), Ref. No. 31, which in turn cites to ***Thomas***	"Eculizumab (5G1.1; Alexion Pharmaceuticals) is a humanized monoclonal antibody that prevents the cleavage of human complement component C5 into its pro-inflammatory components[31], ..."

Samsung Bioepis Exhibit No. 1002
Page 13113

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Pierangeli (AMG1020) at 2123, in a journal article studying mechanisms for a complement-mediated disease, citing Hillmen 2004 (AMG1004), Ref. No. 18, which in turn cites to ***Thomas***	Eculizumab (5G1.1), the humanized anti-C5 mAb, is considered a potential treatment for several chronic inflammatory diseases . . . [E]culizumab has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH]; specifically, it reduces intravascular hemolysis, hemoglobinuria, and the need for transfusion in these patients, providing a proof-of-concept that blockade of complement activation is feasible and tolerable in patients with chronic disease (*18*)."

124. Thomas, in turn, describes Alexion's design and testing of a full-length, IgG4-isotype humanized antibody ("humanized 5G1.1") with anti-C5 affinity, specificity, and complement-blocking activity comparable to the original mouse "5G1.1" antibody. (AMG1023 at 1389.) First, Thomas describes the humanization of variable region sequences from a mouse anti-C5 monoclonal antibody "5G1.1." (AMG1023 at 1393-94.) Next, the humanized variable region sequences were used to produce antibody fragments (*i.e.*, recombinant Fab and scFv), which were assessed for binding to human C5 and the ability to inhibit complement. (AMG1023 at 1394-95.) Finally, Thomas described the production

Samsung Bioepis Exhibit No. 1002
Page 13114

of "an intact humanized antibody (IgG4 isotype)," which was shown to bind C5 with similar affinity to the original "5G1.1" mouse antibody, and to inhibit complement activity in an *in vitro* hemolysis assay with equal potency to the mouse "5G1.1" antibody. (AMG1023 at 1396, 1399.) The researchers explained how they specifically selected the human IgG4 isotype because it "does not activate human complement," and expressed their view that it was "likely to be minimally immunogenic in patients." (AMG1023 at 1399.)

125. Unlike Thomas and the following literature regarding "eculizumab," a POSA would not have understood that Evans (AMG1007) disclosed "eculizumab." A POSA instead would have understood Evans to describe some of the early stage research leading to the later development of the antibody identified as "eculizumab" as described in Thomas. As Dr. Balthasar testified, and I agree, a POSA would have seen that Evans does not ever use the term "eculizumab," and does not teach any full-length humanized antibodies. (ALXN2032 at 199:15-17, 163:5-15.)

126. Initially, in Example 7, Evans describes the generation of a "hybridoma designated as 5G1.1," producing a mouse antibody referred to throughout Evans as "the 5G1.1 antibody" or "the 5G1.1 mAb." (AMG1007 at 37:34-39:30; ALXN2032 at 165:11-21.) Evans also describes experiments to characterize the properties of the "5G1.1" antibody, including assays to assess its

C5 binding and ability to inhibit complement by blocking C5 cleavage. (AMG1007 at 38:43-51, 39:62-40:19; ALXN2032 at 38:43-39:16; 39:62-40:29.) In Example 10, Evans describes experiments to determine the amino acid sequence of "the 5G1.1 mAb" and copy (or "clone") the DNA sequences for its heavy and light chain variable regions. (AMG1007 at 40:32-42:54; ALXN2032 at 169:19-23.)

127. As Dr. Balthasar agreed during deposition, Evans does not teach any full-length antibodies other than the mouse "5G1.1" monoclonal antibody described in Examples 7 through 10. (ALXN2032 at 169:13-18.) In Example 11, Evans only describes the development of mouse and humanized "fragments" by recombinant DNA means, including (1) "Fab" molecules comprised of light chains and "Fd" sequences (the heavy chain portion of an Fab, consisting of VH and CH1 only, *see* AMG1007 at 43:21-61, SEQ ID NOs: 10-12, 16); and (2) "scFv" molecules (variable domain of a heavy chain connected by a synthetic linker to the variable domain of a light chain). (AMG1007, Example 11; ALXN2032 at 169:13-18.) As Dr. Balthasar admitted, these "fragments" were never part of, or extracted from, any full-length antibody, but rather were cloned and produced directly by recombinant means. (ALXN2032 at 163:5-15, 228:4-16.)

Samsung Bioepis Exhibit No. 1002
Page 13116

128. Figure 4 below illustrates (1) the structures that a POSA as of March 15, 2007 would see when reading Evans – the mouse antibody "5G1.1" and humanized recombinant "fragments" with no intact heavy chain constant region, and (2) what a POSA reading Evans would not have seen – a full-length, humanized monoclonal antibody:

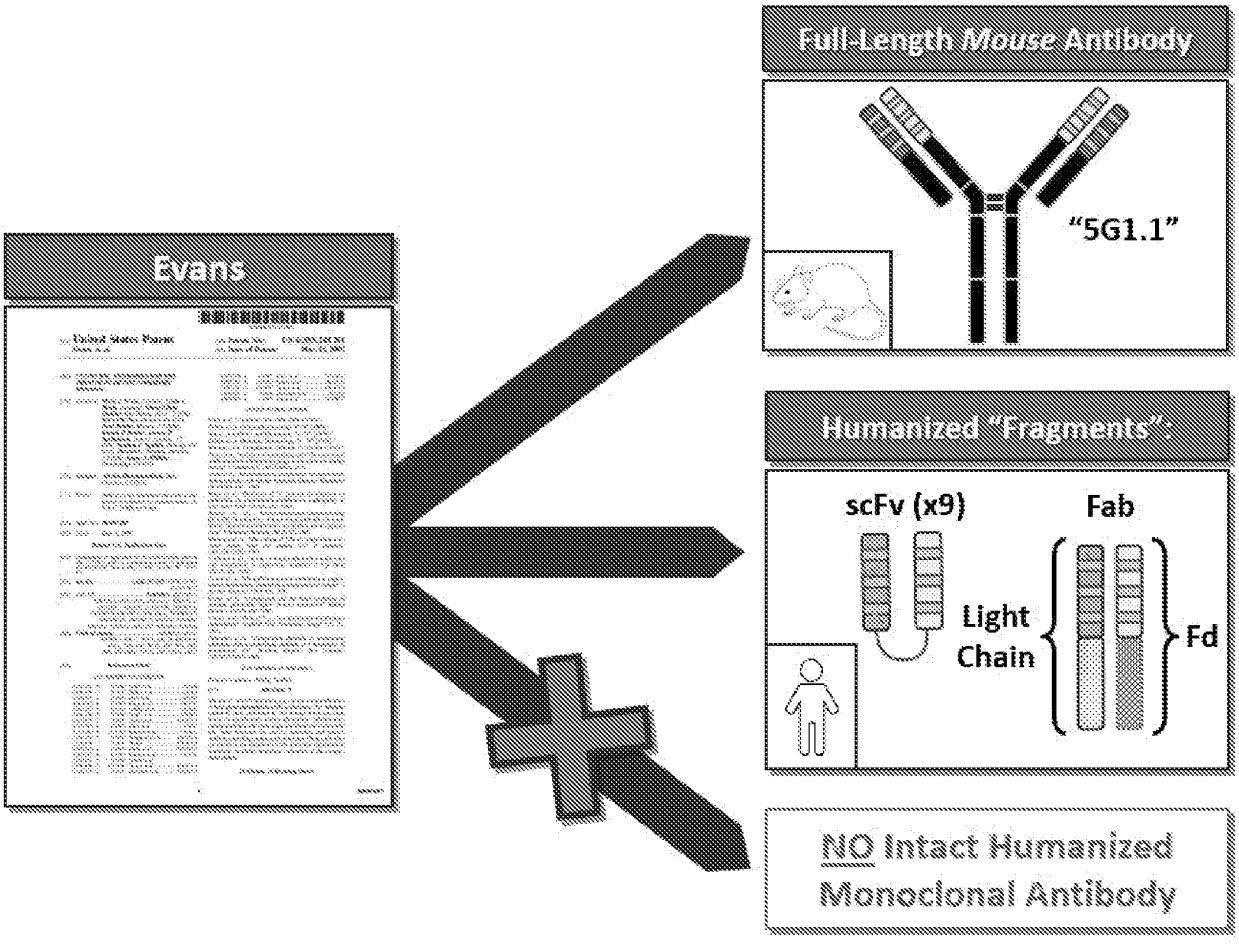


Figure 4: A POSA's understanding of structures disclosed in Evans (AMG1007)

129. Accordingly, I disagree with Dr. Balthasar's Figures 10, 11, 12, 14, 15, and 16 of his Declaration that depict the humanized scFvs of Evans as variable regions on a full-length, intact, bivalent "Y" antibody structure. (AMG1002 at 42, 60, 62, 72, 81, and 84.) Among other things, by including an image of the full heavy chain regions in his depiction of the disclosure of Evans, Dr. Balthasar's figures suggest that Evans disclosed a full-length humanized monoclonal antibody derived from the original "5G1.1" mouse antibody, when in fact the mouse antibody was the ***only*** full-length antibody that Evans described.

130. I also note that, while Dr. Balthasar has selected one of the scFv sequences from Evans that he says aligns "perfectly" with variable region sequences from SEQ ID NOs: 2 and 4 of the '504 patent (*see* AMG1002 ¶ 55, Figs. 6 and 7), that is only because he used his hindsight knowledge of the sequences disclosed in the '504 patent to identify that alignment. A POSA without hindsight might have instead looked to the humanized Fab sequences of Evans, which are disclosed in Evans as light chain and "Fd" sequences. (SEQ ID NOs: 11 and 12, AMG1007 at 43:22-34 and Certificate of Correction at 21-24.) A POSA would have understood that a Fab was a more "complete" structure as compared to an scFv, since a humanized Fab contains both humanized variable regions and CH1 and CL human constant regions. And as the following Figures 5 and 6 demonstrate, the sequence of the Fab fragments in Evans would not have guided a

POSA toward the specific amino acid sequence claimed in the ’504 patent, because in particular, there are significant differences between Evans’s “Fd” sequences (the heavy chain portion of an Fab) and the claimed sequence of the ’504 patent:

Samsung Bioepis Exhibit No. 1002
Page 13119



Figure 5: ’504 patent SEQ ID No. 2 compared with Evans SEQ ID No. 11

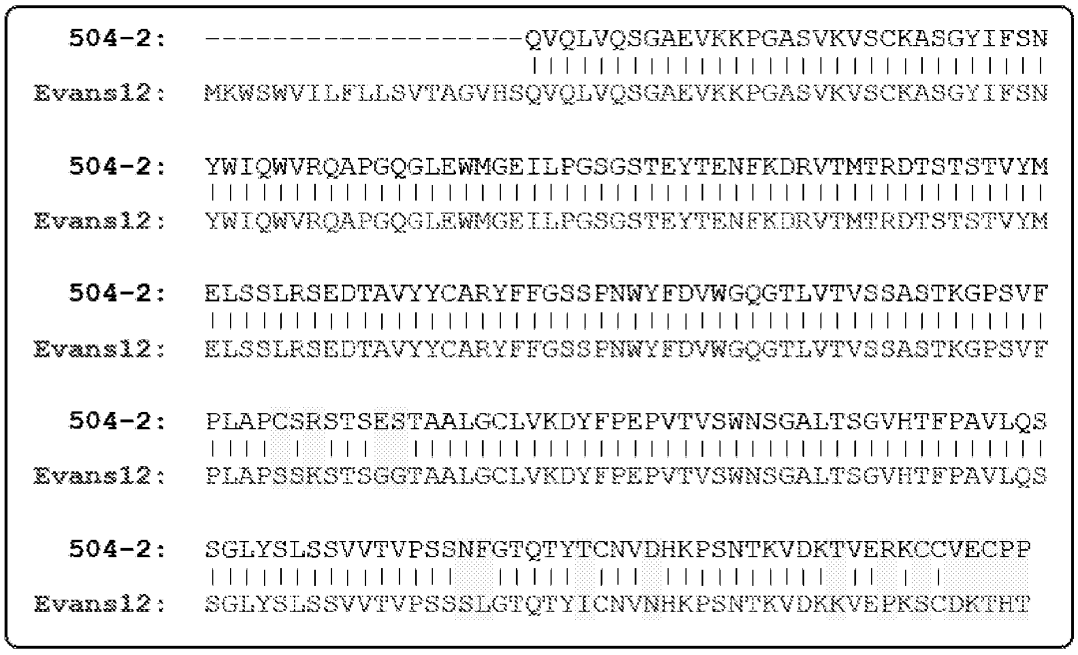


Figure 6: ’504 patent SEQ ID No. 2 compared with Evans SEQ ID No. 12

Samsung Bioepis Exhibit No. 1002
Page 13120

131. This would have been consistent with a POSA's understanding of Evans as describing an early stage of research, prior to the selection of the final, IgG4 isotype, as a POSA would have understood from clinical study publications.

132. I disagree with Dr. Balthasar's opinions suggesting that a POSA would have had any reason to look to Bowdish (AMG1006) or Mueller (AMG1008) for the structure or sequence of "eculizumab." As Dr. Balthasar admitted at deposition, neither Bowdish nor Mueller mention "eculizumab," and none of the references prior to March 15, 2007 describing "eculizumab" and its clinical properties cite to Bowdish or Mueller for a description of "eculizumab." (ALXN2032 at 199:9-12, 102:10-19.) Further, neither Bowdish nor Mueller disclose any *in vitro* or *in vivo* data suggesting that an antibody with a structure different from the IgG4-isotype antibody of Thomas would be effective in binding C5, blocking its cleavage, and safety and effectively treating patients with conditions such as PNH.

133. As of March 15, 2007, references relating to anti-C5 binding and clinical trial publications relating to PNH cited either Thomas, teaching an IgG4 isotype antibody, or Evans, which does not provide clear guidance as to isotype for a therapeutically effective antibody. Based on the art as a whole, as of that date, a POSA would have understood "eculizumab" to be an IgG4 antibody.

E. The Novel, Uniquely-Engineered Amino Acid Sequence of SOLIRIS® Was Not Known to a POSA as of March 15, 2007

134. Currently, but not prior to March 15, 2007, it is known that Alexion's SOLIRIS® utilizes a uniquely engineered, non-naturally occurring heavy chain constant region corresponding to SEQ ID NO: 2 of the '504 patent. I understand that SOLIRIS® was the first antibody with a heavy chain of its kind (containing a hybrid of sequences from both IgG2 and IgG4 constant regions) to be clinically tested in humans, and that Alexion was the first to show that such an antibody could be safe and effective when administered to human patients. (AMG1033 at 1257-58.) I also understand that SOLIRIS® was the first FDA-approved product containing Alexion's uniquely-engineered heavy chain constant region.

135. ***Prior*** to March 15, 2007, however, a POSA would not have been aware of any published clinical testing showing the safety or efficacy in humans of an antibody with the uniquely engineered heavy chain constant region known today to be used SOLIRIS®. Rather, POSA as of March 15, 2007 would have understood "eculizumab" to be an antibody with an ***IgG4*** constant region as described in Thomas (*see* Section VI.D.5 above), and would have attributed the safety and efficacy shown in Phase II and Phase III clinical trials (*e.g.* AMG1004, AMG1047, AMG1012, AMG1005) to that IgG4 antibody.

136. Accordingly, from the perspective of a POSA as of March 15, 2007, a humanized derivative of the "5G1.1" antibody with a hybrid IgG2/IgG4 constant

Samsung Bioepis Exhibit No. 1002
Page 13122

region was an unstudied, uncharacterized entity with no known or characterized C5 binding, no known ability to block C5 cleavage, and no evidence that it was therapeutically useful to treat PNH or any other condition, or even suitable for administration to human patients.[5]

137. The structure of the active molecule in SOLIRIS® that is claimed in the '504 patent and is known today – but was not known before March 15, 2007 – is shown below in comparison to the IgG4 isotype antibody described in Thomas. Unlike the IgG4 antibody of Thomas, the claimed antibody uses the CH1 and "hinge" regions of IgG2, thereby providing a very different antibody than that identified in the literature citing to Thomas.

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[5] I understand Dr. Balthasar argues that a POSA nonetheless would have been motivated to construct a "humanized 5G1.1" antibody using a hybrid "IgG2/IgG4" constant region, in view of literature at the time that speculated about the potential benefits of such a constant region. (AMG1002 ¶¶23, 47 (citing AMG1031, AMG1032).) As I explain below, a POSA would have viewed such statements as speculation based solely on *in vitro* data, and would not have reasonably expected that such a constant region that had never been clinically tested, let alone commercialized, would result in a product suitable and useful for human administration.

Samsung Bioepis Exhibit No. 1002
Page 13123

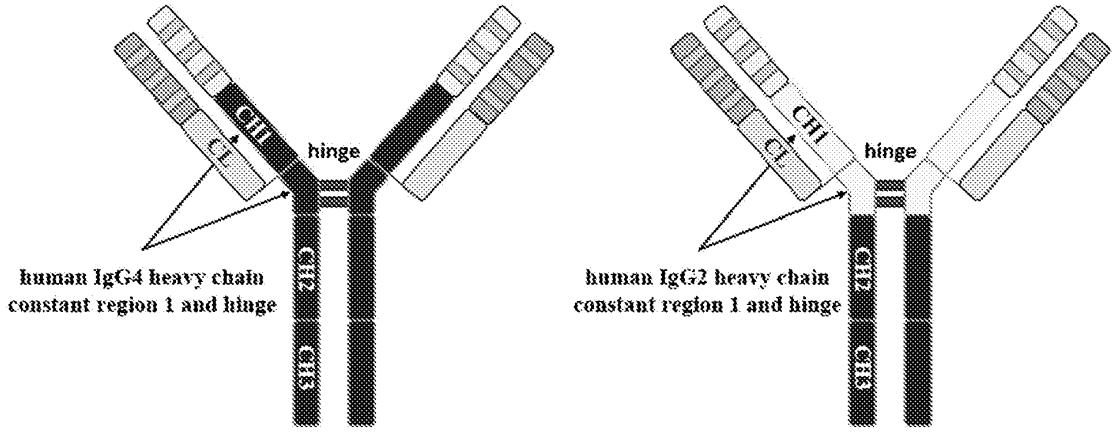


Figure 7: Left – Structure of the IgG4 isotype antibody referenced to as "eculizumab" in the literature as of March 15, 2007

Right – Structure of SOLIRIS®, having a non-naturally occurring, protein-engineered isotype

VII. OPINIONS

A. Dr. Balthasar's Opinions Misread the Prior Art and Rely on Hindsight Analysis

138. I have considered Dr. Balthasar's Declaration in this proceeding, dated February 27, 2019. I disagree with a number of Dr. Balthasar's conclusions, which I believe overstate the teachings in the prior art and reflect a narrative created with significant hindsight bias.

1. A POSA Before March 15, 2007 Would Not Have Understood "Eculizumab" To Contain the Uniquely-Engineered Heavy Chain Constant Region Reflected in SEQ ID NO: 2 of the '504 Patent

139. I disagree with Dr. Balthasar's statement that, as of March 15, 2007, "[a] POSA would have been aware that eculizumab was a humanized anti-C5

monoclonal antibody (h5G1.1) containing a hybrid IgG2/IgG4 constant region . . . ." (*See* AMG1002 ¶43.) Taken as a whole, the prior art that described what "eculizumab is" did not disclose an antibody with such a structure; and to the extent the prior art described antibodies with such a structure (*e.g.*, for use as "isotype control" antibodies), a POSA would not have understood such antibodies to be "eculizumab," or to have any of the properties attributed to "eculizumab" in the clinical literature. To the contrary, the prior art repeatedly would have told a POSA as of March 15, 2007 that "eculizumab" contained an IgG4 isotype, as indicated by Thomas and following publications. (*See* Section VI.D.5 above.)

140. I understand from Dr. Balthasar's deposition testimony that he admits key facts contrary to his position regarding the POSA's understanding of "eculizumab" as of March 15, 2007. For example, Dr. Balthasar agreed that:

- Hillmen '04 (AMG1004), Hill '05 (AMG1005), and Hillmen '06 (AMG1012) all cite to Thomas in statements identifying what "eculizumab" is (ALXN2032 at 125:13-126:9; 128:20-129:10; 130:0-22)
- Bell (AMG1005) cites to Thomas and Evans (AMG1007) for "methods for the preparation of h5G1.1-mAb [identified in Bell as "eculizumab"], h5G1.1-scFv, and other functional fragments" – but

only Thomas describes a full-length, intact humanized antibody (ALXN2032 at 160:18-162:12)

- A POSA would have understood that Thomas's IgG4 antibody is different in structure and sequence from a hybrid IgG2/G4 antibody (ALXN2032 at 97:7-21.)

141. Dr. Balthasar ignores these clear teachings towards Thomas's IgG4 antibody from the clinical literature regarding "eculizumab," and instead relies on a single sentence taken out of context from a single publication, Tacken (AMG1034), to support his conclusion that a POSA as of March 15, 2007 would have understood "eculizumab" to be a hybrid IgG2/IgG4 antibody. (*See* AMG1002 ¶¶ 46-47.) At his deposition, I understand that Dr. Balthasar admitted that Tacken was the ***only*** document that he relies on dated prior to March 15, 2007 that he contends associates "eculizumab" with an IgG2/IgG4 constant region. (ALXN2032 at 104:6-20.)

142. Specifically, Dr. Balthasar relies on the following statement from Tacken, which ends with a citation to Thomas (footnote 19).

> An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [*sic*]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5.[19]

(AMG1034 at 1279, 1285; ALXN2032 at 78:10-15.)

143. In view of the language of the statement itself, and all the literature available to a POSA as of March 15, 2007, including the many clinical references identifying "eculizumab" as the IgG4 antibody of Thomas, a POSA would not have read this statement in Tacken as teaching that "eculizumab" had a hybrid IgG2/IgG4 isotype. As discussed above in Section VI.D.3, a POSA would have understood that the term "eculizumab" could refer to only one single antibody with a distinct structure and primary amino acid sequence – and this one isolated statement in Tacken regarding an "isotype control antibody" was at most ambiguous and far outweighed by the repeated, consistent references in the New England Journal of Medicine and other prominent publications identifying eculizumab as Thomas's IgG4 antibody.

144. First, in my opinion, a POSA would have seen that the language in the cited sentence does not unambiguously state that the IgG2/IgG4 "isotype control antibody" used in Tacken ***is*** "eculizumab." The cited sentence vaguely refers to both "h5G1.1-mAb," which could refer to a class of humanized antibodies, and "5G1.1," which could refer to multiple antibodies or antibody fragments, including the original mouse 5G1.1 antibody. (ALXN2032 at 98:22-99:8, 100:16-24, 165:5-21; 169:6-18; 202:24-203:16.) Moreover, by citing to Thomas, which describes an IgG4 isotype antibody that the other prior art consistently identified as

"eculizumab," this sentence at most would be confusing to a POSA. One possible reading could be that Thomas's antibody was "eculizumab" while Tacken's IgG2/G4 "isotype control" antibody was a different derivative; and another possible interpretation is that Tacken referred to the IgG2/IgG4 "isotype control" antibody as "eculizumab" by mistake (just as it misspelled "eculizamab" [sic]). Either way, a POSA would not have understood Tacken as teaching that "eculizumab" had an IgG2/IgG4 because Tacken does not clearly state what eculizumab is. Moreover, Dr. Balthasar has not explained why a POSA would have credited this isolated, ambiguous statement regarding an "isotype control antibody" in Tacken, while disregarding the numerous clear statements in the key publications regarding "eculizumab" that identify it as the IgG4 antibody of Thomas.

145. In contrast to the multiple publications referencing Thomas, Tacken contains no assessment of the clinical safety or efficacy of eculizumab, but instead is directed to unrelated subject matter – use of a different antibody, "hD1," to increase vaccine efficacy by targeting antigens to dendritic cells. (*See* AMG1034 at 1278.) Tacken provides neither C5 binding data, nor sequence information, for its isotype control antibody, instead citing to Thomas to support the sentence cited by Dr. Balthasar. (*Id.*) This would have suggested to a POSA that the

"eculizumab" referred to was not Tacken's isotype control antibody, but rather the IgG4 antibody described in Thomas.

146. I also disagree with Dr. Balthasar's opinion that Tacken would have indicated to a POSA that Alexion had moved on from the IgG4 isotype antibody of Thomas as its clinical candidate and replaced it with an antibody containing a hybrid IgG2/IgG4 constant region. In particular, references published ***after*** Tacken continued to cite Thomas for the structure of "eculizumab." For example, Hillmen 2006 (AMG1012), a September 2006 publication by Alexion in the New England Journal of Medicine, describes a successful Phase III trial of "eculizumab" in treating PNH and unambiguously references Thomas in defining what "eculizumab" *is*, stating:

> Eculizumab (Soliris, Alexion Pharmaceuticals) *is* a humanized monoclonal antibody directed against the terminal complement protein C5.[13]

(AMG1012 at 1234, 1243 (citing Thomas (AMG1023), Ref. No. 13) (emphasis added); ALXN2032 at 116:16-22.) Hill '05 (AMG1047), a one-year extension study of the 11-patient study reported in Hillmen '04 (AMG1004), was notably published two months ***after*** Tacken, in the same journal as Tacken (Blood), and like Hillmen '06, identified "eculizumab" as the IgG4 antibody of Thomas. (AMG1047 at 2559, Ref. No. 9; ALXN2032 at 113:14-21, 114:19-115:10.) Bell,

Samsung Bioepis Exhibit No. 1002
Page 13129

published a month after Tacken, and Hill '07, a case report published on March 1, 2007, likewise both identify "eculizumab" as the IgG4 antibody of Thomas. (AMG1005 ¶ [0052]; ALXN2028 at 31, Ref. No. 6.) These later references would have confirmed to a POSA prior to March 15, 2007 that Tacken did not represent any change in the identify of "eculizumab," which, from the perspective of a POSA, remained the IgG4 antibody structure described in Thomas.

147. Given Tacken's unrelated subject matter, and only limited and ambiguous reference to "eculizumab," a POSA would not have read Tacken as identifying an IgG2/IgG4 isotype for "eculizumab." Rather, as of March 15, 2007, a POSA would have understood "eculizumab" to have an IgG4 isotype, as taught by the art as a whole. In my opinion, a POSA would have either understood Tacken to be consistent with "eculizumab" being an IgG4 isotype (because of its citation to Thomas as Ref. No. 19), or otherwise, they would have thought that Tacken's referring to its IgG2/IgG4 isotype control antibody by the name of "eculizumab" was a mistake.

148. Dr. Balthasar states that Tacken "cites a publication by Mueller *et al.* (AMG1031; 'Mueller II') as providing information about the hybrid IgG2/IgG4 constant region portion of eculizumab." (AMG1002 ¶ 54.) I disagree with this statement. Tacken does not refer to "eculizumab" in connection with Mueller II. Rather, Tacken states:

> The humanized variable heavy and variable light regions [of the hD1 antibody] were then genetically fused with a human hybrid IgG2/IgG4 constant domain[17] and a human kappa chain constant domain, respectively.

(AMG1034 at 1279 (citing Mueller II, Ref. No. 17).) A POSA would not have read this vague reference to Mueller II in the context of an "hD1" antibody as teaching that the antibody "eculizumab" had an IgG2/IgG4 hybrid constant region. The reference in Tacken to Mueller is for description of the "human hybrid IgG2/IgG4 constant domain" described in Tacken; Mueller is not cited as describing "eculizumab."

149. Dr. Balthasar also cites prosecution history statements in an unrelated Alexion patent application (AMG1049, "the '438 application") that he characterizes as demonstrating a POSA's understanding that "eculizumab" had a hybrid IgG2/IgG4 antibody. (AMG1002 ¶ 45.) I have been informed that these statements, made after the priority date and in an unrelated patent application, are not prior art to the '504 patent. (ALXN2032 at 61:13-24.) But, even if these statements were to be considered prior art, they would not change my opinion that a POSA would have understood "eculizumab" to have an IgG4 isotype, based on the teachings of the prior art as a whole.

Samsung Bioepis Exhibit No. 1002
Page 13131

150. I further note that Dr. Balthasar also relies on (1) a non-prior art article by Rother *et al*, published in November 2007, and (2) the non-prior art "Boone Declaration" dated in 2017 from the prosecution history of the '504 patent for his understanding of "eculizumab's heavy chain." (AMG1002 ¶ 56 (citing AMG1033); AMG1002 ¶ 11 (citing AMG1014 at 767 (Boone Declaration ¶ 6).) I understand that such information was not available to a POSA as of March 15, 2007, and it does not change my opinion that the prior art as of that date consistently and uniformly indicated to a POSA that "eculizumab" was the IgG4 antibody described in Thomas.

151. Figure 8 below illustrates (1) the consistent teaching in the literature ***prior*** to March 15, 2007 that "eculizumab" was identified as the IgG4 antibody of Thomas, and (2) how the information that Dr. Balthasar relies on for identifying "eculizumab" as an "IgG2/IgG4" hybrid isotype antibody was dated after the March 15, 2007 date:

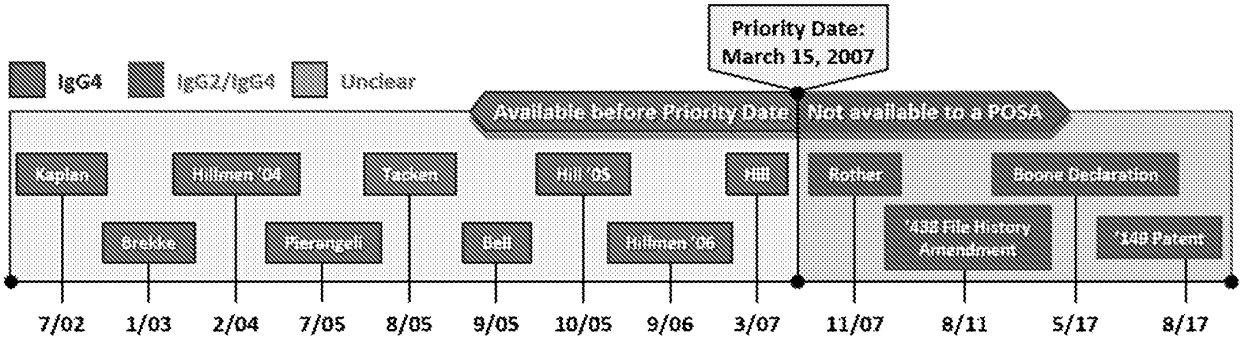


Figure 8: Documents referring to "eculizumab" before and after March 15, 2007

2. The Antibody Sequence Recited in the '504 Patent, and Methods of Treatment and Pharmaceutical Compositions of an Antibody Comprising the Sequence Recited in the '504 Patent, Were Not Publicly Known Before March 15, 2007

152. I also disagree with Dr. Balthasar's assertion that, prior to March 15, 2007, "[a] POSA would have been aware of the amino acid sequence of eculizumab." (AMG1002 ¶50.) Before March 15, 2007, a POSA would not have known the complete, full-length amino acid sequence of SOLIRIS® (eculizumab) – now claimed in the '504 patent – which was not publicly available before that date. The references cited by Dr. Balthasar to support his conclusion do not disclose the complete amino acid sequence claimed in the '504 patent prior to March 15, 2007, and do not change my opinion that a POSA would not have understood that "eculizumab" or any other antibody had the complete claimed sequence prior to that date.

153. Likewise, none of Dr. Balthasar's references dated prior to March 15, 2007 would have disclosed to a POSA that an antibody with the specific sequence recited in claims 1-10 of the '504 patent had ever been formulated into a pharmaceutical composition suitable for human or administration, or that such an antibody had ever been administered to any human patients. From the perspective of a POSA before March 15, 2007, the claimed antibody of the '504 patent was, for all they could tell, never characterized for C5 binding, never tested for any *in vitro* activity, never studied in any animal models or tested for toxicity in animals,

never grown in cells suitable to make quantities needed for clinical trials, never formulated into a pharmaceutical composition that was suitably stable to administer to humans, and never actually studied in humans for therapeutic effects or safety, including potential immunogenicity.

154. Dr. Balthasar first cites a declaration by an Alexion employee, submitted during prosecution of the '504 patent, and that Dr. Balthasar characterizes as showing Alexion used eculizumab – which is now known to correspond to claimed SEQ ID Nos: 2 and 4 – in clinical trials prior to March 15, 2007. (AMG1002 ¶49 (citing the Boone Declaration, AMG1014 at 764-766).) Dr. Balthasar does not argue that the full-length sequence of eculizumab was expressly disclosed over the course of any of the eculizumab clinical trials prior to March 15, 2007, and I understand that the declaration Dr. Balthasar cites was submitted on May 11, 2017, and would not have been accessible to a POSA prior to March 15, 2007. I understand that the use of an antibody in clinical trials by itself is insufficient to disclose the antibody's sequence, and so this does not change my opinion that the full-length sequence of eculizumab was not publicly available prior to March 15, 2007.

155. In the following paragraphs of his Declaration, Dr. Balthasar also relies on Evans, Bowdish, Mueller, and Mueller II (AMG1031). I disagree with Dr. Balthasar's depiction of these references in his Declaration, which significantly

overread the references' teachings. When read correctly, it is clear that none of these references, either alone or in combination, teach the specific, full-length sequence of the antibody used in the pharmaceutical compositions claimed in the '504 patent, as described more fully in Sections VII.D and VII.E below.

156. First, Evans does not teach or suggest the specific, full-length antibody sequence described in claims 1-10 of the '504 patent, or that an antibody having that sequence would bind C5 or be safe and effective in human patients.

157. Evans does not use the term "eculizumab," and does not disclose any full-length humanized antibodies. The only full-length antibody disclosed in Evans is the parental "5G1.1" mouse monoclonal antibody. (*E.g.*, AMG1007 at 38:43-53.) A POSA as of March 15, 2007 would have understood that Evans reflected an earlier stage of research involving discovery of the "5G1.1" mouse antibody and early efforts to design humanized variable region fragments, preceding Alexion's design and selection for clinical testing of a full-length, humanized antibody.

158. Evans provides nine different versions of a humanized "variable" region for anti-C5 antibodies, but does not provide any guidance as to which, if any, were being used in antibodies developed for clinical trials. (*See, e.g.*, AMG1007 at 43:6-14, 43:62-45:4.)

Samsung Bioepis Exhibit No. 1002
Page 13135

159. Evans includes only a brief, generic statement regarding "constant region domains," and does not identify any specific heavy chain constant region that could be used in a humanized antibody, or describe any specific full-length humanized antibodies that were actually made and confirmed to bind C5. (AMG1007 at 45:24-33.) Evans does not suggest or disclose the hybrid IgG2/IgG4 corresponding to SEQ ID NO:2 of the '504 patent, or teach that an antibody incorporating that sequence would be an "antibody that binds C5," or that such an antibody could be suitable for "a method of treating a patient suffering from [PNH]," as claims 1-10 require. In fact, the only constant regions disclosed in Evans are the CH1 regions of Fd fragments, which appear to correspond to IgG1 CH1 sequences rather than IgG2/IgG4.[6] (*See* Section VI.D.5 above.)

160. Bowdish, Mueller, and Mueller II also did not disclose (1) the specific, full-length antibody described in claims 1-10 of the '504 patent; (2) whether an antibody with the claimed sequence would be "an antibody that binds C5," (3) whether an antibody with the claimed sequence would be suitable for use in "treating a patient suffering from [PNH]," or (4) whether that an antibody was

[6] Evans refers to the chimeric version of its "Fd" series of compounds as "5G1.1M1 VH HuG1." (AMG1007 at 43:18-20.)

Samsung Bioepis Exhibit No. 1002
Page 13136

suitable for formulation "pharmaceutical composition" for use in treating human patients suffering from PNH.

161. The subject matter of Bowdish was unrelated to "eculizumab," C5 binding or the of PNH. Bowdish concerned the use of an antibody for use as a "scaffold" to house a peptide (*e.g.*, the hormone TPO), thereby providing greater stability and longer half-life for the peptide in vivo. (AMG1006 at [0005]-[0006].) The antibody used for the "scaffold" in Bowdish could be any antibody, as the technique reported in Bowdish is not specific for any individual antibody sequence. (AMG1006 at [0066].)

162. Bowdish did not describe any assays related to C5 binding or blocking complement-mediated lysis. Example 4 of Bowdish, which Dr. Balthasar relies on in his declaration, assesses the binding of TPO-mimetic peptide (presented on an antibody scaffold) with a TPO receptor (the "cMpl receptor") – a biological interaction that is not part of the complement pathway and is unrelated to cleavage of C5. (AMG1006 at [0192].)

163. I disagree with Dr. Balthasar's characterization of Bowdish as disclosing sequences of "eculizumab" or an "eculizumab-based immunoglobulin." (*See, e.g.*, AMG1002 ¶¶ 50-51, 55.) Bowdish never uses the term "eculizumab." Further, a POSA would not understand Bowdish to be disclosing sequences of the

humanized antibody "eculizumab" described in clinical trials based on Bowdish's references to "5G1.1."

164. A POSA would have understood Bowdish's incorporation by reference of Evans to be more limited than is depicted in Dr. Balthasar's report. For example, in his report, Dr. Balthasar states, "Bowdish references U.S. Pat. No. 6,355,245 (AMG1007; 'Evans') as describing the generation of the h5G1.1 antibody." (AMG1002 ¶ 53.) But Bowdish does not use the term "h5G1.1." Instead, paragraph [0191] of Bowdish states, "Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated herein by reference." (AMG1006 ¶ [0191].) A POSA would have understood that Evans,[7] in turn, used

[7] I understand from counsel that Bowdish cites I understand from counsel that Bowdish does not cite Evans (AMG1007) itself, but rather cites to the "'283 application" from which Evans issued. For convenience and to address the arguments Dr. Balthasar actually made, I will use "Evans" to refer to the document referenced in Bowdish for "[c]onstruction of 5G1.1," and will discuss the contents of Evans (AMG1007) in connection with that reference. But by doing so, I am not admitting that the "'283 application" and Evans are the same document. I understand from counsel that the "'283 application" has not been

Samsung Bioepis Exhibit No. 1002
Page 13138

the term "5G1.1" to refer to its ***mouse*** antibody from the original hybridoma, which is the only full-length antibody disclosed in Evans. In particular, Evans consistently uses the phrase "the 5G1.1 antibody" or "the 5G1.1 mAb" to describe the original mouse antibody obtained from the 5G1.1 hybridoma. (AMG1007 at 19:47-49, Figs. 18-19, Examples 7-10 (37:34-40:29); *see also* AMG1023 at 1389, 1395 (Thomas referring to the original mouse antibody as "5G1.1" and "the 5G1.1 mAb").) Likewise, a POSA would have recognized that Evans was not a proper reference for a full-length "h5G1.1" antibody, because Evans did not disclose any full-length humanized antibodies.

165. Thus, neither Bowdish's reference to using "5G1.1" as a scaffold for a TPO-mimetic peptide (AMG1006 at [0066], [0191]), nor Bowdish's citation to Evans for "construction of 5G1.1" (AMG1006 at [0191]), would have indicated to a POSA that Bowdish's TPO-mimetic compound relates to the structure of "eculizumab," or that the "scaffold" used to make Bowdish's compound had any C5 binding activity or utility in humans.

166. I also disagree with Dr. Balthasar that a POSA would have necessarily inferred that Bowdish disclosed a "humanized 5G1.1" based on a "goat anti-

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introduced by Amgen in this case, and that Dr. Balthasar did not consider it. (ALXN2032 at 191:2-11, 192:7-11, 208:3-8.)

Samsung Bioepis Exhibit No. 1002
Page 13139

human" assay reagent in a FACS experiment with the TPO-mimetic peptide compound. (AMG1002 ¶ 50.) As Dr. Balthasar admitted Bowdish provided no information about that "goat-anti-human" reagent, including its source, its specific target ("epitope"), whether it distinguishes between "humanized" antibodies and other antibodies such as "chimeric" mouse/human hybrids, or its cross-reactivity with antibodies from other species. (ALXN2032 at 210:13-21, 211:13-23, 212:5-9.) It was understood in the field that anti-immunoglobulin antibodies could cross-react with antibodies from non-target species. (ALXN2091 at 623.) Particularly given Bowdish's earlier reference to the mouse "5G1.1" antibody Evans in ¶ [0191], a POSA could not have been certain from Bowdish's use of an unidentified, uncharacterized "anti-human" reagent alone whether Bowdish's TPO-mimetic compound was based on a humanized, chimeric, or mouse immunoglobulin structure.

167. Mueller and the associated article, Mueller II, relate generally to developing antibodies for vascular cell adhesion molecules ("VCAM") to block transplant rejection, again a subject unrelated to C5-binding. Mueller describes anti-VCAM antibodies with "IgG4" and hybrid "IgG2/IgG4" isotypes, as well as negative "isotype control" constructs with the same IgG4 and IgG2/IgG4 constant region, but different variable regions that would not bind VCAM. (AMG1008 at

Samsung Bioepis Exhibit No. 1002
Page 13140

12:19-32; AMG1031 at 442-443.) Neither Mueller nor Mueller II disclose the amino acid sequences of any anti-C5 antibody. (ALXN2032 at 232:17-21.)

168. I disagree with Dr. Balthasar's characterization of Mueller as disclosing "eculizumab's hybrid IgG2/IgG4 heavy chain constant region." (AMG1002 at 56.) Neither Mueller nor Mueller II use the term "eculizumab" or disclose the full-length antibody sequence claimed in the '504 patent. To support his assertions, Dr. Balthasar references Mueller's use of "h5G1.1 CO12 HuG2/G4 mAb" as a control antibody. A POSA, however, would not understand this antibody to correspond to "eculizumab" because, as discussed above, the prior art consistently described "eculizumab" as an IgG4 antibody through references to Thomas. While Mueller also refers to an "h5G1.1 CO12 HuG4" control antibody, it identified ***only*** the "HuG4" control antibody as "anti-C5." (AMG1008 at 12:1-2; *see also* AMG1031 at 446.) A POSA would have understood that to be consistent with Thomas's teachings of a "h5G1.1 HuG4" antibody that binds C5 and blocks complement activity. (*See* AMG1008 at Figs. 11-13,15, and 12:1-2; AMG1023 at 1396, 1399.)

169. Mueller further did not teach: any complete "h5G1.1" or anti-C5 binding antibody sequence; the precise boundaries of the IgG2/IgG4 constant region that would be used with any "h5G1.1" or anti-C5 binding variable region; or any guidance as to what "h5G1.1" or anti-C5 binding variable region should be

used with any constant regions used in Mueller,[8] and would have been too ambiguous to have led a POSA to any particular variable region sequence. (*See* Section VII.E.1 below.)

170. I further disagree with Dr. Balthasar that, as of March 15, 2007, a POSA would have understood the full-length, specific sequence described in claims 1-10 of the '504 patent based on some combination of Evans, Bowdish, Mueller, and Mueller II. A POSA would not have looked to Bowdish, Mueller, or Mueller II for guidance on designing anti-C5 antibodies for human administration because the subject matter of those references was entirely unrelated to anti-C5 binding. A POSA also would not have read Bowdish as disclosing the '504 patent's claimed sequence through its incorporation of Evans because, as discussed above, this incorporation is ambiguous in scope and appears to refer to construction of the mouse 5G1.1 monoclonal antibody rather than humanized sequences.

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[8] As discussed below, I disagree with Dr. Balthasar that Mueller's vague use of the alphanumeric "CO12" in naming its "h5G1.1" isotype control antibodies would have been understood by a POSA to correspond to any particular sequence or structure in Mueller or any other document.

Samsung Bioepis Exhibit No. 1002
Page 13142

171. References to the term "5G1.1" in Bowdish (AMG1006 at [0191]-[0193] and "h5G1.1" in Mueller / Mueller II (AMG1008 at 12:1-2, 12:35-37; AMG) would not have led a POSA to look to those references for the structure of the anti-C5 antibody, "eculizumab," whose safety and efficacy had been reported in clinical trials. As discussed in Section VI.D.3 above, and as Dr. Balthasar agreed at his deposition, without further context, the terms "5G1.1" and "h5G1.1" could refer to multiple potential antibodies or antibody fragments. (*See* Balthasar Dep. Tr. at 97:23-99:20, 100:3-12, 159:1-13, 241:23-242:12.) Accordingly, a POSA would not have understood these terms in Bowdish and Mueller / Mueller II to refer to the antibody known as "eculizumab." Further, multiple publications discussing C5-binding and clinical trials involving "eculizumab" also used these terms – a POSA would have looked to these, more relevant publications, citing Thomas as describing the "eculizumab" antibody, rather than Bowdish or Mueller / Mueller II. (*See, e.g.*, AMG1023 at 1389; AMG1005 at [0052]; AMG1021 at 1017; AMG1019 at 56.)

172. As discussed above, as of March 15, 2007, a POSA would have understood that the design of monoclonal antibodies for human clinical therapy, as well as pharmaceutical compositions of such antibodies, and development of their use in treating human patients, was a complex and unpredictable process. (*See* Sections VI.D.2 and VI.D.4 above.) A POSA would have understood that small

Samsung Bioepis Exhibit No. 1002
Page 13143

changes to antibody sequence – including in the constant region – could significantly impact antibody binding, safety, and efficacy. (*See* Section VI.D.4 above.) Dr. Balthasar's assertions that a POSA would have read Bowdish or Mueller / Mueller II in combination with Evans to reach the full sequence claimed by the '504 patent ignore that, given the unpredictability and complexity in the art at the time, a POSA would have had no reasonable expectation that such a combination would comprise an "antibody that binds C5," would be suitable for "treating a patient suffering from [PNH]," or would be suitable for formulation in a "pharmaceutical composition" for use in treating PNH, as claims 1-10 all require.

173. With a POSA understanding that, in contrast, the IgG4 isotype antibody of Thomas was reported prior to March 15, 2007 as binding C5, blocking its cleavage, and having been used in clinical trials to safely and effectively treat PNH (where presumably it was also formulated into a pharmaceutical composition suitable for such clinical use), a POSA would not have any reason or motivation to deviate from that antibody, and instead combine Bowdish or Mueller / Mueller II with Evans to obtain an uncharacterized antibody with unknown properties that could not have been reasonably been predicted.

Samsung Bioepis Exhibit No. 1002
Page 13144

B. Claims 1-3 and 7-10 of the '504 Patent Were Not Anticipated by Hillmen '04 (Ground 1)

174. Amgen's Ground 1 contends that claims 1-3 and 7-10 of the '504 patent would have been anticipated by the clinical trial publication Hillmen '04 (AMG1004).

175. In my opinion, Amgen's Ground 1 fails because, among other things, Amgen cannot show that Hillmen disclosed each element of the claimed invention, either expressly or inherently. Specifically, Hillmen did not disclose the full-length sequence recited in claims 1-3 and 7-10 of the '504 patent.

176. Hillmen was a journal publication reporting on the successful use of "eculizumab," a humanized monoclonal antibody targeting C5, to treat PNH in a human clinical trial. (AMG1004 at 2.) Hillmen did not disclose any amino acid sequences for "eculizumab."

177. I understand from counsel that, for a document to anticipate a patent claim, every element of the patent claim needs to be disclosed in that one document, either expressly (*i.e.*, as stated in the document), or inherently (meaning that, based on what is stated in the document itself, a POSA prior to March 15, 2007 would know that the claimed invention was ***necessarily*** disclosed by that document).

178. In my opinion, Hillmen did not disclose the claimed sequence of the '504 patent (SEQ ID NOs: 2 and 4) by its mention of "eculizumab," because a

POSA prior to March 15, 2007 would not know from reading Hillmen that the term "eculizumab" ***necessarily*** disclosed an amino acid sequence corresponding to SEQ ID NOs: 2 and 4. As discussed above, the full-length sequence claimed in the '504 patent was not publicly known prior to March 15, 2007. (*See* Section VI.E above.) And in fact, a POSA reading Hillmen would have understood that "eculizumab" had a ***different*** structure and sequence than the antibody with SEQ ID NOs: 2 and 4 claimed in the '504 patent.

179. In particular, a POSA reading Hillmen and the other literature available as of March 15, 2007 would have understood "eculizumab" to have be the ***IgG4*** isotype antibody described in Thomas (AMG1023). (*See* Section VI.D.5 above.) As I discuss above, Hillmen cites to Thomas for a disclosure of what "eculizumab is." (AMG1004 at 553 (Ref. No. 15).) This is consistent with the teachings of the prior art as a whole, and would have indicated to a POSA that the "eculizumab" antibody used in Hillmen contained an IgG4 isotype, as taught by Thomas. (*See* Section VI.D.5 above.)

180. A POSA would have understood that an IgG4 isotype antibody would have a different heavy chain sequence from the sequence contained SEQ ID NO: 2, which, as we know today, corresponds a non-natural, engineered IgG2/IgG4 hybrid constant region sequence. As of March 15, 2007, it was not publicly known that the unique, monoclonal antibody "eculizumab," which had been successfully tested

in clinical trials, had an IgG2/IgG4 hybrid constant region, and all of the evidence in the literature as of that date pointed to it having a naturally-occurring IgG4 constant region.

181. A POSA would not have been able to independently determine the amino acid sequence of the antibody clinically tested in Hillmen because Alexion did not disclose the sequence of the clinical study drug, kept study participants under strict confidentiality, and maintained the physical antibody supplies under lock and key with strictly limited access. (AMG1015 at 734-741.) And even if the eculizumab protein was available to the public, which it was not, determining the entire sequence of a full-length antibody from protein alone would have required considerable specialized skill in protein sequence determination beyond the abilities of a POSA for the '504 patent.

182. I disagree with Dr. Balthasar's assertions that Hillmen was enabling – *i.e.*, that it would have allowed a POSA to practice the claimed invention without undue experimentation – because, according to Dr. Balthasar, a POSA would have looked to Bowdish and Evans, or Mueller and Evans, for the sequence of eculizumab. (*See* AMG1002 ¶¶ 75, 85.) First, Hillmen did not cite or incorporate by reference Bowdish, Evans, or Mueller, and I understand from counsel that it is improper to combine multiple documents for purposes of anticipation. Second, Hillmen did not contain any indication that the "eculizumab" antibody used in that

Samsung Bioepis Exhibit No. 1002
Page 13147

study would have the sequences that Dr. Balthasar selects from Bowdish, Evans, and Mueller. Hillmen cites Thomas as describing "eculizumab," from which a POSA would have understood "eculizumab" to be an IgG4 antibody with a very different sequence than the one Dr. Balthasar improperly combines from Bowdish, Evans, and Mueller. (*See* AMG1004 at 553; AMG1047 at 2559.) Finally, there is nothing in Bowdish, Evans, and Mueller that disclosed the specific amino acid claimed in the '504 patent in any case, for the reasons stated in Section VI.E.

183. With no sequence information available directly from Hillmen and Hill, and both these references citing Thomas, which teaches a very different antibody structure than the specific amino acid sequence claimed in the '504 patent, a POSA would not have been able to create an antibody that binds C5, with the specific amino acid claimed in the '504 patent, based on the disclosures of Hillmen without significant experimentation.

184. Also, in my opinion, Hillmen did not disclose, and would not have enabled a POSA to make without undue experimentation, (1) a method of using the specific claimed antibody of the '504 patent for treating a patient suffering from PNH, of (2) any "pharmaceutical composition" of the specific claimed antibody of the '504 patent suitable for use in the claimed method of treating PNH patients recited in claims 1-3 and 7-10 of the '504 patent. Nothing in Hillmen would have provided a POSA with any guidance on how to carry out such a method of

treatment or make such a pharmaceutical composition, or whether it would have even been possible to do so, because there is simply no information at all in Hillmen regarding an antibody with the claimed sequence of the '504 patent.

C. Claims 4 and 5 of the '504 Patent Would Not Have Been Obvious In View Of Hillmen Combined with Bell (AMG1005) (Ground 2), and Claim 6 Would Not Have Been Obvious in View of Hillmen, Bell, and Wang (AMG1028) (Ground 3)

185. Amgen contends that claims 4 and 5 of the '504 patent would have been obvious over the combination of Hillmen and Bell (AMG1005) (Ground 2), and that claim 6 would have been obvious in view of Hillmen, Bell and Wang (AMG1028) (Ground 3). As Grounds 2 and 3 raise overlapping issues, I disagree with both for the same reasons, I will address them both together here.

186. In my opinion, Amgen's Grounds 2 and 3 fail, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Hillmen in combination with Bell (and Wang, for claim 6).

187. First, none of Hillmen, Bell, nor Wang, when read alone or in combination, disclosed the specific amino acid sequence claimed in the '504 patent. For Grounds 2 and 3, Dr. Balthasar relies solely on Hillmen as providing the claimed amino acid sequence. (AMG1002, ¶97.) But as discussed above, from the perspective of a POSA prior to March 15, 2007, Hillmen did not disclose an antibody having the specific sequence claimed in the '504 patent, or any

pharmaceutical compositions of that antibody for use in treating PNH, or any other complement-mediated condition. (*See* Section VII.B above.)

188. Likewise, nothing in Bell (AMG1005) or Wang (AMG1028) disclosed the claimed amino acid sequence recited in the '504 patent. I understand Dr. Balthasar agrees. (AMG1002 at ¶ 130; ALXN2032 at 151:4-12, 160:7-10, 194:17-20, 257:13-18.) Like Hillmen and Hill, Bell and Wang discuss the antibody "eculizumab," but neither reference provides the specific amino acid sequence recited in claims 4-6 Further, Bell, like Hillmen and Hill, would have suggested to a POSA that "eculizumab" was Thomas's IgG4 isotype, and therefore would have pointed a POSA to an antibody structure and sequence that is different from the hybrid, non-naturally occurring isotype of claimed antibody of the '504 patent. (AMG1005 ¶[0052] (citing Thomas)); *see* Section VII.D.1 below.)

189. A POSA prior to March 15, 2007 would have had no reason or motivation to deviate from the IgG4 antibody structure of Thomas that Hillmen and Bell associated with the therapeutically useful "eculizumab" antibody. And, a POSA provided with Hillmen and Bell would not have been motivated to make a new, untested antibody using a clinically-untested non-naturally occurring hybrid constant region – or to make pharmaceutical compositions of such an antibody for the treatment of PNH – when Hillmen and Bell taught that "eculizumab,"

identified as an IgG4 antibody, was safe and effective for human use. (*See* Section VI.D.5 above.)

190. Wang (AMG1028) would not have taught a POSA otherwise. Wang provided no structural information at all regarding "eculizumab," and only described experiments testing what happens when a 30 mg/ml solution of "eculizumab" is passed through a nebulizer device. (AMG1028 at [0169]-[0173].) Nothing in Wang, even combined with Hillmen and Bell, would have motivated a POSA to make the pharmaceutical compositions of claim 6 of the '504 patent for use in treating patients suffering from PNH, or would have given a POSA a reasonable expectation of success in doing so.

191. I also note that nothing in Bell (AMG1005) or Wang (AMG1028), even together, disclosed the specific pharmaceutical composition recited in claim 6: "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution." Neither Bell nor Wang describes any pharmaceutical compositions of the claimed antibody of the '504 patent, let alone the specific composition of claims 6. And even with respect to "eculizumab" – which a POSA prior to March 15, 2007 would *not* have thought to be the claimed antibody – Bell and Wang did not disclose a 300 mg single-use dosage form, or any single-use dosage form comprising a 10 mg/ml antibody solution.

D. Claims 1-5 and 7-10 of the '504 Patent Would Not Have Been Obvious Over Bell, Bowdish, and Evans (Ground 4), and Claim 6 Would Not Have Been Obvious Over Bell, Wang, Bowdish and Evans (Ground 5)

192. Amgen contends that claims 1-5 and 7-10 of the '504 patent would have been obvious over the combination of Bell (AMG1005), Bowdish (AMG1006) and Evans (AMG1007) (Ground 4), and that claim 6 would have been obvious in view of Bell, Wang (AMG1028), Bowdish, and Evans (Ground 5). As Grounds 4 and 5 raise overlapping issues, I disagree with both for the same reasons, I will address them both together here.

193. In my opinion, Amgen's Grounds 4 and 5 fail, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Bell, Bowdish, and Evans, or in further combination with Wang for claim 6. None of Bell, Wang, Bowdish, nor Evans, when read alone or in combination, disclosed the specific amino acid sequence claimed in the '504 patent. Nothing in Bell (or Wang) would have motivated a POSA to look to Bowdish or Evans to create the claimed sequence. And even if a POSA were to have made the exact, untaught combination of sequences from Bowdish and Evans in the way that Dr. Balthasar does in hindsight, a POSA would have had no motivation or reasonable expectation of success in using such an antibody to treat patients suffering from PNH as required by claims 1-10. A POSA also would not have been motivated or reasonably expected to succeed in making any

pharmaceutical compositions of an antibody with the claimed sequence (including the specific composition of claim 6) that would be suitable for use in the claimed method of treating patients suffering from PNH.

1. Bell (and Wang) Did Not Disclose the Specific Sequence of Claims 1-10, and Would Not Have Motivated a POSA to Make An Antibody With the Claimed Sequence

194. Dr. Balthasar relies on Bell (and Wang for claim 6) for their disclosures regarding "eculizumab" – but he admits that Bell and Wang did ***not*** disclose the claimed amino acid sequence of the '504 patent. (AMG1002 at ¶ 130; ALXN2032 at 151:4-12, 160:7-10, 194:17-20, 257:13-18.)

195. Bell, in fact, would have guided a POSA towards use of an IgG4 isotype that is different from the claimed antibody of the '504 patent, which has a different, uniquely-engineered amino acid sequence corresponding to a hybrid IgG2/IgG4 constant region.

196. Bell was a U.S. Patent application relating to use of compounds to block complement for the treatment of PNH. A POSA would have read paragraph 52 of Bell as teaching that the "eculizumab" antibody described in Bell had an IgG4 isotype, based on Bell's citation and incorporation by reference of Thomas, which taught the IgG4 isotype. (*See* Section VII.D.5 above.) Specifically, Bell stated:

> Particularly useful anti-C5 antibodies are h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1. ***Methods for the preparation of h5G1.1-mAb***, h5G1.1-scFv and other functional fragments of h5G1.1 are described in U.S. Pat. No. 6,355,245 and "Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single Chain Fv", ***Thomas et al., 1401, 1996***, the disclosures of which are incorporated herein in their entirety by this reference. ***The antibody h5G1.1-mAb is currently undergoing clinical trials under the trade-name eculizumab***.

AMG1005 at [0052].

197. Although paragraph 52 of Bell also cited and incorporated by reference Evans, a POSA would not have understood this as teaching an alternative isotype for the "eculizumab" antibody. As discussed above, while Evans did disclose "scFv" compounds and other functional fragments like "Fab," Evans did ***not*** disclose any full-length humanized antibodies, and only described human constant regions generically. (*See* Section VI.D.5 above.) Evans in particular did not make any reference to IgG2/IgG4 antibodies. (ALXN2032 at 163:25-164:19.) In fact, the only human heavy chain constant regions described in Evans are the

Samsung Bioepis Exhibit No. 1002
Page 13154

CH1 regions of "Fd" fragments[9] (SEQ ID NOs: 11 and 12) that do not align with the constant regions of the claimed sequence. (*See* Section VI.D.5 above.)

198. Accordingly, Bell's citation to Evans was not inconsistent with the understanding that Bell, and the other available literature, identified "eculizumab" as having an IgG4 isotype. A POSA would have understood that Bell could have only referenced Evans for the humanized "fragments" it disclosed, and that Bell in turn cited Thomas for the disclosure of the full-length "eculizumab" antibody that was the subject of Bell's clinical trials in PNH. Figure 9 below illustrates how a POSA would have understood Bell's teaching that "eculizumab" was the IgG4 antibody of Thomas, consistent with the other prior art available prior to March 15, 2007:

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[9] Evans defines an "Fd" fragment as the heavy chain portion of an "Fab," meaning a truncated heavy chain that contains VH and CH1. (AMG1007 at 43:18-19.)

Samsung Bioepis Exhibit No. 1002
Page 13155

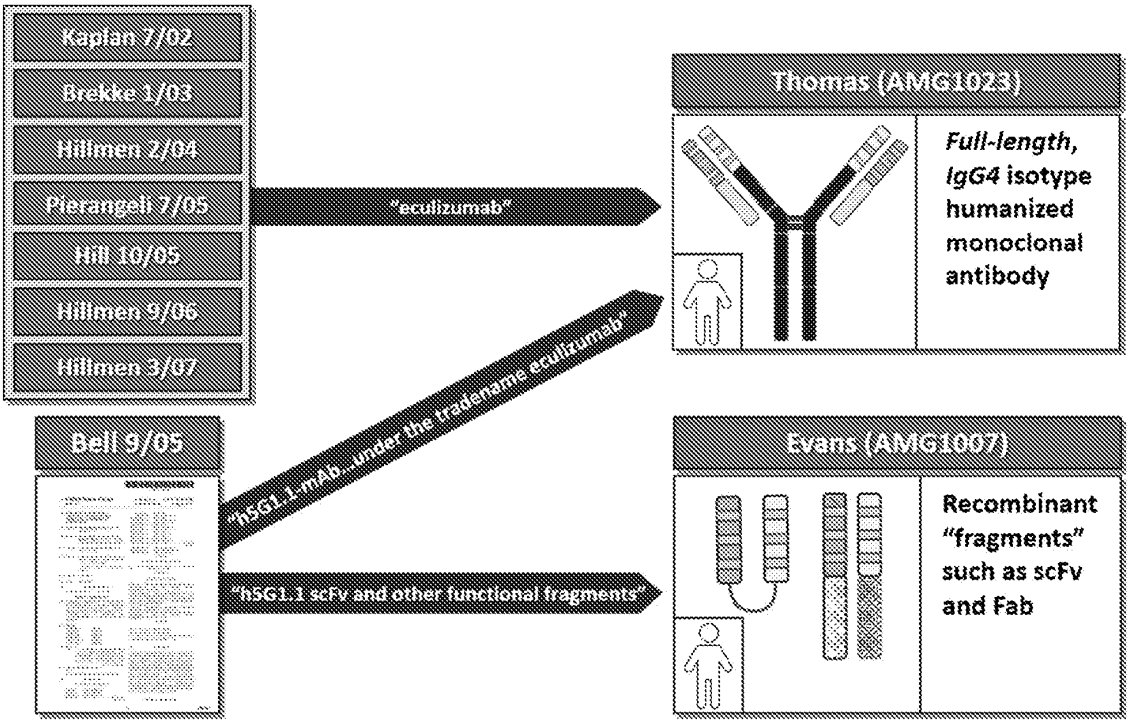


Figure 9: A POSA's understanding of Bell's teaching regarding "eculizumab," "h5G1.1 scFv," and "other function fragments

199. And if there was any doubt regarding the structure of the "eculizumab" antibody Bell referred to with respect to its evidence of clinical safety and efficacy in treating PNH (AMG1005 at [0081]-[0096]), a POSA's review of the other related literature would have confirmed that Bell was referring to Thomas's IgG4 antibody. In particular, as Dr. Balthasar acknowledged, the clinical studies reported in Bell for "eculizumab" were the same as those reported in Hillmen (AMG1004) and Hill (AMG1047) – two references that unambiguously

cited Thomas as the reference for what "eculizumab is." (AMG1004 at 553 (Ref. No. 15); AMG1047 at 2559 (Ref. No. 9); ALXN2032 at 115:16-23.)

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Combine Bell and Wang with Bowdish and Evans

200. A POSA starting with Bell for its teaching of "eculizumab" as a safe and effective treatment for PNH, as Dr. Balthasar does, would have had no reason or motivation to deviate from the IgG4 antibody structure of Thomas that Bell associated with the therapeutically useful "eculizumab" antibody, and turn instead to (1) Bowdish, which Bell did not cite, and contained no information regarding anti-C5 antibodies (*see* Section VII.A.2 above); or (2) Evans, which did not disclose any full-length humanized antibodies, and at best may have suggested an IgG1 antibody based on the "Fd" sequences it disclosed (*see* Section VI.D.5 above). And, a POSA provided with Bell would not have been motivated to make a new, untested antibody using a clinically-untested non-naturally occurring hybrid constant region, when Bell taught that "eculizumab," identified as an IgG4 antibody, was safe and effective for human use.

201. I disagree with Dr. Balthasar's arguments regarding why he claims a POSA would have been motivated to combine Bell, Wang, Bowdish, and Evans. Dr. Balthasar's sole explanation for why a POSA would have been motivated to combine these references is that a POSA would have looked to Bowdish and Evans

Samsung Bioepis Exhibit No. 1002
Page 13157

to try to determine the sequence of "eculizumab" following review of Bell. I disagree that a POSA would have read Bell, and then looked to Bowdish and Evans for the "eculizumab" sequence, as Dr. Balthasar asserts. (*See* AMG1002 ¶ 114.)

202. First, I note that that neither Bell, nor the Thomas or Evans references cited in Bell, cited to Bowdish for teaching "eculizumab," or for any other antibody. Nor would anything else in Bell have directed a POSA to Bowdish. For example, nothing in Bowdish concerns the subject matter of Bell, including, *e.g.*, antibody binding of C5, using anti-C5 antibodies to block complement activity, or treatment of PNH.

203. Bowdish's use of the term "5G1.1" in connection with its TPO-mimetic construct would not have guided a POSA to Bowdish for teaching of "eculizumab" because, as discussed above, the term "5G1.1" was not understood to refer specifically to the antibody "eculizumab," and could refer to a variety of antibodies depending on the context. (*See* Section VI.D.3 above.) And as used in Bowdish, when referring to "[c]onstruction of 5G1.1," a POSA would have understood Bowdish to be referring to the mouse antibody of Evans, not "eculizumab" – a full-length intact antibody that was not disclosed anywhere in Evans.

Samsung Bioepis Exhibit No. 1002
Page 13158

204. Dr. Balthasar's argument to connect Bell to Bowdish requires him to assume that a POSA understood that "eculizumab" had a hybrid IgG2/IgG4 constant region. (AMG1002 ¶¶ 139-140; ALXN2032 at 196:15-23, 198:21-199:3.) His argument fails for that reason alone, because as I explained above, the teaching in Bell and the other predominant clinical literature as of March 15, 2007 was that "eculizumab" was an IgG4 isotype antibody of Thomas, not a hybrig IgG2/IgG4 isotype. (*See* Section VI.D.5 above.)

205. Even assuming Dr. Balthasar's incorrect position that a POSA would have understood "eculizumab" to already have an IgG2/IgG4 isotype, a POSA would not have combined Bell with Bowdish because a POSA would not have immediately recognized that the sequences in Figure 13 of Bowdish included humanized constant regions or an IgG2/IgG4 isotype. As Dr. Balthasar testified, Bowdish does not state that the sequences in Figure 13 are humanized or that they correspond to an IgG2/IgG4 constant region, and a POSA would have had to perform a sequence alignment using "BLAST" or another tool to determine these characteristics. (ALXN2032 at 199:19-23, 212:10-214:13.) A POSA attempting to design an anti-C5 antibody would have had no motivation to perform such an alignment, however, because Bowdish's TPO-mimetic was not identified as targeting C5, and, as discussed, Bowdish's reference to "5G1.1" would not have unambiguously identified the antibody "eculizumab." Nothing in Bowdish

specifically guided a POSA to use BLAST or a similar search tool to analyze the sequences for its TPO-mimetic compound. (ALXN2032 at 214:19-24.) Further, Dr. Balthasar's Declaration does not provide any demonstration of what the results would have been if a POSA had performed such an alignment prior to March 15, 2007. (ALXN2032 at 214:25-215:8.)

206. I also disagree with Dr. Balthasar's conclusion that a POSA would have understood that the sequences in Bowdish Figure 13 were humanized based on the FACS experiment described in Bowdish Example 4. (*See* AMG1002 ¶ 90.) As I noted above (*see* Section VII.A.2 above), a POSA would not have been able to conclude that the sequences in Bowdish were humanized solely because Bowdish referred to use of an unspecified, uncharacterized "anti-human IgG" reagent that could have had any of a number of possible epitopes and levels of cross-reactivity.

207. Accordingly, given the unpredictability associated with humanized therapeutic antibody design as discussed in Sections VI.D.2 and VI.D.4 above, and the substantial expense and unpredictability of developing and testing a humanized monoclonal antibody for human therapeutic use as discussed in Section VI.D.2 above, a POSA would have no motivation to deviate from the thoroughly-studied "eculizumab" antibody that a POSA would have believed was an IgG4 isotype. A POSA in particular would not have been motivated to make such an untested,

Samsung Bioepis Exhibit No. 1002
Page 13160

unstudied antibody with a non-naturally occurring hybrid IgG2/IgG4 isotype region, because there were no reports in the literature of ***any*** antibody with that isotype that had been clinically tested, and accordingly, a POSA could not have reasonably expected such an antibody to be therapeutically useful or suitable for human administration.

208. A POSA further would not have combined Bell and Bowdish based on Bell's reference to Evans. (*See* AMG1005 ¶ [0052].) A POSA would not have been motivated to combine Bowdish after review of Evans because Evans does not reference Bowdish, and Bowdish is directed to unrelated subject matter – it does not discuss antibody binding of C5 to block complement, or treatment of PNH, which is the subject of Evans. Nor would a POSA have associated Bowdish with Bell and Evans just because they all included some variant of the term "5G1.1" (*e.g.*, "5G1.1" in Evans and Bowdish; "h5G1.1-mAb" in Bell). As I discuss above in Section IV.D.3, a POSA would have understood that the term "5G1.1" and its derivatives (*e.g.*, "h5G1.1") were terms that could refer to many different variants depending on their context. A POSA searching for information on "eculizumab" would have known that a search for "5G1.1" instead would have been overbroad, and would have captured information that was not instructive on the specific structure and specific properties of "eculizumab." For example, Evans used the term "5G1.1" to refer to the original mouse antibody from the "5G1.1" hybridoma,

which a POSA would have understood was not "eculizumab." (AMG1007 at 19:47-49, Figs. 18-19, Examples 7-10 (37:34-40:29); *see* ¶ 164 above.) And I agree with Dr. Balthasar that, even when the term "h5G1.1" was used – which it was ***not*** in Bowdish – a POSA would have understood that term could refer to a variety of different antibody variants that are not "eculizumab," unless "eculizumab" was expressly specified. (ALXN2032 at 98:2-99:8, 159:1-10, 202:24-203:14.) Bell did specify that its "h5G1.1-mAb" was "eculizumab," but then further identified it as the IgG4 antibody of Thomas (*see* Section VII.D.1 above) – which would not have motivated a POSA to look to Bowdish for its reference to "5G1.1" of Evans.

3. A POSA Would Not Have Been Motivated Make the Specific Claimed Antibody that Dr. Balthasar Assembles in Hindsight from Bowdish and Evans

209. Even if a POSA were to have turned from Bell and Wang to Bowdish and Evans – despite there being no reason for a POSA without hindsight to have done so – nothing in the combination of these four documents would have motivated a POSA to make the specific amino acid sequence recited in claims 1-3 of the '504 patent.

210. There is no dispute that Bowdish did not disclose the entire amino acid sequence recited in claims 1-10 of the '504 patent. (ALXN2032 at 181:18-182:4.) Further, Dr. Balthasar admits that the amino acid sequences that he relies

Samsung Bioepis Exhibit No. 1002
Page 13162

on from Bowdish – the sequences described in Bowdish Figs. 13A and 13B – are not the antibody recited in claims 1-10 of the '504 patent. (ALXN2032 at 184:10-16.) Dr. Balthasar also admits that neither Bowdish nor Evans uses the term "eculizumab." (ALXN2032 at 199:9-17.)

211. I disagree with Dr. Balthasar's reading of Bowdish's single statement regarding Evans regarding "[c]onstruction of 5G1.1." In my opinion, Dr. Balthasar's interpretation of that statement is mistaken and contrary to how it would have been understood by a POSA. Further, I understand from counsel that Dr. Balthasar's interpretation of Bowdish's statement concerning Evans is legally mistaken as well.

212. The statement at issue appears in Example 4 of Bowdish, which states:

> The TPO mimetic peptide graft in Fab clone X4b has been transplanted into the heavy chain CDR3 region of another antibody framework, 5G1.1. . . . Construction of 5G1.1 is described in U.S. Application Ser. No. 08/487,283,[10] incorporated herein by reference.

[10] As noted above, I understand from counsel that "U.S. Application Ser. No. 08/487,283" is the patent application from which Evans issued, and that Dr.

AMG1006 at [0191].

213. First, a POSA would have understood Bowdish's reference to Evans, "Construction of 5G1.1 is described in U.S. Application Ser. No. 08/487,283, incorporated herein by reference," to be a limited statement referencing Evans's disclosure of the "5G1.1" parental mouse monoclonal antibody. As discussed above, and as Dr. Balthasar agreed at deposition, a POSA reading Evans would have understood that the "5G1.1" antibody of Evans was the original mouse "5G1.1" antibody, and that Evans does not describe any other full-length antibody. (ALXN2032 at 165:11-24, 169:6-18.) I understand from counsel that a statement regarding "incorporation by reference" must be read in its context[11] – and nothing in that statement would indicate to a POSA any intent to incorporate the disclosures of Evans beyond what it states: "construction of 5G1.1," a mouse antibody. Accordingly, a POSA would not have read the statement in Bowdish as

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Balthasar's opinion is deficient because he failed to consider and discuss the application. For purposes of this declaration, however, I will address Dr. Balthasar's arguments as if they were proper.

[11] For example, in contrast to Bowdish's incorporation by reference of Evans, ¶ [0001] of Bowdish incorporates three provisional patent applications "in their entirety." (AMG1006 ¶ [0001].)

Samsung Bioepis Exhibit No. 1002
Page 13164

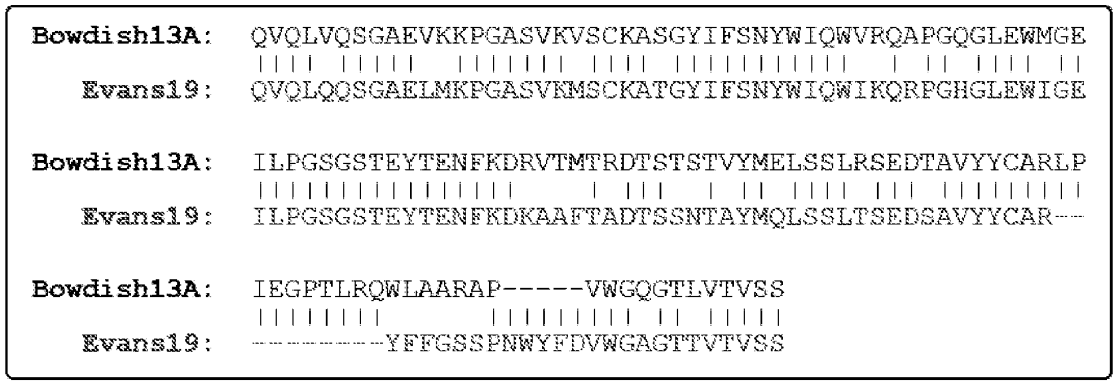
incorporating, *e.g.*, the humanized scFv fragments described in Evans, which were created after construction of the 5G1.1 mouse antibody. (*See* AMG1007 at 42:56-45:48.)

214. A POSA reading Bowdish, and seeing its incorporation by reference of Evans's mouse "5G1.1" antibody, would not have understood that it disclosed the claimed antibody of the '504 patent, which is a humanized antibody. If a POSA were to consider the sequence of Evans's mouse "5G1.1" antibody in view of Bowdish's Figs. 13A and 13B sequences, they would see misalignment beyond the region of Bowdish's "TPO-mimetic" peptide, and would not have further envisioned any combination of sequences that would result in the claimed antibody of the '504 patent.

215. Bowdish's reference to Evans's mouse "5G1.1" antibody would not have taught a POSA anything about the C5 binding properties or other properties of Bowdish's TPO-mimetic compound or the "scaffold" it came from, because a POSA would that Bowdish's TPO-mimetic compound had a very different sequence and structure from Evans's original mouse antibody. The following figure illustrates the sequence alignment of Bowdish's Figs. 13A (SEQ ID NO: 67, heavy chain) and 13B (SEQ ID NO: 69, light chain) with the variable heavy chain and variable light chain of the "5G1.1" mouse antibody from Evans (Evans Fig. 19 (variable heavy chain) and Evans Fig. 18 (variable light chain). This figure

Samsung Bioepis Exhibit No. 1002
Page 13165

confirms that a POSA looking from Bowdish to Evans for "[c]onstruction of 5G1.1" would not be guided towards the claimed antibody of the '504 patent:



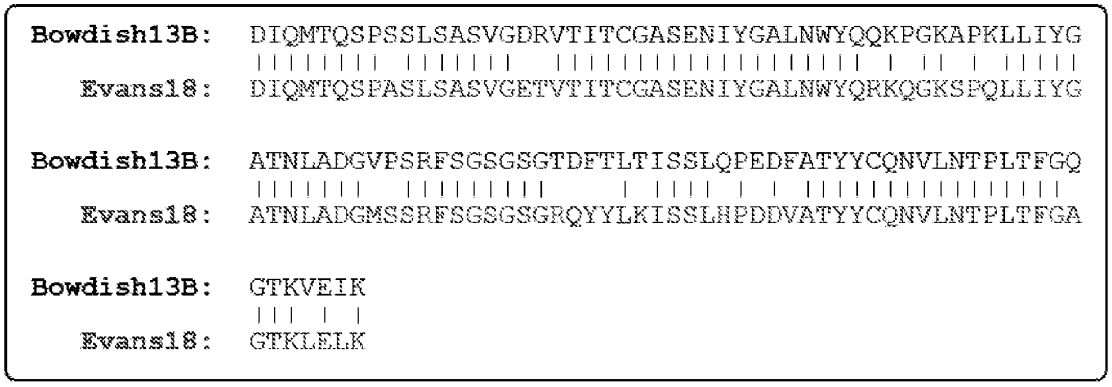


Figure 10: Bowdish Figure 13A (SEQ ID NO: 67) compared to Evans Fig. 19

Bottom: Bowdish Fig. 13B compared to Evans Fig. 18

Samsung Bioepis Exhibit No. 1002
Page 13166

216. Further, I understand that Alexion has obtained the full amino acid sequence of the "5G1.1" antibody of Evans from the HB-11625 hybridoma. (ALXN2075 at 2-3.) The following figure illustrates the sequence alignment of Bowdish's Fig. 13A (SEQ ID NO: 67) with the full heavy chain of the "5G1.1" mouse antibody from Evans. As with the figure above, this further confirms that a POSA looking from Bowdish to Evans for "[c]onstruction of 5G1.1" would not be guided towards the claimed antibody of the '504 patent:

Samsung Bioepis Exhibit No. 1002
Page 13167

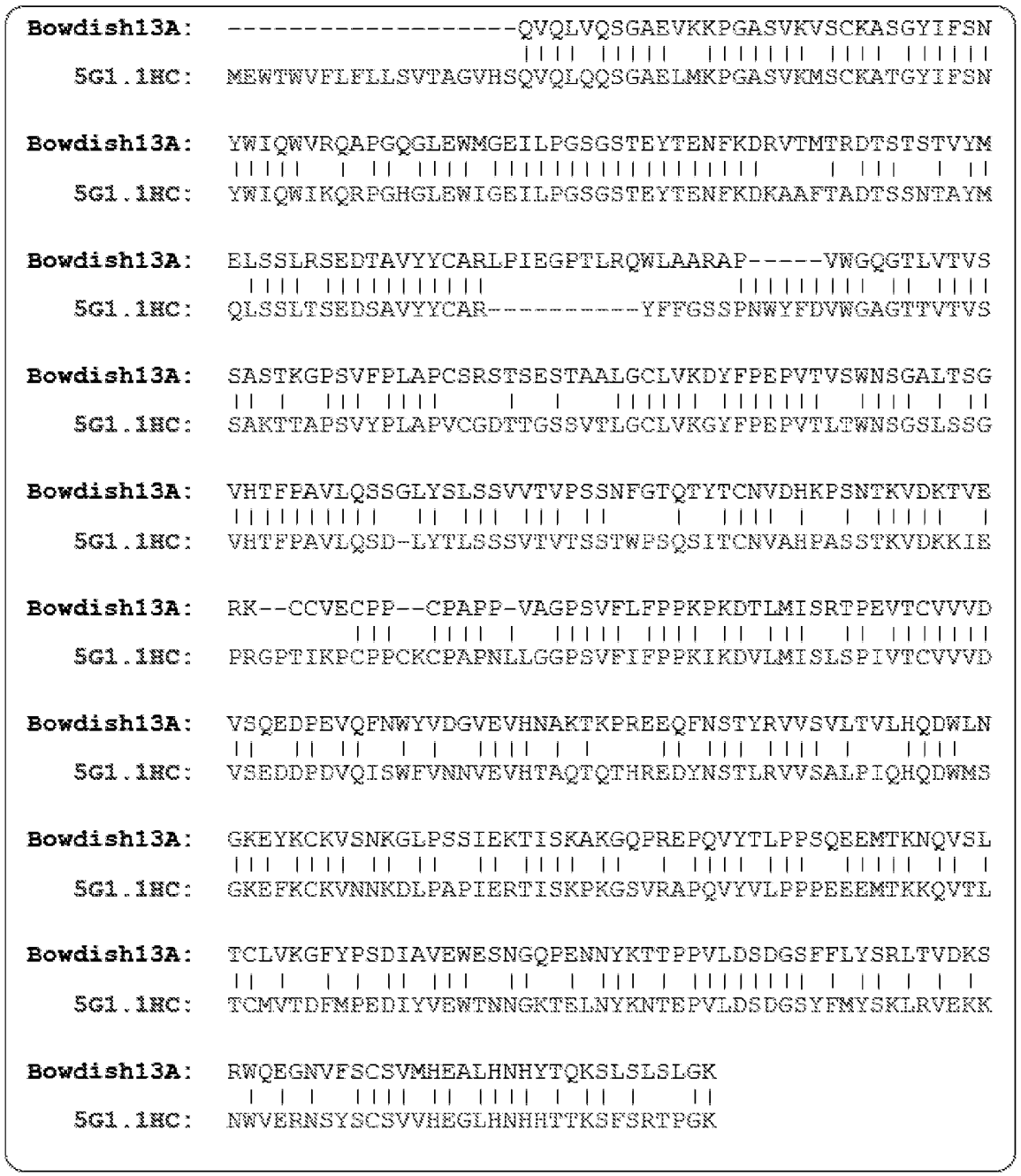


Figure 11: Bowdish Figure 13A (SEQ ID NO: 67) compared to heavy chain of 5G1.1 antibody from HB-11625

Samsung Bioepis Exhibit No. 1002
Page 13168

217. And even if Bowdish and Evans were combined in full, they did not disclose or render obvious uniquely engineered amino acid sequence recited in claims 1-10 of the '504 patent. For example, if a POSA were to look to Evans for construction of the "scaffold" antibody used to generate Bowdish's TPO-mimetic peptide, they would have been lost. As Dr. Balthasar admitted, Evans does not describe ***any*** full-length antibody (including Bowdish's "scaffold" antibody), aside from the "5G1.1" mouse antibody, which does not align with the sequences disclosed in Bowdish. (ALXN2032 at 163:12-15, 169:6-23, 221:14-16.)

218. A POSA also would not have looked to the scFv fragments of Evans to understand the sequence of the full-length "scaffold" antibody in Bowdish. As discussed in Sections VI.D.2 and VI.D.4 above, scFv and full-length antibodies were understood to be very different structures with very different properties, and a POSA would not have confused an scFv for a full-length immunoglobulin from which Bowdish's TPO-mimetic compound was made. Again, I note that Dr. Balthasar's figures are misleading in this regard, because a POSA would not have envisaged Evans's scFv sequences as part of an intact antibody structure such as was used to generate Bowdish's TPO-mimetic compound, but would have understood Evans's scFvs to be a distinct, recombinant DNA compounds different from the full-length structures described in Bowdish.

Samsung Bioepis Exhibit No. 1002
Page 13169

219. The following figure illustrates (1) how a POSA prior to March 15, 2007 would have understood the information disclosed in Bowdish as it incorporates the '283 application (a mouse antibody); (2) how a POSA would have understood the other disclosures of Evans that Bowdish did ***not*** incorporate ("fragments" including scFvs and Fabs,), and (3) how Dr. Balthasar's Figure 10 is mistaken for depicting Evans as describing part of a full-length humanized antibody – which is ***not*** actually described anywhere in Evans or in Bowdish.

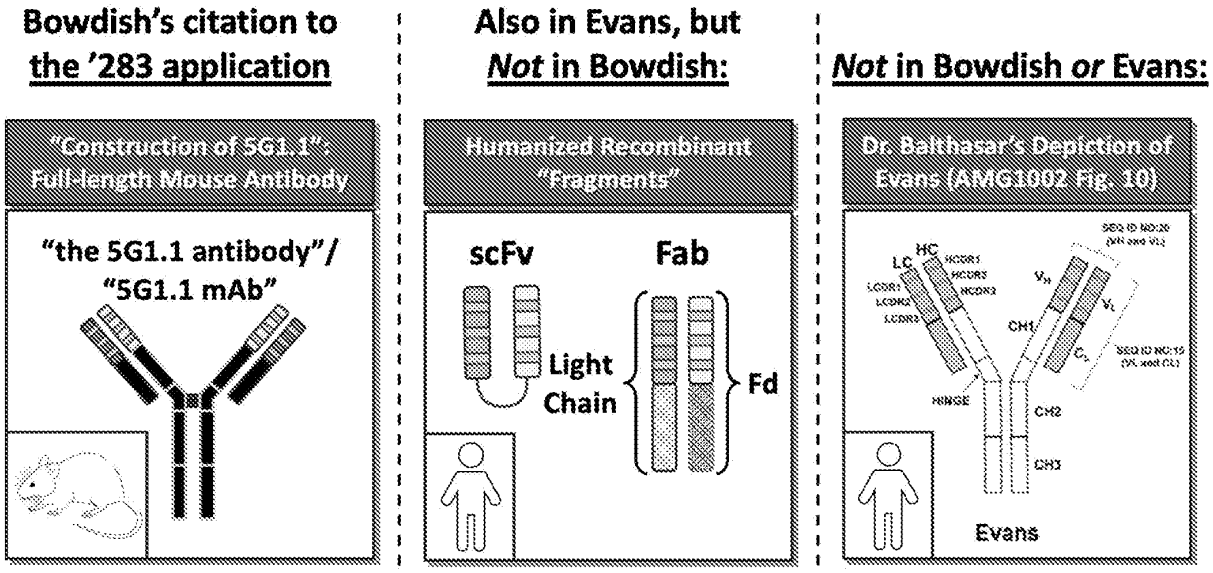


Figure 12: A POSA's understanding of Bowdish's reference to the '283 application, and what material was outside the referenced subject matter

220. Further, even if Dr. Balthasar were correct to combine Bowdish's TPO-mimetic sequences with CDR sequences from Evans, he ignores that Evans refers to at least two, and possibly at least four potential definitions of the CDR

region: the "sequence variability" definition (Kabat), the "structural variability" definition (Chothia), and the overlap between them. (AMG1007 at 5:15-36.) Dr. Balthasar is incorrect when he states that "all of the 5G1.1 heavy chains in Evans contain the same CDR3 sequence," as Evans actually discloses at least two CDR3 regions – one containing 11 amino acids, and one containing 13 amino acids, and possibly two sequences of 12 amino acids in their region of overlap – based on use of the two definitions. (*See, e.g.*, AMG1007 at 5:15-36, 42:64-43:5, Figs. 18 and 19.)

221. It is my opinion that Dr. Balthasar's declaration demonstrates a significant use of hindsight. For example, I disagree with Dr. Balthasar's sequence alignments in Figures 5 and 13, which compare sequences from Bowdish to the claimed SEQ ID NO: 2 from the '504 patent. "SEQ ID NO: 2" was not publicly available as of the priority date. A POSA would not have had the guidance of the disclosure of SEQ ID NO:2 from the '504 patent to help select sequences to combine from Bowdish and Evans and, as a result, for the reasons stated here, a POSA would not have been able to envisage the claimed sequence from the vague disclosures in Bowdish.

222. I also disagree with Dr. Balthasar's statement, "[A] POSA would have known that the only portion of the sequence disclosed in Bowdish's Figures 13A-13B that is different from the original h5G1.1 'scaffold' antibody disclosed in

Samsung Bioepis Exhibit No. 1002
Page 13171

Bowdish is the portion of SEQ ID NO: 67 that corresponds to the TPO peptide." (*See* AMG1002 ¶ 134.) This is not correct. Bowdish does not use the term h5G1.1, and as discussed above, a POSA would have understood based on Example 4 of Bowdish that the original "5G1.1" scaffold antibody was the mouse antibody in Evans. Comparing the mouse antibody in Evans with the sequence in Figure 13, there are additional sequence differences outside of the TPO peptide region, which give the humanized and mouse antibodies different properties.

223. I also disagree with Dr. Balthasar's depiction in Figure 12. (AMG1002 at 96.) As I discussed above (*see* Section VI.D.5), I disagree with Dr. Balthasar's depiction of the disclosure from Evans, because Evans does not disclose a full-length, humanized antibody – only humanized antibody fragments, such as scFv. A POSA would have understood that the scFv structures of Evans were ***not*** partial sequences from a full-length antibody, but they were their own stand-alone, recombinantly-generated compounds, which were never part of any full-length humanized antibody.

224. I further disagree with Dr. Balthasar's use of the term "h5G1.1" in his depiction of the "scaffold" that was used in Bowdish. The term "h5G1.1" is not used in Bowdish, there is no evidence that the antibody described in Example 4 of Bowdish was in fact humanized, and Evans does not disclose any full-length, humanized antibody sequences. I further disagree with Dr. Balthasar's depiction in

Samsung Bioepis Exhibit No. 1002
Page 13172

Figure 14. Again, Dr. Balthasar does not accurately depict the disclosure of Evans, which did not disclose a full-length humanized antibody, but only humanized antibody fragments, such as scFv. I also disagree with the use of the term "h5G1.1," which is not used anywhere in Bowdish. Neither Figure 12 nor Figure 14 reflect the multiple steps of sequence selection and combination that a POSA would have to undertake to arrive at the claimed full-length sequence from the disclosures of Bowdish.

4. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Make, and Would Not Have Reasonably Expected Success in Making, the Claimed Pharmaceutical Compositions for Treatment of PNH from Bell, Bowdish and Evans (or Wang for Claim 6)

225. Even if Dr. Balthasar were correct that a POSA could have assembled the specific amino acid sequence of the claimed antibody in the exact way he does from Bowdish and Evans, he still has not shown:

- How a POSA would have been motivated to use the claimed antibody in a "method of treating a patient suffering from [PNH]" (as the claims require), or would have reasonably expected to succeed in doing do;
- How a POSA would have reasonably expected to achieve success in using the claimed antibody to obtain the "immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH)" recited in claims 9 and 10; and

- How a POSA would have further been motivated to make, or reasonably expected to succeed in making, the claimed ***pharmaceutical compositions*** of the specific amino acid sequence recited in claims 1-10 of the '504 patent, that would be suitable for use in the claimed methods of treating patients suffering from PNH.

226. In my opinion, Dr. Balthasar ignores the known complexity and unpredictability in antibody design as of March 15, 2007, including the design of humanized monoclonal antibodies; the challenges, expenses, and unpredictability of clinical research of such monoclonal antibodies; and the design of pharmaceutical compositions of such antibodies suitable for human therapeutic use to treat PNH without undue harm to the patient. (*See* Sections VI.D.2 and VI.D.4 above.)

227. Dr. Balthasar conclusively states that "[a] POSA would have had a reasonable expectation of success in making the claimed pharmaceutical compositions because of the history of success with using eculizumab to treat PNH, and because generating the claimed antibody and anti-C5 antibody-containing compositions would have required only routine techniques." (AMG1002 ¶ 123.) He further states that success with pharmaceutical compositions and treatment of PNH with the antibody he assembles in hindsight from Bowdish and Evans would be reasonably expected because of the preparation

Samsung Bioepis Exhibit No. 1002
Page 13174

of "eculizumab" compositions by Bell and Wang, and the success of "eculizumab" in published human clinical trials. (AMG1002 ¶ 143.)

228. Dr. Balthasar is mistaken, because he equates the antibody he constructs from Bowdish and Evans with "eculizumab" as taught by Bell and the other clinical literature. But, as discussed above, that literature consistently identified "eculizumab" as a very different antibody (Thomas's IgG4 isotype antibody) than the claimed antibody sequence. Nothing in Bowdish and Evans, or Bell and Wang, would have taught or given a POSA a reasonable expectation of success that a different antibody with the specific amino acid sequence of claims 1-10 of the '504 patent would even be "an antibody that binds C5," let alone whether it would be suitable for "treating a patient suffering from [PNH]" (as all of the claims provide).

229. Even if the IgG4 antibody of Thomas identified in the pre-March 15, 2007 literature as "eculizumab," and the different antibody with the sequence claimed in the '504 patent, shared some amino acid sequences in common, a POSA would not have reasonably expected that the two antibodies shared properties in common, because the impact of their ***differences*** in amino acid sequence could not have been reasonably predicted. (*See* Section VI.D.4 above.) A POSA would have been aware that those differences impacted by amino acid sequence could include, for example, differences in affinity and specificity for C5; differences in

"fine specificity" for C5 (*i.e.*, the epitope, which as discussed below, could be critical); differences in pharmacokinetic properties; differences in safety or immunogenicity in humans; differences in therapeutic effect in humans; and differences in the ability to be formulated into a pharmaceutical composition suitable for human administration. (*See* Sections VI.D.2 and VI.D.4 above.)

230. With respect to binding interactions, a POSA would have understood that, for therapy with an anti-C5 antibody, not only were binding affinity and specificity important, but "fine specificity" (the ability of the antibody to bind the antigen at a specific epitope) was understood to be critical to therapeutic activity.[12] For example, the following figure, contained in a review article published in 1995, illustrates the complement pathway, and highlights the target of anti-C5 monoclonal antibody therapy as understood at that time (such as with Thomas's IgG4 isotype anti-C5 antibody):

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[12] As I discuss below in Section VII.F.2, I note that, despite the publication of this review and other information as early as 1995 expressing interest in therapeutic development of anti-C5 monoclonal antibodies to treat PNH and other complement-mediated conditions, no one else succeeded in bringing any anti-C5 antibody to market before before the approval of SOLIRIS® on March 16, 2007.

Samsung Bioepis Exhibit No. 1002
Page 13176

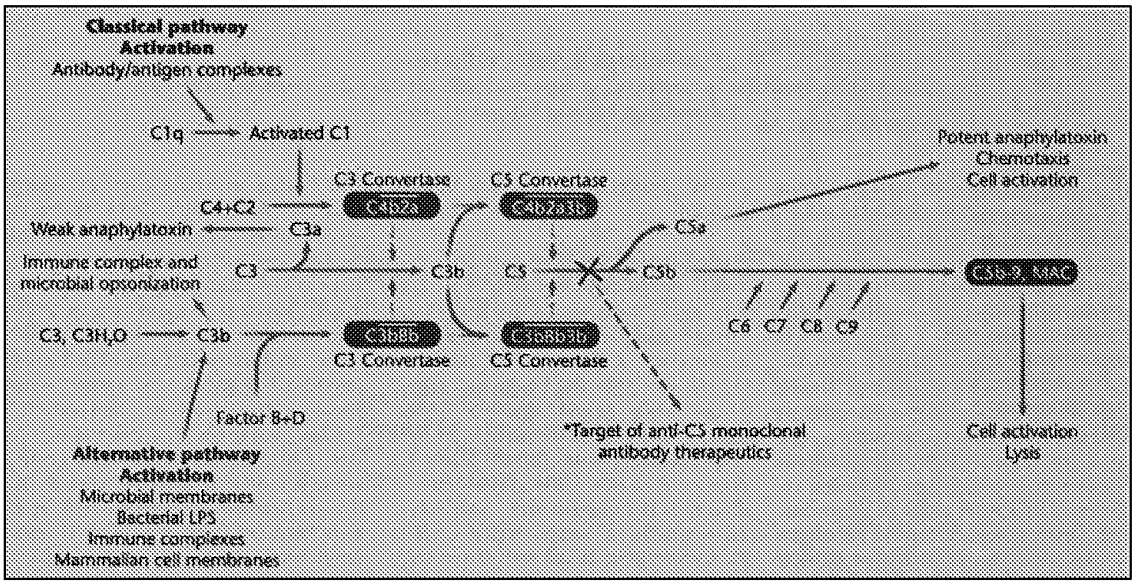


Figure 13: Mattis & Rollins (1995), Fig. 1 (AMG1039 at 840**)**

231. As this figure illustrates, a POSA would have understood that it was not enough for an anti-C5 to merely bind to C5 to have its therapeutic effect, but the antibody would have to bind C5 in a way that blocks its enzymatic cleavage into C5a and C5b, and the downstream effects that result from the components C5a and C5b. For example, Thomas noted that "[a] clinically useful C5 inhibitor must block generation of ***both*** C5a and C5b-9, as both of these molecules have potent pro-inflammatory effects," and pointed to a prior compound ("N19-8 scFv") that bound to C5 but did not effectively block C5 generation. (AMG1023 at 1398-99.)

232. For the antibody that Dr. Balthasar constructs in hindsight from Bowdish and Evans to match the claimed sequence, a POSA would have had no

information regarding any of its critical properties, including any of its binding properties, its *in vitro* biological assay activity (*e.g.*, in hemolytic assays), its ability to be formulated into a pharmaceutical composition (let alone the specific 300 mg single unit dosage form, 10 mg/ml concentration antibody solution formulation of claim 6), or usefulness of the antibody or a pharmaceutical composition of the antibody in treating PNH or any other condition.

233. The following figure illustrates how (1) a POSA prior to March 15, 2007 would have believed that there was extensive information confirming the C5 binding, *in vitro* activity, safety and efficacy for the IgG4 isotype antibody of Thomas, which the art identified as "eculizumab," and (2) how a POSA would have had no information regarding an antibody with the specific claimed sequence of the '504 patent, which was not disclosed prior to March 15, 2007 and was not reported in the literature prior to that date as having been tested *in vitro*, in animals or in humans:

Samsung Bioepis Exhibit No. 1002
Page 13178

Understanding of a POSA Prior to March 15, 2007

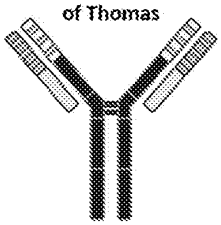
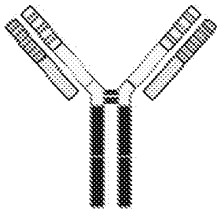
	Identified as "Eculizumab"?	Binds to C5?	Blocks C5 activity in vitro?	Treats PNH?	Suitable for formulation and human administration?
"h5G1.1 HuG4" of Thomas 	YES	YES Similar binding to mouse 5G1.1	YES Same *in vitro* activity as mouse 5G1.1	YES Efficacy reported in Phase II/Phase III studies	YES No major safety/ immunogenicity issues in clinical trials
Claimed Antibody – Sequence *Not Known* Prior to March 15, 2007 	NO	?	?	?	?

Figure 14: A POSA's understanding prior to March 15, 2007 of (1) the IgG4 humanized antibody of Thomas, and (2) an antibody with the then-unknown amino acid sequence claimed in the '880 patent

234. Accordingly, even if a POSA provided with Bell ,Wang, Bowdish and Evans could have somehow envisioned or made an antibody with the specific claimed amino acid sequence prior to March 15, 2007, they still would not have been motivated to use that antibody for the pharmaceutical compositions claimed in the '504 patent, and would not have reasonably expected to succeed in doing so.

Samsung Bioepis Exhibit No. 1002
Page 13179

E. Claims 1-5 and 7-10 of the '504 Patent Would Not Have Been Obvious Over Bell, Evans, and Mueller (Ground 6), and Claim 6 Would Not Have Been Obvious Over Bell, Wang, Evans and Mueller (Ground 7)

235. Amgen contends that claims 1-5 and 7-10 of the '504 patent would have been obvious over the combination of Bell (AMG1005), Evans (AMG1007) and Mueller (AMG1008) (Ground 6), and that claim 6 would have been obvious in view of Bell, Wang (AMG1028), Evans, and Mueller (Ground 7). As Grounds 6 and 7 raise overlapping issues, I disagree with both for the same reasons, I will address them both together here.

236. In my opinion, Amgen's Ground 6 and 7 fail, because, among other things, Amgen cannot show that each element of the claimed invention was known or obvious in view of Bell, Evans and Mueller (or further in view of Wang, for claim 6).

237. As with Grounds 4 and 5, Dr. Balthasar's arguments in Grounds 6 and 7 starts with the premise that Bell (and Wang, for claim 6) taught all of the claim elements except for the unique claimed amino acid sequence – which Dr. Balthasar concedes was not cited in Bell or Wang. (AMG1002 ¶ 176, ALXN2032 at 151:4-12, 160:7-10, 194:17-20, 257:13-18.) With respect to Bell and Wang, Dr. Balthasar again focuses on a POSA being motivated by their teachings regarding "eculizumab," and with Bell in particular, its teachings that "eculizumab" was an

anti-C5 antibody what was clinically tested and shown to be safe and effective in treating PNH. (AMG1002 ¶¶ 176-178.)

1. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Combine Bell (and Wang) with Evans and Mueller, or to Make the Specific Claimed Antibody of the '504 Patent

238. For the same reasons as stated above with respect to Bowdish and Evans in Grounds 4 and 5, a POSA would not have had any motivation to jump from Bell – which taught that "eculizumab" was a therapeutically effective and safe IgG4 isotype antibody – to Evans and Mueller to look for a ***different***, uncharacterized antibody with a different, hybrid IgG2/IgG4 constant region. (*See* Section VI.D.2 above.) Nothing in Bell, or the Thomas and Evans documents that Bell cites, cited or directed a POSA to look at Mueller. And a POSA in particular would have had no motivation to look to Mueller for methods of treating patients with PNH, or pharmaceutical compositions suitable for use in such a treatment. Bell already confirmed to a POSA as of March 15, 2007 that Thomas's IgG4 antibody could be used to treat PNH (and sufficiently formulated to be suitable for such treatment in a clinical study); and a POSA would not have reasonably expected that a different antibody with a different, non-natural hybrid constant region that had never been reported as being tested in people, or even studied for C5 binding, would be useful for compositions as claimed in the '504 patent.

Samsung Bioepis Exhibit No. 1002
Page 13181

239. And even if a POSA had considered Evans and Mueller simultaneously, neither Evans nor Mueller, alone or in combination, would have disclosed to a POSA prior to March 15, 2007 the specific, full-length antibody sequence claimed in the '504 patent. (*See* Section VII.A.2 above.)

240. I disagree with Dr. Balthasar that a POSA would have been motivated to combine Evans and Mueller. Evans and Mueller did not reference each other, and a POSA would not have looked to Mueller to design constant regions for the humanized variable regions described in Evans because Mueller is not related to C5-binding or treatment of PNH, the subject of Evans. Mueller has no experiments or data on C5 binding or blocking complement. Mueller only references "h5G1.1" antibodies, with either IgG4 or IgG2/G4 heavy chain constant regions, as "isotype control[s]" in studies measuring the activity of anti-VCAM antibodies. (AMG1008 at 12:27-30; AMG1031 at 442 443, 448.)

241. Additionally, a POSA would not have looked to Mueller to design constant regions for the Evans' variable regions because the prior art taught that the clinically proven anti-C5 therapy for PNH, "eculizumab," had an IgG4 isotype. Based on the teachings of Thomas and multiple other references guiding a POSA towards the IgG4 isotype, a POSA would have had no motivation to look to Mueller to alter what a POSA would have understood to be the isotype of an already tested antibody with therapeutic effect.

Samsung Bioepis Exhibit No. 1002
Page 13182

242. I disagree that a POSA would have been motivated to look to Mueller because of any alleged benefits regarding its hybrid "G2/G4" constant region – which, from the perspective of a POSA prior to March 15, 2007, had never been used in ***any*** antibody that had been formulated as a pharmaceutical composition or tested in a clinical trial. As disclosed by Thomas and the numerous references citing Thomas, a POSA would have understood that there was already an effective, anti-C5 antibody used for treatment of PNH – eculizumab – and that this antibody had an IgG4 isotype. (AMG1004 at 553; AMG1047 at 2559; AMG1012 at 1234; ALXN2028 at 31; AMG1005) at [0052]; AMG1021 at 1018; AMG1019 at 56; AMG1020 at 2123.) As discussed in Section VI.D.2 above, as of March 15, 2007, the process of designing a functional, humanized monoclonal antibody was known to be complex and time-consuming, involving multiple rounds of design iteration and testing. Understanding the unpredictability and expense associated with this process, including due to the potential negative impacts of isotype-switching on antibody function (*see* Section VI.D.4 above), a POSA would not have been motivated to investigate a new isotype, and risk losing the already established therapeutic benefit of "eculizumab," which a POSA would have understood to be an IgG4 tested in clinical trials.

243. Even if a POSA had chosen to adopt an IgG2/IgG4 hybrid isotype – which a POSA would not have consider, given the unpredictability of antibody

Samsung Bioepis Exhibit No. 1002
Page 13183

design, and the absence of any evidence regarding how such an isotype would perform in humans or in pharmaceutical compositions – a POSA would not have necessarily selected the IgG2/IgG4 hybrid constant regions described in Mueller. As of March 15, 2007, a POSA would have understood that a hybrid IgG2/IgG4 isotype could be constructed in multiple ways, and would have had many choices for this design other than the sequence described in Mueller.

244. I disagree with Dr. Balthasar's suggestion that Evans and Mueller would have been linked because both allegedly disclosed "humanized 5G1.1" or "h5G1.1." (AMG1002 ¶¶ 178-179.).) First, this statement is inaccurate because Evans does not disclose any full-length "humanized 5G1.1" antibodies, but instead only humanized antibody "fragments." Again, to be clear, a POSA would have understood that the "fragments" of Evans were not the partial sequences of a full length antibody, in the way that Evans disclosed the variable region sequences of a full length mouse antibody. Evans's "fragments" were standalone molecules manufactured by recombinant DNA means from the ground up, and they never belonged to, and were not pieces or components of, any larger full-length humanized antibody. (*See* Section VI.D.5 above; ALXN2032 at 228:2-16.)

245. Moreover, as explained in Section VI.D.3 above, and as Dr. Balthasar confirmed at his deposition, the term "5G1.1" could encompass multiple antibodies and antibody fragments, and a POSA would not have understood "5G1.1" as

Samsung Bioepis Exhibit No. 1002
Page 13184

necessarily identifying "eculizumab." (ALXN2032 at 97:23-99:20, 100:3-12.) For example, Dr. Balthasar admitted he could not determine that the "h5G1.1 IgG4" antibody described in Mueller was the same as the IgG4 antibody described in Thomas. (ALXN2032 at 241:23-242:12.) Multiple prior art references used the "5G1.1" terminology, including clinical publications describing C5 binding and clinical testing of eculizumab, and a POSA would not have looked to Mueller over these other, more relevant publications.

246. In addition, Dr. Balthasar cites the alphanumeric "CO12" as providing guidance for the combination of a particular variable region disclosed in Evans with constant regions disclosed in Mueller. A POSA would not have understood "CO12" to refer specifically to the clinically-tested antibody "eculizumab." A POSA would have understood "eculizumab" to be the unique name for which Alexion had sought approval for its clinical tested antibody (*see* Section VI.D.3 above), but a POSA could not have been sure what "CO12" was or referred to. For example, "CO12" is used in Evans in the name of an scFv, whereas in Mueller it is used in the name of a full-length antibody. (*See* AMG1007 at 44:4-13; AMG1008 at 12:34-37.) Accordingly, a POSA could not have reasonably assumed that the term always referred to the same molecule. Particularly in view of teachings in the art that eculizumab had an IgG4 isotype, a POSA would not have been guided to

Mueller, or towards any combination of sequences from Evans in combination with Mueller, based on use of the undefined designation "CO12."

247. I disagree with Dr. Balthasar that "[o]verlapping sequences" would have caused a POSA to combine sequences from Mueller and Evans. (AMG1002 ¶ 168.) Dr. Balthasar appears to base this conclusion on overlap between the light chain constant region of Mueller's 3F4 antibody and the light chain constant region from "5G1.1 scFv CO12." Dr. Balthasar fails to explain, however, why a POSA would have been motivated to combine Evans' variable region sequences with an IgG2/IgG4 constant region, given that Mueller also discloses a second control antibody, "h5G1.1 CO12 HuG4 mAb," that a POSA would have believed to be the clinically effective "eculizumab," and would have been more likely to follow.

248. It is my opinion that a POSA would not have been able to readily combine the correct variable region sequences from Evans with Mueller's hybrid IgG2/IgG4 constant region based on the teachings of those references. Rather, Dr. Balthasar uses significant hindsight to pick and choose sequences from Evans and Mueller to reach the specific sequence claimed in the '504 patent.

249. For example, as Dr. Balthasar admitted at his deposition, Mueller does not indicate exactly where the IgG2/IgG4 heavy chain sequences in its anti-VCAM antibodies begins or ends. (ALXN2032 at 233:22-234:4.) Dr. Balthasar uses hindsight to extract the correct constant regions from Mueller's disclosure of a full

length "3F4" anti-VCAM antibody by inferring that the correct boundaries of the IgG2/IgG4 constant regions sequences would be what remained after subtracting the 3F4 variable region, and through comparison to the claimed sequence, which would not have been available to a POSA before March 15, 2007. (*See* AMG1002 ¶¶ 132-135; ALXN2032 at 233:3-234:4.) As Dr. Balthasar further testified, Mueller does not disclose any complete "h5G1.1" or anti-C5 binding antibody sequences. (ALXN2032 at 232:22-233:14.) Accordingly, there is no disclosure in Mueller of how the IgG2/IgG4 constant sequences he extracts would fit with any particular, undefined "h5G1.1" variable region.

250. Even if a POSA would have understood that the term "CO12" in Mueller referred to the "CO12" scFv in Evans – which Dr. Balthasar has not shown – neither Mueller nor Evans provide guidance as to exactly which sequences, or the precise extent of the sequences, a POSA would have used from the Mueller "h5G1.1 CO12 HuG2/G4" and Evans "5G1.1-scFv-CO12" constructs to create a functional, full-length, anti-C5 antibody. Without such guidance, a POSA could have easily selected sequences that failed to correspond to the claimed antibody sequence rather than those selected by Dr. Balthasar.

251. Dr. Balthasar also does not explain why, even if a POSA were to have considered using IgG2/IgG4 constant regions described in Mueller, a POSA would have selected variable region from Evans, rather than Thomas, to combine with

Samsung Bioepis Exhibit No. 1002
Page 13187

those constant regions. The light chain variable region sequences described in Thomas differ from the variable regions of Evans's "5G1.1-scFv-CO12" construct – and from SEQ ID NO: 4 of the '504 patent – at position 38. (*See* AMG1023 at 1396 (Fig. 4); AMG1007 at Certificate of Correction, p. 42-44.) Accordingly, a POSA that chose to follow Thomas (which Bell also cited) as opposed to Evans for the variable region sequences would not have arrived at the claimed amino acid sequence of the '504 patent.

252. A POSA as of March 15, 2007 would have had no motivation to select any of the variable regions disclosed in Evans and combine it with the IgG2/IgG4 constant regions described in Mueller, thereby potentially destroying the desirable clinical properties associated with the IgG4 isotype described in Thomas and publications citing Thomas, and understood at the time to be the isotype for "eculizumab." As discussed above, the term "CO12" would have been too ambiguous to provide guidance to a POSA to select a particular set of variable region sequences from the multiple variable region sequences disclosed in Evans, and combine it with a particular set of constant regions disclosed in Mueller.

253. Even if a POSA had sought to combine variable sequences from Evans with constant regions from Mueller, there is no guidance in either Evans or Mueller as to how to do so – for example, neither reference provides guidance as to exactly what lengths of the disclosed variable and constant regions should be

Samsung Bioepis Exhibit No. 1002
Page 13188

combined. (*See* ALXN2032 at 233:22-234:4.) The Mueller II publication would only have created further ambiguity regarding the boundaries of the "HuG2/G4" construct, because Mueller I (AMG1008) contains an extra amino acid (alanine) at the beginning of what Dr. Balthasar identifies as the IgG2/G4 constant region, but that does ***not*** appear in the "HuG2/G4" construct described in Mueller II (AMG1031). (*See* AMG1008 at 59 ("3F4 Human G2/G4 Expression Plasmid Insert Sequence" at position 138); AMG1031 at 449 (Fig. 9).)

254. It is also my opinion that Dr. Balthasar's depiction of the combination of Evans and Mueller in his declaration reflects significant use of hindsight. For example, I disagree with Dr. Balthasar's alignments in Figures 16-17 of his declaration (*see* AMG1002 at 122-123), which compare sequences from Mueller and Evans against SEQ ID NO: 2 and SEQ ID NO: 4 recited in the '504 patent. A POSA as of March 15, 2007 would not have had the guidance of the disclosure of SEQ ID NO: 2 and SEQ ID NO: 4 from the '504 patent to help select sequences to combine from Evans and Mueller, and accordingly would not have reached the claimed full length sequence of the '504 patent.

Samsung Bioepis Exhibit No. 1002
Page 13189

2. A POSA Without the Benefit of Hindsight Would Not Have Been Motivated to Make, and Would Not Have Reasonably Expected Success in Making, the Claimed Pharmaceutical Compositions for Treatment of PNH Conditions from Bell, Wang, Mueller and Evans

255. As with Grounds 4 and 5, it is my opinion that, even if a POSA had followed Dr. Balthasar's exact combination of sequences from Evans and Mueller that he assembles in hindsight, despite there being no motivation or teaching to do so in the specific way leading to the claimed antibody sequence, the claimed pharmaceutical compositions of the '504 patent would still be nonobvious.

256. In particular, Dr. Balthasar still has not shown:

- How a POSA would have been motivated to use the claimed antibody in a "method of treating a patient suffering from [PNH]" (as the claims require), or would have reasonably expected to succeed in doing do;
- How a POSA would have reasonably expected to achieve success in using the claimed antibody to obtain the "immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH)" recited in claims 9 and 10; and
- How a POSA would have further been motivated to make, or reasonably expected to succeed in making, the claimed ***pharmaceutical compositions*** of the specific amino acid sequence recited in claims 1-10

Samsung Bioepis Exhibit No. 1002
Page 13190

of the '504 patent, that would be suitable for use in the claimed methods of treating patients suffering from PNH.

257. Again, Dr. Balthasar ignores the known complexity and unpredictability in antibody design as of March 15, 2007, including the design of humanized monoclonal antibodies; the challenges, expenses, and unpredictability of clinical research of such monoclonal antibodies; and the design of pharmaceutical compositions of such antibodies suitable for human therapeutic use to treat PNH without undue harm to the patient. (*See* Sections VI.D.2 and VI.D.4 above.)

258. Dr. Balthasar conclusively states that a POSA would have had a reasonable expectation of success in making the specifically claimed antibody because it "would have required only basic molecular and cellular biology techniques." (AMG1002 ¶ 192.) He further states that success with pharmaceutical compositions and treatment of PNH with the antibody he assembles in hindsight from Evans and Mueller would be reasonably expected because of the preparation of "eculizumab" compositions by Bell and Wang, and the success of "eculizumab" in published human clinical trials. (AMG1002 ¶ 191.)

259. Dr. Balthasar is mistaken, because he equates the antibody he constructs from Evans and Mueller with "eculizumab" as taught by Bell and the other clinical literature. But, as discussed above, that literature consistently

Samsung Bioepis Exhibit No. 1002
Page 13191

identified "eculizumab" as a very different antibody (Thomas's IgG4 isotype antibody) than the claimed antibody sequence. Nothing in Evans and Mueller, or Bell and Wang, would have taught or given a POSA a reasonable expectation of success that a different antibody with the specific amino acid sequence of claims 1-10 of the '504 patent would even be "an antibody that binds C5," let alone whether it would be suitable for use in "treating a patient suffering from [PNH]," as is required by all of claims 1-10.

260. Even if the IgG4 antibody of Thomas identified in the pre-March 15, 2007 literature as "eculizumab," and the different antibody with the sequence claimed in the '504 patent, shared some amino acid sequences in common, a POSA would not have reasonably expected that the two antibodies shared properties in common, because the impact of their ***differences*** in amino acid sequence could not have been reasonably predicted. (*See* Section VI.D.4 above.) A POSA would have been aware that those differences impacted by amino acid sequence could include, for example, differences in affinity and specificity for C5; differences in "fine specificity" for C5 (*i.e.*, the epitope, which as discussed below, could be critical); differences in pharmacokinetic properties; differences in safety or immunogenicity in humans; differences in therapeutic effect in humans; and differences in the ability to be formulated into a pharmaceutical composition

Samsung Bioepis Exhibit No. 1002
Page 13192

suitable for human administration. (*See* Sections VI.D.2, VI.D.4 and VII.D.4 above.)

261. For the antibody that Dr. Balthasar constructs in hindsight from Evans and Mueller to match the claimed sequence, a POSA would have had no information regarding any of its critical properties, including any of its binding properties, its *in vitro* biological assay activity (*e.g.*, in hemolytic assays), its ability to be formulated into a pharmaceutical composition (let alone the specific 300 mg single unit dosage form, 10 mg/ml concentration antibody solution formulation of claim 6), or usefulness of the antibody or a pharmaceutical composition of the antibody in treating PNH.

262. Accordingly, even if a POSA provided with Bell, Evans and Mueller (and Wang) could have somehow envisioned or made an antibody with the specific claimed amino acid sequence prior to March 15, 2007, they still would not have been motivated to use that antibody for the specific methods of treating PNH and pharmaceutical compositions claimed in the '504 patent, and would not have reasonably expected to succeed in doing so.

F. Objective Indicia Support the Nonobviousness of Claims 1-10 of the '504 Patent

263. I understand from counsel that the nonobviousness of a patented invention may be supported by objective evidence ("objective indicia of nonobviousness").

Samsung Bioepis Exhibit No. 1002
Page 13193

264. In my opinion, objective evidence supports the nonobviousness of the invention claimed in the '504 patent, including: (1) a long-felt but unmet need in the industry that was satisfied by the patented invention; (2) the failure of others to develop the patented invention; (3) copying of the patented invention by others; (4) the commercial success of the patented invention; and (5) praise in the industry for the patented invention. I disagree with Dr. Balthasar's opinions to the contrary. (*See* AMG1002 ¶ 215.)

1. SOLIRIS® is the Commercial Embodiment of the '504 Patent

265. I understand from counsel that, to be considered, objective evidence of nonobviousness should have a "nexus" to the claimed invention. Counsel has informed me that if (1) the objective evidence is tied to a specific product, and (2) that product embodies the claimed features of the claimed invention, then there is a presumption that the objective evidence has a "nexus" to the claimed invention.

266. In my opinion, the commercial product SOLIRIS® embodies the claimed features of claims 1-10 of the '504 patent. Claims 1-10 of the '504 patent each cover methods of treating PNH using pharmaceutical compositions comprising an antibody with the unique amino acid sequence reflected in heavy and light chain sequences SEQ ID NOs: 2 and 4. (AMG1001 at 39:2-4.) As discussed above, it is known today (but was **not** known prior to March 15, 2007) that the active ingredient in SOLIRIS® (eculizumab) is an antibody comprising

SEQ ID NOs: 2 and 4, which works to treat PNH and other indicated complement-mediated conditions by binding to C5 and blocking its cleavage. (*See* Section VI.E; ALXN2032 at 262:2-19.)

267. I also understand that SOLIRIS® was originally approved for, and presently has an indication for, "[t]he treatment of patients with [PNH] to reduce hemolysis." (ALXN2005 at 1, 2 (Section 1); ALXN2053 at 1, 3.) I further understand that SOLIRIS® is in supplied as a 300 mg single-dose vial that contains 30 ml of a 10 mg/ml solution of eculizumab, which is known today to have the specific amino acid sequence of SEQ ID NOs: 2 and 4 recited in the '504 patent. (ALXN2005 at 1, 5 (Section 11); ALXN2053 at 1, 21.)

268. In my opinion, the objective evidence showing the success of SOLIRIS® -- therapeutically as a long-needed, life-saving therapy, as well as commercially – has a direct nexus with the patented invention of the '504 patent. The specially engineered anti-C5 antibody claimed by its unique amino acid sequence in claims 1-10 of the '504 patent is the agent that is directly responsible for the outstanding clinical benefits that SOLIRIS® provides as the first-approved treatment for patients suffering from PNH. (ALXN2053 at 22 (Section 12.1); ALXN2030 at 1.)

269. While the claims of the '504 patent are limited to methods of treating PNH, I further note that the claimed antibody recited in the '504 patent is also

Samsung Bioepis Exhibit No. 1002
Page 13195

responsible for the clinical benefits to patients effectively treated by SOLIRIS® for several other rare conditions, including: (1) the life-threatening hemolytic condition atypical hemolytic uremic syndrome ("aHUS"); (2) the chronic autoimmune neuromuscular disease myasthenia gravis ("MG"); and (3) neuromyelitis optica spectrum disorder ("NMOSD"), a debilitating autoimmune disease of the central nervous system. (ALXN2053 at 1.)

2. SOLIRIS® Fulfilled a Long-Felt, Unmet Need for a Treatment of PNH, Which Others Failed to Satisfy

270. In my opinion, SOLIRIS® fulfilled a long-felt, unmet need for a treatment of PNH.

271. As I discuss in Section VI.A above, PNH was known prior to March 15, 2007, and is known today, as a chronic, debilitating and potentially life-threatening disease, where patients' red blood cells are constantly under attack by the body's own complement system. PNH has been referred to as the "most vicious acquired thrombophilic state known to medicine." (ALXN2050 at 1161-1170.) Symptoms of PNH, such as hemoglobinuria (dark urine caused by periods of acute hemolysis ("paroxysms"), chronic and potentially disabling fatigue, dysphagia, recurrent pain, and severe anemia, severely impacted patients' quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.) Patients could also experience life-threatening blood clots, or "thrombosis." (*Id.*)

Samsung Bioepis Exhibit No. 1002
Page 13196

272. SOLIRIS® was not only first anti-C5 antibody approved for any condition, but was the first treatment approved by the FDA for patients suffering from PNH. I understand that the FDA considered SOLIRIS® to be a significant medical breakthrough, granting it an expedited "Priority Review" that is reserved for drugs that are expected to have a substantial impact on the treatment of a serious disease. (ALXN2006 at 993; ALXN2030 at 1.) SOLIRIS® was also granted "Orphan Drug" status for treatment of PNH in the FDA and the EU, recognizing that it was a much-needed therapy for a rare and untreated disease. (ALXN2019 at 1270.)

273. Prior to SOLIRIS®, there were no drugs directed to regulation of the body's complement system to treat PNH. Symptoms of PNH, such as hemoglobinuria (dark urine caused by periods of acute hemolysis ("paroxysms"), chronic and potentially disabling fatigue, dysphagia, recurrent pain, and severe anemia, severely impacted patients' quality of life. (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234; ALXN2049 at 1-2.) Patients could also experience life-threatening blood clots, or "thrombosis." (AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234; ALXN2049 at 1-2.) Because there were no drugs directed towards regulation of complement as a treatment for PNH, patients were forced to rely on other, potentially invasive, therapies that could only address individual

Samsung Bioepis Exhibit No. 1002
Page 13197

symptoms of the disease, such as blood transfusions. (*See* AMG1004 at 6; AMG1047 at 2559; AMG1012 at 1234.)

274. Reporting on the lack of effective treatments for PNH, Hillmen 2006, a pivotal Phase III clinical trial report for SOLIRIS® published in the New England Journal of Medicine stated, "there [was] no therapy that effectively reduce[d] intravascular hemolysis or improves the symptoms in patients with PNH" prior to SOLIRIS®. (AMG1012 at 1234; see also AMG1047 at 2559 ("There is no effective treatment for the ongoing hemolysis in PNH.").) Prior to SOLIRIS®'s approval, PNH patients were often "transfusion-dependent," meaning that their survival depended on receiving frequent blood transfusions. (AMG1004 at 557; AMG1047 at 2559.)

275. The approval of SOLIRIS® "marked a distinct change in how physicians were able to treat patients with paroxysmal nocturnal hemoglobinuria." (ALXN2049 at 1.) I note how that physicians specializing in hematology – those responsible for managing and treating PNH patients – have praised SOLIRIS® for its marked therapeutic benefits and improvement in the lives of PNH patients. For example, as said by Dr. Peter Hillmen, a consultant hematologist at Leeds Teaching Hospital, "[e]culizumab has dramatically changed PNH…[u]ntil eculizumab arrived there was no specific treatment for PNH apart from transfusion and occasionally bone marrow transplant." (ALXN2049 at 1.)

Samsung Bioepis Exhibit No. 1002
Page 13198

276. Dr. Robert A. Brodsky, director of the division of hematology and Clara Lucas Lynn Chair in Medicine at The John Hopkins University, similarly praised eculizumab as a groundbreaking first-in-class treatment. According to Dr. Brodsky, prior to SOLIRIS®, "We had very little to offer patients. . . . Several years ago the only thing we would have had to offer [a PNH patient in crisis] was narcotics and maybe fluids. Now that eculizumab is approved, all I have to do is call down to the pharmacy and tell them that we need to start the patient on this drug." (ALXN2049 at 2.) Others in the hematology field have offered similar testimonials and accolades for SOLIRIS®. (ALXN2050) ("The advent of eculizumab has resulted in a dramatic improvement of the natural history of PNH patients with improvement in virtually every aspect of these patients' lives.").)

277. In sum, there is no question that the invention claims 1-10 of the '504 patent, as embodied by SOLIRIS®, satisfied a long-felt need, unmet need for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH, where prior existing treatment options had been limited and ineffective.

278. In my opinion, the nonobviousness of the '504 patent is also supported by the failure of others to solve the problem that was addressed by the claimed invention of the '504 patent and its commercial embodiment, SOLIRIS®. As Dr. Balthasar notes, researchers were interested in, and had published on, the

Samsung Bioepis Exhibit No. 1002
Page 13199

concept of anti-C5 monoclonal antibody therapy, including its potential for use in the treatment of PNH, as early as the mid-1990s. (AMG1002 at ¶ 35; ALXN2032 at 262:23-264:13; AMG1039 at 2-3.) But it was not until the launch of SOLIRIS® that any solution to the severe problem of untreated PNH was introduced into the market.

279. The failure of others to develop an anti-C5 therapy, or ***any*** therapy, for the treatment of PNH over the course of more than a decade is, in my view, strong objective evidence of the difficulty of developing monoclonal antibodies for human therapeutic use, and the nonobviousness of the claimed invention of the '504 patent in particular.

3. SOLIRIS® Is A Commercial Success

280. SOLIRIS® was approved by the FDA on March 16, 2007 for the treatment of patients with PNH to reduce hemolysis. (ALXN2005 at 1; ALXN2006 at 993; ALXN2030 at 1.)

281. I understand that since its approval, SOLIRIS® has been commercially successful, with over $1 billion in U.S. sales each year in each of the last three years.

282. In my opinion, the commercial success of SOLIRIS® is directly linked to the claimed invention of the '504 patent. As I explain in Section VII.F.1 above, the invention of claims 1-10 of the '504 patent is coextensive with the clear

Samsung Bioepis Exhibit No. 1002
Page 13200

therapeutic benefits of SOLIRIS® that are highly valued by physicians and their patients suffering from PNH (*see* Section VII.F.2 above).

4. Industry Praise

283. Praise in the industry for SOLIRIS® further supports my opinions on the nonobviousness of the '504 patent. As shown above in Section VII.F.2, SOLIRIS®, the commercial embodiment of the claimed invention of the '504 patent, has received extensive praise from the medical industry, and in particular from the physicians who are responsible for maintaining the survival and quality of life of their PNH patients, and had few options before SOLIRIS®.

284. I also understand that Alexion has received several significant awards honoring the groundbreaking nature of its development and introduction of SOLIRIS®, including the Prix Galien USA 2008 Award for Best Biotechnology Product, and the Prix Galien France 2009 Award for Most Innovative Drug for Rare Disease. (ALXN2020; ALXN2021.)

5. Copying

285. I am also aware that Amgen, who is challenging the '504 patent in this case, and other companies including Samsung Bioepis and Generium, are seeking to copy, or have already copied, eculizumab – which, as we known today, is the uniquely engineered antibody with SEQ ID NOs: 2 and 4 that is the sole active

agent in SOLIRIS and the claimed pharmaceutical compositions of the '504 patent. (ALXN2088 at 1; ALXN2090 at 2; ALXN2089 at 1.)

286. The copying by others of the claimed antibody comprising SEQ ID NOs: 2 and 4 is, in my view, further objective evidence of the nonobviousness of the '504 patent's invention. If it were simple to recreate the clinical benefits of properties of SOLIRIS without using the specific amino acid sequence of eculizumab (as known today) claimed in the '504 patent, then these companies could have tried to develop their own antibodies with different amino acid sequences not recited in the '504 patent claims. But they did not do so. Instead, it appears that these companies took the exact amino acid sequence recited and claimed in the '504 patent, and have tried to copy it in an effort to provide patients with the same clinical benefits provided by SOLIRIS®.

287. This supports my opinion, as explained above, that the process for designing a humanized, monoclonal antibody is unpredictable and requires an extensive investment of resources with no guarantee of eventual success – and these companies are more willing to copy SOLIRIS® and the claimed invention rather than develop their own unique antibodies, as Alexion did.

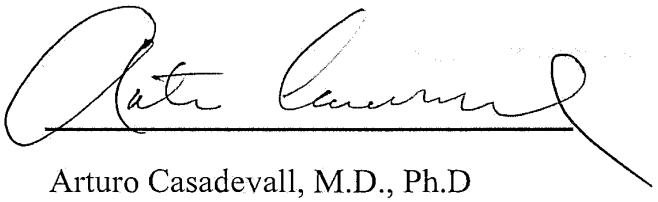
Samsung Bioepis Exhibit No. 1002
Page 13202

VIII. CONCLUSION

288. For the reasons stated above, claims 1-10 of the '504 patent were not anticipated or made obvious in view of any of the art or combinations of art alleged in Amgen's Grounds.

Samsung Bioepis Exhibit No. 1002
Page 13203

I declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.



Arturo Casadevall, M.D., Ph.D

Dated: November 22, 2019

Appendix A

Sept. 17, 2019

CURRICULUM VITAE

Arturo Casadevall

PERSONAL DATA

W. Harry Feinstone Department of Molecular Microbiology and Immunology
Johns Hopkins Bloomberg School of Public Health
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Baltimore, MD 21205
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FAX: 410-955-0105
E-Mail: acasad1@jhu.edu

EDUCATION AND TRAINING

Degree/Year Institution and Field Postdoctoral Training Medical or Other Licensure

Year	Degrees/Certificate	Discipline	Institution
Undergraduate			
1979	B.A. (Magna Cum Laude)	Chemistry	Queens College, CUNY
Doctoral/graduate			
1983	M.S.	Biochemistry	New York University
1984	Ph.D.	Biochemistry	New York University
1985	M.D.	Medicine	New York University
Postdoctoral			
1985-1988	Bellevue Hospital - NYU Medical Center Internship and Residency in Internal Medicine		
1988-1989	Albert Einstein/Montefiore Medical Center Fellowship in Infectious Diseases		
1989-1991	Postdoctoral Fellowship with Dr. Matthew D. Scharff of Cell Biology, Albert Einstein College of Medicine		
1991	Cold Spring Harbor Course on Yeast Genetics		

Medical Board or Other Certification

2013-2023	American Board in Internal Medicine Certified in the Subspecialty of Infectious Diseases American Board in Internal Medicine Specialist in Internal Medicine
1990	Diplomate in the Subspecialty of Infectious Diseases
1988	Diplomate in the Specialty of Internal Medicine
1986	National Board of Medical Examiners Diploma

PROFESSIONAL EXPERIENCE *(annotate as appropriate)*

Alfred & Jill Sommer Prof. & Chair Dept of Molecular, Microbiol. & Immunol	2015-Present	JH Bloomberg Sch. of Public Health
Visiting Prof of Med. & Microbiol. & Immunol.	2015-present	Albert Einstein College of Medicine
Director, Ctr for Immunological Sciences	2013-15	Albert Einstein College of Medicine
Leo and Julia Forchheimer Professorship	2006-15	Albert Einstein College of Medicine
Chair, Dept of Microbiology & Immunology	2006-15	Albert Einstein College of Medicine
Interim Chair, Dept of Microbiol. & Immunol.	2005-06	Albert Einstein College of Medicine
Selma and Jacques Mitrani Professorship	2002-06	Albert Einstein College of Medicine

Director, Division of Infectious Diseases	2000-06	Montefiore Medical Ctr-Albert Einstein
Professor, Med. & Microbiol. & Immunology	2001-15	Albert Einstein College of Medicine
Assoc. Prof, Med. & Microbiol. & Immunol.	1996-01	Albert Einstein College of Medicine
Asst. Prof. Med. & Microbiol. & Immunol.	1992-96	Albert Einstein College of Medicine

PROFESSIONAL ACTIVITIES

American Association for the Advancement of Science
American Association of Immunologists
American Society for Clinical Investigation
American Society for Microbiology
Medical Mycology Society of the Americas
Fellow, Infectious Disease Society of America
Harvey Society
Interurban Clinical Club
Practitioner's Society
National Academy of Medicine
American Academy of Arts and Sciences

Service to Scientific Societies

1998-2000	Vice-President, New York Mycology Society
2000-02	President of New York Mycology Society
1998, 2002	Nominating committee for American Society for Microbiology (ASM) Division F officers
1998-2000	Councilor, New York Society for Infectious Diseases
2005	ASM Division F Chair Elect
2005	Nominated as Candidate for President of ASM
2006-09	Chair, ASM Career Development Committee
2004-07	ASM Abbot Award Selection Committee
2007-10	ASM Committee on Awards
2008-11	ASM Membership Election committee
2008-11	ASM Communications Committee
2008-11	ASM Minority Recruitment Committee
2008-present	ASM Minority Affairs Committee
2014-16	American Association of Immunology Minority Affairs Committee
2008-09	Medical Mycology Society of America President
2011-14	Elected Member-at-Large, AAAS Section on Medical Sciences
2014-16	American Association for Immunology Minority Affairs Committee
2012-15	Research Committee of the IDSA
2016-19	Elected Chair of the Board of Governors of the American Academy of Microbiology
2017	Elected Member of the American Academy of Arts and Sciences

Conference Organizer, Session Chair

1997	13th Congress of the International Society of Human and Medical Mycology, Parma Italy. Convener of symposium titled: Cell-mediated versus antibody mediated-protection mechanisms in fungal diseases: an ongoing dilemma.
1997	Program committee: The Fourth NIAID Workshop in Medical Mycology, Lake Tahoe
1999	Scientific Committee: Fourth International Meeting on Cryptococcus and Cryptococcosis, London
2000	Organizer, Bacteriology and Mycology Horizons for the 21st century. A symposium in honor of Dr. William Branche, NIH, Shannon Building
2001	Convener, Symposium Host defense against fungi: application toward therapeutics and vaccine development. American Society of Microbiology, Orlando

2002 Scientific Committee: Fifth International Meeting on Cryptococcus and Cryptococcosis, Adelaide, Australia
2005 Scientific Committee: Six International Meeting on Cryptococcus and Cryptococcosis, Boston
2005 United States National Organizing Committee. International Union of Microbiological Societies Meeting. Representative for the American Society of Microbiology. San Francisco
2004 IDSA Program Committee
2006 IDSA Program Chair
2006 Scientific Committee. 13th Congress of the International Society of Human and Medical Mycology, Paris, France
2006 Scientific Committee. ASM Biodefense Meeting, Baltimore
2007 Co-chair, ASM colloquium on 'The fungal kingdom: diverse and essential roles in the earth's ecosystem' Developer of Division F program for ASM General meeting
2009, 2010 ASM Colloquium Advisory Committee
2010, 2012, 2015, 2017 Organizing committee for Model Host Meeting, Crete
2011 Gordon Conference on Chemical & Biological Terrorism Defense 2011 organizing committee
2010-2013 Keystone Symposia Scientific Advisory Board
2013-16 ASM General Meeting Program Chair

Consultantships
2006-11 Consultant, Pain Therapeutics
2012-14 Pfizer Resident Professors Program

Research Program Building / Leadership
2000-06 Director, Div. of Infectious Diseases Montefiore Medical Ctr-Albert Einstein
I was responsible for: 1) supervising clinical activities of the Division of Infectious Diseases in two hospitals (Montefiore and Weiler); 2) recruitment physician scientists; 3) mentoring faculty and fellows.

2006-14 Chair, Dept of Microbiology & Immunology Albert Einstein College of Medicine
I was responsible for: 1) supervising basic science department; 2) recruited siz new faculty scientists; 3) mentored faculty, fellows and graduate students.

2015-present Chair and Alfred and Jill Sommer Professor, Bloomberg Distinguished Professor, W. Harry Feinstone Department of Molecular Microbiology & Immunology Johns Hopkins Bloomberg School of Public Health

EDITORIAL ACTIVITIES
1994 Journal of Medical and Veterinary Mycology, Guest Section Editor
1995-1997 Journal of Medical and Veterinary Mycology, Associate Editor
1995-2001 International Journal of Infectious Diseases, Editor
1997-2005 Infection and Immunity - Editorial Board
2005-2009 Infection and Immunity, Editor
1997-present Revista Iberoamericana de Micologia, Editorial Board
1996-present Emerging Infections Disease Editorial Board
2000 Section Editor-Host-Pathogen Interactions. Current Opinion in Microbiology
2004-present Expert Opinion on Emerging Drugs, Editorial Board
2005-present BMC Infectious Diseases, Editorial Board
Future Microbiology – Editorial Board
Faculty of 1000 Contributor
2003-present Nature Reviews in Microbiology – Highlights Advisor
2007-present Journal of Experimental Medicine – Editorial Board
2004-2012 Journal of Clinical Investigation – Editorial Board

2012-present Journal of Infectious Diseases Editorial Board
2010-present mBio – Founding Editor and EIC
2013 Section Editor-Host-Pathogen Interactions. Current Opinion in Microbiology

Journal Reviewer (partial list)
Antimicrobial Agents and Chemotherapy
American Journal of Epidemiology
American Journal of Pathology
Canadian Journal of Microbiology
Cell
Cellular Immunology Clinical Microbiology Reviews
Clinical Infectious Diseases
Emerging Infectious Diseases
FEMS Immunology and Medical Microbiology
Fungal Genetics and Biology
Genes and Development
Journal Clinical Investigation
Journal of Experimental Medicine
Journal of Infectious Diseases
Infection and Immunity
Immunity
Journal of Clinical Microbiology
Journal of Molecular Evolution
J. Immunological Methods
Journal of Immunology
Journal of Medical and Veterinary Mycology
J. Neuroimmunology
International Journal of Infectious Diseases
Immunity
Infectious Diseases in Clinical Practice
Lancet
Microbes and Infection
Journal of Molecular Biology
Nature Medicine
Revista Iberoamericana de Micologia
Molecular and Cellular Biology
Laboratory Investigation
Life Sciences
Microbes and Infection
New England Journal of Medicine
J. Dental Res.
Pediatric Infectious Diseases
PNAS
Trends in Microbiology

Advisory Committees, Review Groups/Study Sections
1994 National Cooperative Drug Discovery Group Study Section
1995, 1996 (Member 1996-2000); Chair 1998-2000NIH Bacteriology and Mycology 2 Study Section
1995 NSF Outside Reviewer
1998 Italian AIDS Program outside Reviewer
1996, 1997, 1998, 1999, 2003 Burroughs Wellcome Trust (United Kingdom) Outside Reviewer

1998	VA Merit Review outside Reviewer
1999	AIDS Study Section AAR1 Ad hoc Reviewer
2000	USDA SBIR Ad hoc Reviewer
1999	NIAID Strategic Plan Task Force
2000-15	St. Jude Fellowship for Pediatric Infectious Diseases
2002-07	Burroughs Wellcome Fund Advisory Committee
2001-5	NIH MIDRC (Microbiology and Infectious Diseases Research Committee) Study Section
2002	NIAID Blue Panel on Bioterrorism Research
2002-05	City University of New York Jonas Salk Award reviewer
2002	Ad Hoc Consultant to Board of Scientific Counselors for NCI
2002	Ad Hoc Consultant to Board of Scientific Counselors for NIAID
2003	National Research Council Workshop on Biotechnology and Bioterrorism
2004	Chair, Expert Panel for NIAID Invasive Aspergillosis Animal Models contract
2004	External Advisory Comm. for Pathomics Strategic Initiative, Lawrence Livermoreational Lab
2004	CDC Advisory panel on Anthrax Immune Globulin
2004-06	Scientific Advisory Board for the NIAID Immune Epitope Database contract
2004-07	Abbot Laboratories Award in Clinical and Diagnostic Immunology Selection Committee
2007-10	NIAID Board of Scientific Counselors 2005-2010; Co-Chair
2005-14	National Science Advisory Board for Biosecurity (NSABB)
2005	Chair, NAS Workshop 'NEW DIRECTIONS IN THE STUDY OF ANTIMICROBIAL THERAPEUTICS – IMMUNOMODULATORS
2005	Chair, NHLBI Working group Innate Immunity HIV & HIV-related Lung Infections
2007	Army Basic Research Review
2009	External Reviewer University of Colorado Department of Microbiology 2009
2011	Keystone Symposia SAB (ad hoc) 2009; Member 2010-2013; Cbair Immunology section
2010-16	National Academy Sci Committee on Science Technology and Law
2009-11	National Academy Sci Committee to Review the FBI Investigation of the 2001 Bacillus anthracis Mailings
2010	NIAID Genomics Blue Ribbon Panel
2012	Pioneer Award Review Panel
2012-17	Co-Chair, N IAID Board of Scientific Counselors
2013	Review of Boston University Microbiology Program
2013-17	Scientific Council Institut Pasteur, Paris, France
2014	Co-Chair, Committee on the Future Direction of the NIAID Intramural Research Program
2014	NIH Advisory Council to the Director on long-term planning for the NIH intramural research program
2014	Review of Washington University Department of Microbiology
2014	Advisory Comm to the (NIH) Director Long-Term Intramural Research Program (LT-IRP)
2015	Review of Jefferson University Department of Microbiology
2015-2016	National Academy of Sciences Comm of Federal Regulations and Reporting requirement
2015-present	National Commission Forensic Science Board, Commissioner
2016	External Advisory Committee for the Mount Sinai Department of Microbiology
2016-present	National Academy of Sciences Committee on Dual Use Research of Concern: Options for Limited Communication 2016
2018	Advisory Board Center for Integrity in Forensic Science

HONORS AND AWARDS

Awards, Honors

1979	Stanley Konkol Memorial Award
1979	Chemistry Department Service Award

1979-83	Salk Scholarship
1979-85	Medical Scientist Training Program Fellowship
1989	Montefiore Fellow of the Year Award
1990	Pfizer Postdoctoral Fellowship Award
1992	James S. McDonnell Scholar Award
1996	Burroughs Wellcome Trust Fund Developmental Therapeutics Award
1997-98	Foundation for Microbiology Lectures Program
1999	Elected to the American Society for Clinical Investigation
1999	Melini Award
2001	Leo M. Davidoff Society (for outstanding teaching)
2001	Sam Rosen Award for outstanding teaching in Pre-Clinical Curriculum
2002	Alpha Omega Alpha
2002	Elected to Fellowship in American Academy of Microbiology
2002	Burroughs Wellcome Visiting Professorship to University of Wisconsin
2004	Elected to American Association of Physicians
2005	Solomon A Berson Medical Alumni Achievement Award in Basic Science -NYU Sch. of Med
2006	Elected AAAS Fellow
2006	Maxwell L. Littman Award (mycology award)
2007	Rhoda Benham Award from Medical Mycology Society of America
2007	NIH Merit Award
2008	ASM William Hinton Award (for mentoring scientists from underrepresented groups)
2008	Albert Einstein College of Medicine Faculty Mentoring Award
2010	Elected to the Interurban Club
2014	Commencementt Speech, Albert Einstein College of Medicine graduation
2014	ASM Founders Award Distinguished Service Award
2014	Elected to Institute of Medicine of the National Academy of Sciences
2015	Delta Omega Alpha Chapter

Invited Talks, Panels

NAMED LECTURES

2008 IDSA Kass Lecturer
2009 14th Farness Lecturer, U. Arizona 2009
2010 Marshall S. Horwitz Faculty Achievement Award 2010
2010 Nelson Lecture, Bozeman, Montana
2010 Theobald Smith Lecture at Albany
2010 Arthur White Lecture, U Indiana
2011 Louis Weinstein Lecture, Tufts University
2012 Jessie Boden Lloyd Visiting Professor for 2012 and gave the Jessie Boden Lloyd Lecture in Immunology, Calgary.
2012 ICAAC Lecturer
2012 Jenner Lecture, St Georges Hospital, London
2013 Michael Apicella Lecture, Iowa
2013 NIAID Kinyoun Lecture, Bethesda, MD
2013 Faculty of Science 50th Anniversary Speaker, University of British Columbia, Vancouver CA
2014 Bernard Fields Lecture Scripps, CA
2014 American Association of Immunology Minority Affairs Committee Guest Lecture
2015 McGinnis Memorial Lecture at Duke University, NC
2015 McCollum Colloquium Speaker, Dartmouth (student invited speaker)
2015 Douglas D. McGregor Research Lecture, Cornell University, Ithaca
2016 Naff Lecture, Case Western Reserve, Cleveland
2016 Robert McGhee Distinguished Lecture, University of Arkansas

2016 Medoff Lecture, Washington University Division of Infectious Disease
2016 Karling Lecture, Mycology Society of America
2017 Harry Smith Memorial Lecturer, Birmingham, United Kingdom
2017 Westmere Lecturer, Birmingham, United Kingdom
2017 Brown-Williamson Lecturer, Queens College, The City Univeristy of New York

PUBLICATIONS (813)

1. Baker AD, **Casadevall A**, Gafney HD, Gellender M (1980) Photochemical Reactions of Tris (Oxalato) Iron III. J. Chem. Ed. 57:314-315.

2. Baker AD and **Casadevall A** (1980) A Clock Reaction with Paraquat. J. Chem. Ed. 57:515-516.

3. **Casadevall A**, Day LA (1982) DNA Packing in the Filamentous Viruses fd, xf. Pf1, and Pf3. Nucleic Acids Res. 10:2467-2481.

4**. Casadevall A**, Day LA (1983) Silver and Mercury Probing of Deoxyribonucleic Acid Structures in the Filamentous Viruses fd, If1, IKe, Xf, Pf1, and Pf3. Biochem. 22:4831-4842.

5. Putterman DG, **Casadevall A**, Boyle PD, Yang H-L, Frangione B, Day LA. (1984) Major Coat Protein and Single-Stranded DNA-binding Protein of the Filamentous Virus Pf3. PNAS 81:699-703.

6. **Casadevall A**, Day LA (1985) The Precursor Complex of the Pf3 Bacteriophage. Virology 45:260-272.
7. Day LA, **Casadevall A**, Prescott B, Thomas GJ (1988) Raman Spectroscopy of Mercury (II) Binding to Two Filamentous Viruses: Ff (fd, M13, f1) and Pf1. Biochem. 27:706-711.

8. **Casadevall A**, Day LA (1988) Thermal Differences Circular Dichroism of Pf1 Filamentous Virus and Effects of Mercury (II) Siver (I), and Copper (II). Biochem. 27:3599-3602.

9. Day LA, Marzec CJ, Reisberg SA, **Casadevall A.** (1988) DNA Packing in Filamentous Bacteriophages. Ann. Rev. Biophys. Biophysical Chem. 17:509-539.

10. **Casadevall A**, Pirofski L, Catalano MT (1990) Primary Group A Streptococcal Peritonitis in Adults. Am. J. Med. 88:5-63N-64N.

11. Pirofski L, **Casadevall A**. (1990) Mixed Staphylococcal and Cryptococcal Epidural abscess in a patient with AIDS. Rev. Infect. Dis. 12:964-965.

12. Pirofski L, **Casadevall A**, Rodriquez L, Zuckier L, Scharff MD (1991) Current State of the Hybridoma Technology. J. Clin. Immunol., 10, No. 6 (November Supplement), 5S-14S.

13. **Casadevall A**, Scharff MD (1991) The Mouse Antibody Response to Infection with *Cryptococcus neoformans*: V_H and V_L Usage in Polysaccharide Binding Antibodies. J. Exp. Med. 174:151-160.

14. Pettoello-Mantovani M, **Casadevall A**, Kollmann TR, Rubinstein A, Goldstein H. (1992) Enhancement of HIV-1 Infection by the Capsular Polysaccharide of *Cryptococcus neoformans*. Lancet 339:21-23.

15. **Casadevall A**, Mukherjee J, Devi S, Schneerson R, Robbins J, Scharff, M.D. (1992) Antibodies elicited by a *Cryptococcus neoformans* -tetanus toxoid conjugate vaccine have the same specificity as those elicited in infection. J. Infect. Dis. 165:1086-93.
16. **Casadevall A**, Dobroszycki J, Small C, Pirofski, L. (1992) *Haemophilus Influenzae* Type b Bacteremia in Adults with AIDS and at Risk for AIDS. Am. J. Med. 92:587-590.

17. **Casadevall A**, Freundlich LF, Pirofski L. (1992) Septic shock from *Pseudomonas paucimobilis*. Clin. Infect. Dis. 14:784.

18. **Casadevall A**, Freundlich L, Marsh L, Scharff MD. (1992) Extensive Allelic Variation in *Cryptococcus neoformans*. J. Clin. Microbiol. 30:1080-1084.

19**. Casadevall A**, Mukherjee J, Scharff MD. (1992). Monoclonal antibody based ELISAs for Cryptococcal polysaccharide. J. Immunol. Methods. 154:27-35.

20. Mukherjee J, Scharff MD, **Casadevall A** (1992). Protective murine monoclonal antibodies to *Cryptococcus neoformans*. Infection and Immunity 60:4534-4541.

21. Mukherjee J, **Casadevall A**, Scharff, MD (1993) Molecular characterization of the humoral responses to *Cryptococcus neoformans* infection and glucuronoxylomannan-tetanus toxoid conjugate immunization. J. Exp. Med. 177:1105-1116.

22**. Casadevall A**, Fan M. (1992) The *URA5* gene of *Cryptococcus neoformans* var. *gattii*: Evidence for a close phylogenetic relationship between *C. neoformans* var. *gattii* and *C. neoformans* var. *neoformans*. J. Gen. Appl. Microbiol. 38:491-495.

23. Spitzer, ED, Spitzer S, Freundlich L, **Casadevall A.** (1993) Persistence of initial infection in recurrent *Cryptococcus neoformans* meningitis. Lancet 341:595-596.

24. **Casadevall A**, Dobroszycki J Small C, Pirofski, L. (1993) Bacteremic *H. influenzae* type b infection and HIV. Am. J. Med. 95:119.

25. Mukherjee J, Pirofski L, Scharff MD**, Casadevall A**. (1993) Antibody mediated protection in mice with lethal intracerebral *Cryptococcus neoformans* infection. PNAS 90:3636-3640.

26**. Casadevall A**, Spitzer ED, Webb D, Rinaldi MG (1993) Susceptibilities of serial *Cryptococcus neoformans* isolates from patients with recurrent cryptococcal meningitis to Amphotericin B and fluconazole. Antimicrobial.Agents.Chemotherapy 37:1383-1386.

27. Mukherjee J, **Casadevall A**, Scharff MD (1993) Mu switch region deletion is associated with both T cell independent and T cell dependent responses. Molecular Immunology 30:1049-1055.

28. Currie BP, Freundlich LF, Soto MA, **Casadevall A** (1993) False negative cerebrospinal fluid cryptococcal latex agglutination tests for patients with culture positive cryptococcal meningitis. J. Clin. Microbiol. 31:2519-2522.

29**. Casadevall A** (1993) Cryptococcosis: The case for immunotherapy. CliniGuide to Fungal Infections 4:1-5.

30**. Casadevall A** (1993) *Cryptococcus neoformans*: Ecology and Pathogenesis. CliniGuide to Fungal Infections 4:1-5.

31. Mantovani MP**, Casadevall A**, Goldstin H, (1993) The Presence of Cryptococcal Capsular Polysaccharide Increases the Sensitivity of HIV-1 Coculture in Children. Annals New York Academy of Sciences 693:281-283.

32. Mukherjee S, Lee S, Mukherjee J, Scharff, MD, **Casadevall A** (1994). Monoclonal antibodies to *Cryptococcus neoformans* capsular polysaccharide modify the course of intravenous infection in mice. Infect. Immun. 62:1079-1088.

33. Mukherjee J, Zuckier, L, Scharff, MD, and **Casadevall A** (1994). Therapeutic efficacy of monoclonal antibodies to *Cryptococcus neoformans* Glucuaonoxylomannan alone and in combination with amphotericin B. Antimicrob. Agents Chemotherap. 38:580-587.

34. Currie BP, Freundlich LF, **Casadevall A** (1994) Restriction fragment length polymorphism analysis of Cryptococcus *neoformans* isolates from environmental (pigeon excreta) and clinical sources in New Yor*k* City. J. Clin. Microbiol. 32:1188-1192.

35. Fan M, Currie BP, Guttell R, Ragan M**, Casadevall A** (1994). The 16S-like, 5.8S, and 23-S-like rRNAs of the two varieties of *Cryptococcus neoformans*: sequence, secondary structure, and phylogenetic analysis and restriction fragment polymorphisms. J. Med. Vet. Mycology 32:163-180.

36. **Casadevall A**, Scharff, M.D. (1994). Serum Therapy Revisited: Animal models of infection and the development of passive antibody therapy. Antimicrob. Agents Chemotherap. 38:1695-1702.

37. Lee SC, Dickson DW, Brosnan CF, **Casadevall A** (1994) Human astrocytes inhibit *Cryptococcus neoformans* by a nitric oxide-mediated mechanism. J. Exp. Med. 180:365-369.

38. Wang Y**, Casadevall A** (1994) Susceptibility of melanized and non-melanized *Cryptococcus neoformans* to nitrogen and oxygen-derived oxidants. Infect. Immun. 62:3004-3007.

39. **Casadevall A**, DeShaw M, Fan M, Dromer F, Kozel TR, Pirofski L. Molecular and idiotypic analysis of antibodies to *Cryptococcal neoformans* Glucuronoxylocannan. Infect. Immun. 62:3864-3872.

40. Zebedee SL, Koduri RJ, Mukherjee J, Mukherjee S, Lee S, Sauer DF, Scharff MD, **Casadevall A** (1994) Mouse-Human chimeric Immunoglobulain G1 Chimeric antibodies with activities against *Cryptococcus neoformans*. Antimicrob. Agents Chemotherap. 38:1507-1514.

41. Ghannoum MA, Spellberg BJ, Ibrahim AS, Ritchie JA, Currie BP, Spitzer E, Edwards J, **Casadevall A** (1994) Sterol composition of *Cryptococcus neoformans* in the presence and absence of fluconazole. Antimicrob. Agents Chemotherap. 38:2029-2033.

42. Currie BP, **Casadevall A** (1994) Estimation of the prevalence of *Cryptococcus neoformans* infections among patients infected with the Human Immunodeficiency Virus in New York City. Clin. Infect. Dis. 19:1029-1033.

43. Pettoello-Mantovani M, **Casadevall A**, Goldstein H. (1994) Enhancement of HIV-1 Infectivity *in Vitro* by Capsular Polysaccharide of *Cryptococcus neoformans* and *Haemophilus influenzae.* AIDS Research and Human Retroviruses 10:1079-1087.

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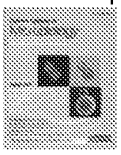
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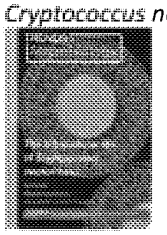
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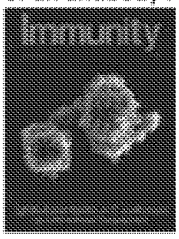
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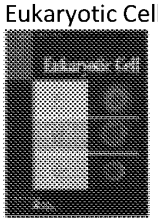
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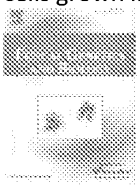
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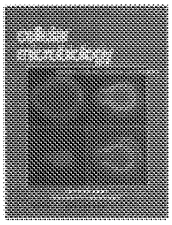
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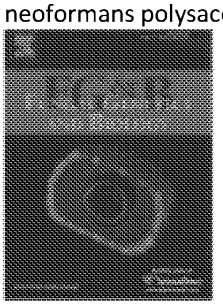
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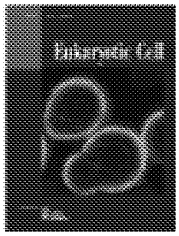
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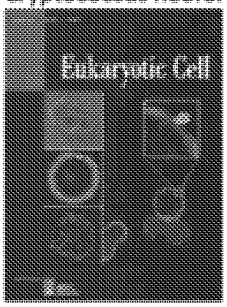
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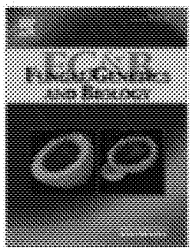
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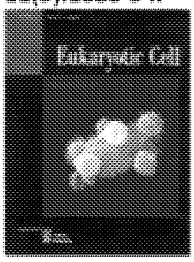
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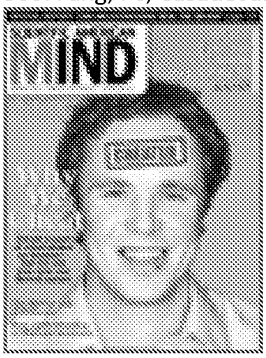
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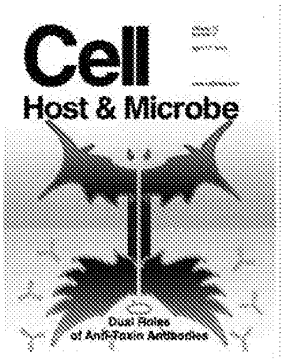
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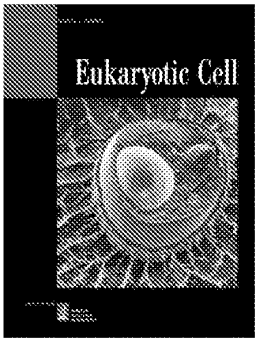
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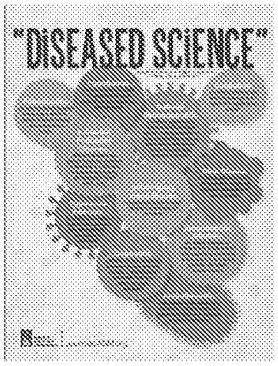
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US Patent 8,586,090 E. Dadachova and A. Casadevall Melanin nanoshells for protection against radiation and electronic pulses.

Applications pending
J. Achkar, A. Casadevall, R. Rosales and A. Ziegenbalg Serologic test for the rapid diagnosis of tuberculosis.
E. Dadachova, A. Casadevall, H. Strickler and R.D. Burk Radioimmunotherapy and imaging of tumor cells that express viral antigens.
E. Dadachova, A. Casadevall, M.A. Sesay, H. Damania, P.E. Smariga Radiolabeled monoclonal antibodies, methods of preparation using TCEP and uses thereof.
E. Dadachova, A. Casadevall, M.A. Sesay, H. Damania, P.E. Smariga Disposable column system for purification of radiolabeled antibodies.
E. Dadachova and A. Casadevall Methods for increasing efficacy of radioimmuno-therapy of melanoma.
JM Friedman, AJ Friedman, G. Han, MS Navati, KP Davies, MT Tar, AA Alfieri, A Casadevall, E Dadachova, HC Eisenman, Jasmin and D Spray Versatile nanoparticulate biomaterial for controlled delivery and/or containment of therapeutic and diagnostic material.
E. Dadachova, C. Gravekamp, A. Casadevall. Radiobacteria for therapy of cancer.
E. Dadachova and A. Casadevall. Oral administration of melanin for protection against radiation.

TEACHING

Mentoring
Advisees (predoctoral PhD advisor)

1996	Yulin Wang	Ph.D.
1997	Sarah Franzot	Ph.D.
1998	Lin Chen	Ph.D.

1999	Wendy Cleare	Ph.D.
1999	Nikoletta Lendvai	Ph.D.
2000	Neely Mozaffarian	Ph.D.
2000	Angel Rosas	Ph.D.
2002	Johanna Rivera	Ph.D.
2002	Reid Schwebach	Ph.D.
2003	Judith Steenbergen	Ph.D.
2004	Javier Garcia-Rivera	Ph.D.
2006	Marcela Torres	Ph.D.
2006	Luis Martinez	Ph.D.
2007	Yong Luo	Ph.D.
2008	Mauricio Alvarez	Ph.D.
2009	Magdia DeJesus	Ph.D.
2009	Carolyn Saylor	Ph.D.
2010	Cara Chrisman	Ph.D.
2011	Patricia Andrade	Ph.D.
2011	Andres Nicola	Ph.D. (University of Brasilia)
2012	Radames Cordero	Ph.D.
2012	Alena Janda	Ph.D.
2013	Jacky Chow	Ph.D.
2013	Carolina Coelho	Ph.D. (University of Coimbra)
2014	Sabriya Stukes	Ph.D.
2015	Lisa Brown	Ph.D.
2016	Anthony Bowen	Ph.D.
2017	Carlos de Leon Rodriguez	Ph.D.
2017	Eric Jung	Ph.D.
2018	Joudeh Freiji	M.D.

Postdoctoral Fellows (Name, Years, Current Position)

Brian Currie, M.D., M.P.H. 1992-1993 Assist. Dean, Clinical Research, Montefiore Med. Center; Professor, Dept. Med., Dept. Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY

Sushovita Mukherjee, M.D. 1992-1996 Not Available

Jean Mukherjee, D.V.M., Ph.D. 1996-1997 Assist. Prof., Dept. Biomed. Sci. (Infectious Diseases), Cummings Sch. Vet Med., Tufts University, North Grafton, MA

Aharona Freedman, M.D. 1993-1998 Assist. Clinical Prof., Dept. Pediatrics (Infectious Diseases), Albert Einstein College of Medicine, Bronx, NY

Joshua Nosanchuk, M.D. 1996-1998 Prof., Dept. Med. (Infectious Diseases), Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Bettina Fries, M.D. 1997-1999 Prof., Dept. Med. (Infectious Diseases), Stony Brook University, NY

Marta Feldmesser, M.D. 1994-2001 Assoc. Prof., Dept. Med. (Infectious Diseases), Dept. Obstetrics & Gynecology and Women's Health, Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Carlos Taborda, Ph.D. 1999-2002 Assoc. Prof., Dept Microbio., Institute Biomed. Sci., University of Sao Paulo, Sao Paulo, Brazil

David Goldman, M.D. 1996-2003 Assoc. Prof., Dept. Med. (Infectious Diseases), Dept. Pediatrics, Dept. Microbio. & Immuno., Albert Einstein College of Medicine, Bronx, NY

Stephanie Tucker, Ph.D. 1999-2003 Not Available

Oscar Zaragoza, Ph.D. 2001-2006 Principal Investigator, Dept. Microbio., Instituto de Salud Carlos III, Marid, Spain

Diane McFadden, Ph.D. 1999-2006 Assoc. Director, Northeast Biodefense Center, Columbia University, New York, NY
Marcela Torres, Ph.D. 2006-2007 Scientist, Regeneron Pharmaceuticals Inc., Tarrytown, NY
Helene Eisenman, Ph.D. 2003-2008 Assist. Prof., Dept. Microbio., Baruch College, New York, NY
Erin McClelland, Ph.D. 2003-2008 Assist. Prof., Dept. Basic Sci. (Microbio. & Immuno.), The Commonwealth Medical College, Scranton, PA
Susana Frases-Carvajal, Ph.D. 2004-2009 Scientist, Biotech. Lab., National Institute of Metroloy, Rio de Janeiro, Brazil
Yong Luo, M.D., Ph.D. 2007-2009 Residency, Long Island Jewish Medical Center, New Hyde Park, NY
Aviva Diamond, Ph.D. 2009-2010 Post-doc with Ian Willis, Albert Einstein College of Medicine, Bronx, NY
Emma Robertson, Ph.D. 2008-2011 Post-doc with Kirsten Nielsen, University of Minnesota, Minneapolis, MN
Andre Nicola, M.D., Ph.D. 2006-2011 Prof. and Researcher, Graduate Program in Genomic Sciences and Biotechnology, Catholic University of Brasilia, Brazil
Nareen Abboud, Ph.D. 2009-2011 Research Program Manager, Montefiore Medical Center, Bronx, NY
Monica Garcia-Solache, M.D., Ph.D. Postdoctoral fellow with Louis Rice, Brown University.
Rafael Prados, Ph.D. 2009-2014 Assist. Prof., Albert Einstein College of Medicine, New York, NY
Mary Pohl, Ph.D. 2011-2014 Senior Scientisit, Oncobiologics, Inc.
Julie Wolf, Ph.D. 2010-2015 ASM, Washington, DC
Radames Cordero, Ph.D. 2015-2017, Research Associate, Johns Hopkins University
Coelho, Carolina, Ph.D. 2015-2018, MRC Centre for Medical Mycology, University of Exeter
Maggie Wear, Ph.D. 2016-2019, Assistant Scientist, Johns Hopkins University

Awards for junior scientists in Dr. Casadevall laboratory

1995-2000	David Goldman MD	NIH Physician Scientist Award
1996-99	Rona Freedman MD	Aaron Diamond Scholarship
1999-2004	Rona Freedman MD	NIH Physician Scientist KO8 Award
1993	Wendy Cleare	American Heart Minority Scholarship
1994	Wendy Cleare	NIH Minority Award Supplement
1996-2001	Marta Feldmesser MD	NIH Physician Scientist KO8 Award
1995-97	Sarah Piancastelli Franzot (PhD student)	Fulbright Scholarship
1997-99	Joshua Nosanchuk MD	Mycology IDSA Award
1997-2002	Joshua Nosanchuk MD	NIH Physician Scientist KO8 Award
	Johanna Rivera	NIH Marc Graduate Student Fellowship.
1998-2000	Bettina Fries MD	Mycology IDSA Award (Declined due overlap)
1998-2001	Bettina Fries MD	Howard Hughes Postdoctoral Award
	Bettina Fries MD	NIH Physician Scientist KO8 Award
2001-03	Dianne McFadden PhD	Life Sciences Postdoctoral Fellowship Award
	Dianne McFadden PhD	NIH F32 Postdoctoral Award (Declined due to overlap)
	Javier Garcia	NIH Marc Graduate Student Fellowship
	Helene Eisenman PhD	NIH F32 Postdoctoral Award
	Erin McClelland PhD	Revson Fellowship
2007-12	Jacqueline Achkar MD	NIH K23 Award

Thesis committees

I have participated in dozens of PhD committees and defenses but did not keep track of these

Training grant participation

9/1/97-5/31/13 Molecular Pathogenesis of Infectious Diseases 5T32AI007506-09
NIH/NIADD
PI: Casadevall

Until 06 (training faculty) after 06 (PI)

9/1/94-6/30/21 The Molecular and Cellular Basis of Infectious Diseases (MCBID) Program
2T32AI007417-21A1
NIH/NIADD
PI: Casadevall

Teaching

Course Leader for **GRADUATE MICROBIAL PATHOGENESIS**; 6 credit graduate school course at the Albert Einstein College of Medicine Sue Golding Graduate Division which teaches the fundamentals of microbial pathogenesis. 1996 and 1999.

2000-present	Lecturer in Graduate Pathology Course - Albert Einstein College of Medicine
	Lecturer in Graduate Critical Reading Course- Albert Einstein College of Medicine
2001-present	Lecturer in Immunology Medical School Module - Albert Einstein College of Medicine
2000-2014	Lecturer in Graduate Immunology Course - Albert Einstein College of Medicine
2000-14	Lecturer in Infectious Disease Course - Albert Einstein College of Medicine
1999	Lecturer at Rockefeller Microbial Pathogenesis course
2000-14	Lecturer at NYU Microbial Pathogenesis course
2013-present	Lecturer at Columbia Ethics Course
2015	Lecturer in IBS course, Johns Hopkins Sch of Public Health
2015	Lecturer in Graduate Immunology Course, Johns Hopkins Sch of Public Health
2015	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2016	Lecturer in Graduate Immunology Course, Johns Hopkins Sch of Public Health
2016	Lecturer in Public Health Biology Course, Johns Hopkins Sch of Public Health
2016	Lecturer in Biomedical Sciences, Johns Hopkins Sch of Public Health
2017	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2017	Lecturer in Bacterial Pathogenesis course, Johns Hopkins Sch of Public Health
2017	Lecturer in Responsible Conduct of Research course, Columbia University
2017	Lecturer in Biophysics course, Johns Hopkins University
2017	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health
2017	Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2017	Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2017	Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2017	Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2017	Lecturer in Pediatric Ground Rounds, Johns Hopkins Sch of Medicine
2017	Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health
2018	Lecturer in Biology of Parasitism, Johns Hopkins Sch of Public Health
2018	Lecturer in Bacterial Pathogenesis course, Johns Hopkins Sch of Public Health
2018	Lecturer in Responsible Conduct of Research course, Columbia University
2018	Lecturer in Biophysics course, Johns Hopkins University
2018	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health
2018	Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2018	Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2018	Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2018	Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2018	Lecturer in Parasitology, Johns Hopkins Sch of Public HEalth
2018	Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health
2019	Lecturer in R3 Course, Johns Hopkins Sch of Public Health
2019	Lecturer in Responsible Conduct of Research course, Columbia University
2019	Lecturer in Biophysics course, Johns Hopkins University
2019	Lecturer in Current Issues in Public Health, Johns Hopkins Sch of Public Health

2019 Lecturer in Evolution of Infectious Diseases, Johns Hopkins Sch of Public Health
2019 Lecturer in Graduate Immunology, Johns Hopkins Sch of Public Health
2019 Lecturer in Introduction to the Biomedical Sciences, Johns Hopkins Sch of Public Health
2019 Lecturer in Pathobiology of Disease, Johns Hopkins Sch of Medicine
2019 Lecturer in Parasitology, Johns Hopkins Sch of Public HEalth
2018 Lecturer in Public Health Biology, Johns Hopkins Sch of Public Health

PART II
RESEARCH GRANT PARTICIPATION

Current Grants:

Period of Performance: 04/01/2015–01/31/2020
Title of Grant: Biology of Fungal Melanin
Grant Number: 5 R01 AI052733-13
Sponsoring Agency: NIH/NIAID
Direct Costs/yr: $131,898
PD/PI: Casadevall
Objective: The specific aims of this grant are to establish the mechanism by which melanin promotes the virulence of *C. neoformans in vivo*, to establish the protective efficacy of antibody to *Cryptococcus neoformans* melanin and laccase and the mechanism of antibody action, to investigate the molecular events of *C. neoformans* melanin biosynthesis.

Period of Performance: 08/01/2015–05/31/2020 (NCE)
Title of Grant: Synergy of Host Defense Mechanisms in the Lung
Grant Number: 5 R01 HL059842-17
Sponsoring Agency: NIH/NHLBI
Direct Costs/yr: $250,000
PD/PI: Casadevall
Objective:The goal of this project is to establish the relationship between macrophage damage and CN non-lytic exocytosis, to establish the mechanism by which host annexins contribute to CN non-lytic exocytosis, and to identify the fungal components that facilitates non-lytic exocytosis.

Period of Performance: 11/01/2016 – 10/31/2021
Title of Grant: Host inositol regulation of AIDS-Associated Cryptococcus brain infection
Grant Number: R01 AI123315
Sponsoring Agency: NIH
Direct Costs/yr: $60,000
PD/PI: Xue
Objective: Performing detailed GXM analysis using physical chemistry approaches, including using monoclonal antibody and light scattering; detection and isolation of different polysaccharide fractions under conditions with different carbon sources (inositol or glucose) for their role in BBB crossing in vitro; and potential development of protective antibody for inositol transporters.

ACADEMIC SERVICE

Institutional Administrative Appointments

1995-7 Member, Graduate Committee, Albert Einstein College of Medicine
1998-9 Member, Assistant Professor Promotion Committee, Albert Einstein College of Medicine
2005-6 Member, Search committee Dean, Albert Einstein College of Medicine
2012-3 Member, Search Committee Chair of Pediatrics, Albert Einstein College of Medicine
2013-4 Member, Search committee Chair of Medicine, Albert Einstein College of Medicine

2015 Member, Search Committee for Bloomberg Distinguished Professor, Johns Hopkins Sch Med
2015 Member, Committee Department of Biochemistry & Molecular Biology review site visit
2015 Member, Committee Sidney Kimmel Medical College of Thomas Jefferson University, Department of Microbiology & Immunology External Review

PRESENTATIONS

INVITED PRESENTATIONS (Partial List)

1992 Grand Rounds. Downstate Department of Medicine
Grand Rounds. New York University Department of Medicine
Dept of Pathology. Stony Brook University

1993 2nd International Conference on Cryptococcus and Cryptococcosis Milan, Italy

1994 Dept of Med. Grand Rounds. Newark School of Medicine
Systemic antifungals: discovery, development and applied therapeutics. New York City
Dept of Medicine. Mount Sinai School of Medicine
Dept of Medicine. Memorial Sloan-Kettering Hospital
Medical Mycology Society of the Americas, Las Vegas Meeting
New York University. Update on Fungal Infections Symposia, NY
Dept of Rheumatology. New York University, NY
Infectious Disease Society of America, Orlando, FL
International Congress of Mycology-Vancouver, Canada
2nd NIAID Workshop on Medical Mycology, Flagstaff, Az.
Dept of Medicine. Boston University.

1995 Dept of Structural Biology. Public Health Res. Institute, NYC
Dept of Medicine. Torrance-UCLA Med. Ctr., Los Angeles, CA
Dept of Medicine. Cincinnati School of Medicine. Cincinnati, OH
Dept of Microbiology. Georgetown School of Med., Georgetown, MD
Div. of Infectious Diseases. Memorial Sloan-Kettering Hospital, NYC
3rd NIAID Workshop on Medical Mycology. Big Ski, Montana
International Workshop on Molecular Pathogenesis of Fungal Infections. Wurzburg, Germany
Infectious Diseases, Duke University, Durham, NC
Dept of Chemistry, Queens College, CUNY

1996 Medical Mycology Society of the Americas, New Orleans
3rd International Conference on Cryptococcus and Cryptococcosis, Paris, France
Spanish Mycology Association, Valencia, Spain
Cuban Medical Convention, Miami Beach, Fla.
Dept of Biology, Hunter College, CUNY
ESATYBC Conference, Catskills, NY
Hunter College, NYC
NIH Workshop on The role of humoral immunity in the treatment and prevention of Infectious Diseases Washington, DC
Dept of Microbiology. Medical College of Ohio, Toledo
Merck Pharmaceuticals, Rahway, NJ
Medical Mycology Society of New York Lecture

1997	13th Congress of the International Society of Human and Medical Mycology, Parma Italy. Convener of symposium titled: Cell-mediated versus antibody mediated-protection mechanisms in fungal diseases: an ongoing dilemma.
	American Society of Microbiology General Meeting Symposium, Miami, Fla.
	FASEB conference, Colorado
	New York Academy of Sciences Lecture
	Rockefeller University
	IDSA Symposium on new therapeutic strategies for fungal infections
	Department of Microbiology, Oklahoma Health Sciences Center
	Mount Sinai School of Medicine-Molecular Medicine Seminar Series
	Woods Hole Mycology Course Lecturer
	NIAID Workshop: Bridging the gap for Underrepresented Minority Research Scientists
1998	Wistar Institute
	Grand Rounds Beth Israel Hospital
	Department of Microbiology, Medical College of Ohio
	Division of Infectious Diseases, Columbia University
	Society for Industrial Microbiology Annual Meeting, Denver, Co
	Department of Health, State of New York, Albany, NY
	Department of Microbiology, Stony Brook University, NY
	Anderson Lecture, Charlottesville, Va
	Woods Hole Mycology Course Lecturer
1999	ASM Division F Divisional Lecture
	Cold Spring Harbor Symposium on Microbial Pathogenesis and Host Response.
	1999 Joint Committee Meeting of the US-Japan Cooperative Medical Science Program
	Nelson Lecture at the University of Montana in Bozeman
	Santa Fe symposia on Defense of the Brain
	International Meeting on Tuberculosis, Stockholm, Sweden
	ASM Symposium Millennial Challenges to Vaccines
	Trudeau Institute
	NHLBI Symposium on Pulmonary Immunobiology and Inflamation, NIH
	U.S.-Japan Cooperative Science Program Joint Committee, Bethesda, MD
	Woods Hole Mycology Course Lecture
	NIAID Workshop: Bridging the gap for underrepresented Minority Research Scientists
2000	Boston University
	14th Congress of the International Society of Human and Medical Mycology, Buenos Aires, Argentina. Convener of symposium titled: Vaccines and Preventive Antibodies; Also speaker on symposium on Fungal Morphogenesis and Virulence
	1st Japanese Mycology Forum, Tokyo, Japan, Keynote Speaker
	Foundation Lecture British Mycology Society Meeting, Stratford-upon-Avon, England
	Gordon Conference on Fungal Pathogenesis
	New York University - Division of Infectious Diseases
	40th ICAAC. Toronto. Vaccines for the 21st Century: New disease Targets on Horizon.
	Ritterson Memorial Lecture, University of Rochester Medical Center
	Genome Therapeutics Corporation, Waltham, MA
	Immunology for nonviral infections, Trudeau Institute, Saranac Lake
	Yale University

2001	ASM Symposium Host defense against fungi: application toward therapeutics and vaccine development, Orlando, FL New York Medical College (Division of Infectious Disease) University of Minnesota (Department of Microbiology) Elli Lilly, Indianapolis, IN CSH Symposium on Microbial Pathogenesis and Host Response 22nd International Conference Chemotherapy (Amsterdam) Fungal Therapy, NJ Medical School Symposium Dept of Microbiology, University of Pennsylvania National Institute of Health Department of Microbiology, Charleston Newark School of Medicine
2002	Keystone Symposia on Molecular and Cellular Biology 5th Conference on Cryptococcus and Cryptococcosis, Adelaide Australia Gordon Conference on Fungal Pathogenesis IUMS Symposium, Paris ASM Symposium New Concepts in Physiology and Biochemistry of Pathogenic Fungi Salt Lake City, UT Woods Hole Mycology Course Lecture Dept of Microbiology, University of Michigan Dept of Microbiology, University of Wisconsin Dept of Microbiology, University of Louisiana Division of Infectious Diseases, Albany 2nd Conference on Vaccines, Instituto Superiore di Sanita, Rome Division of Infectious Diseases, Columbia University
2003	Dept of Genetic Medicine, Cornell University Dept of Immunology and Virology, U. Mass Medical School 9th Congress of the European Confederation of Medical Mycology, Amsterdam, Netherlands 15th Congress of the International Society of Human and Animal Mycology Duke University Medical School Participant, Banbury Conference. Toward a More Unified Understanding of Infectious Disease CSH Symposium on Microbial Pathogenesis and Host Response 15th Congress of the International Society of Human and Medical Mycology, San Antonio. Convener of symposium titled: Protective Antibodies; Also speaker on symposium on Fungal Morphogenesis and Virulence Keynote Speaker, Mount Sinai Medical Resident Forum NABI Pharmaceuticals, Rockville, MD South Dakota Health Research Foundation ACS Glycobiology Symposium, ACS Meeting, New York. Washington University School of Medicine Miami University, Oxford Ohio New York University Division of Infectious Diseases Grand Rounds Memorial Sloan Kettering
2004	Immune Compromised Host Society - Grenada, Spain Keystone Symposia on Bioterrorism and Emerging Infectious Diseases, Keystone, CO.

Mathematical Biosciences Inst. 'Disease Models of Host-Pathogen Interactions' Columbus OH
Public Health Research Institute, Newark, NJ
ASM Meeting Symposium: 'Immune Mechanisms in Polymicrobial Infections', New Orleans
Keynote Speaker, Candida Meeting, Austin. TX
11th International Congress of Infectious Diseases, Cancun, Mexico
Mycology Unit, Pasteur Institute
Coexistence and Collisions at the Host/Microbe Interface, Burroughs Wellcome Fund, Miami, Fl.
American Phytopathological Society Mycology Committee, Anaheim, CA
New York University – Department of Microbiology
FASEB Summer Research Conference on Polysaccharides, Tucson, AZ
University of Iowa – Division of Infectious Diseases
University of Gainesville, FL -- Department of Oral Biology
Wyeth Vaccine Division, Pearl River, NY
University of Colorado Health Science Center – Dept of Microbiology
Biodefense Regional Center of Excellence meeting in Bethesda, MD
Environmental Protection Agency workshop on Virulence Factor-Activity Relationships
American Society of Tropical Medicine and Hygiene
5th Louis Pasteur Conference on Infectious Diseases, Pasteur Institute

2005 Plenary Session, Mycology Division of IUMS, San Francisco
La Jolla Institute of Allergy and Immunology
Scripps Institute
Keynote Speaker – 6th International Conference on Cryptococcus and Cryptococcosis
Focus on Fungal Infections 15, Miami, FL
ASM Biodefense Workshop
ASM Meeting Symposium, Atlanta, GA
IUMS Meeting, San Francisco
CDC Distinguished Lecturer
Koch Centennial Postulates Workshop, Berlin
Keynote Speaker, University of Michigan Public Health Retreat
New York Hospital in Queens
Maimonides Hospital
NIH, Biodefense Clinical Research Branch
FDA, Immunology Section
JASON General Meeting, San Diego
Monoclonal Antibody Meeting, Rome, Italy
Eastern Pennsylvania Branch of the American Society for Microbiology
Thaler Lecture, Aeras Global TB Vaccine Foundation
Koch's postulate - Centennial Workshop
University of Kansas, Department of Microbiology
New York Academy of Sciences
NIAID scientists from the Division of AIDS (DAIDS)

2006 Biodefense clinical research workshop (poxvirus meeting) Bethesda, MD
ASM 2006 Biodefense meeting. Panel Discussion
Grand Rounds, University of Virginia
Department of Microbiology, Drexel University
ASM 2006 Candida Meeting

	International Conference on Emerging Infectious Disease, Atlanta
	International Society for Human and Animal Mycoses, Paris
	Maxwell L. Littman Award Lecture – New York Society for Medical Mycology
	ASM General Meeting in Orlando, FL
	B cell workshop Trudeau Institute
	New York Medical College
	Maxwell L. Littman Award Lecture – New York Society for Medical Mycology
2007	University of Texas Southwestern Medical School
	University of Connecticut
	Keynote speaker, XIII Fungal Genetics Conference
	Berkeley U
	University of California San Francisco
	University of Illinois – Urbana Champaign
	ASM General Meeting Toronto Canada
	Princeton U - Program on Science and Global Security's Carnegie Biodefense Seminar
	Keynote Speaker Second FEBS Advanced Lecture Course Human Pathogens
	U. Louisville Distinguished Speaker Lecture
	Harold C. Neu Conference (Chicago)
	University of Wisconsin – Graduate Student Invited Speaker
	University of Alabama
	Keynote Speaker Merck Retreat
	APUA Congress - Boston
2008	IDSA Kass Lecture
	U Mass Worcester
	ISDA/ICAAC
	Schimelbureau Amsterdam
	Gordon Conference
	EPA conference on emerging threats
	Brooklyn College Dept Biology Keynote Retreat Speaker
	St. Louis University
	VA ASM Branch Lectureship speaker
	NIAID Biodefense Network Meeting
	University of Minnesota
2009	Aztra Zeneca, MA, Waltham
	University of Buffalo
	Rio Grande ASM Branch Keynote speaker
	UAB Program in Immunology
	Puerto Rico ASM Branch Keynote Speaker
	Critical Path for ID Therapeutics Targeting Host NIAID/DMID/OBRA Workshop
	Forum on Microbial Threats (IOM)
	Rinat-Pfizer, SF
	IOM Committee on Science, Technology and Law
	Semmering Vaccine Symposium, Vienna
	University of Wurzburg symposium on Living with Pathogens
	University of Pittsburg
	Merck
	Medical Mycology Society of New York
	Novartis

Tufts University
Wadsworth Center
Intermountain ASM Branch Keynote Speaker
Southeastern ASM Branch Keynote Speaker
Florida ASM Branch Keynote Speaker
Hawaii Branch ASM Keynote Speaker
Farness Lecture, Tucson, AZ
Duke University, Dept of Genetics

2010 Keynote Speaker, First International Conference on Model Hosts, Crete Greece
Keynote Speaker European Fungal Genetics Conference, Amsterdam, Netherlands
Distinguished Faculty Seminar in Infectious Diseases, Medical College of Wisconsin
Association of Medical School Microbiology and Immunology Chairs
Forum on Microbial Threats (IOM)
Vienna Biocenter, Vienna, Austria.
Columbia University Dept of Microbiology and Immunology
Mount Sinai Dept of Infectious Diseases
8th World Congress on Trauma, Shock, Inflammation and Sepsis, Munich, Germany
ASM General Meeting, San Diego
ICCAC, Boston
IDSA, Vancouver
Ann Arbor, MI
University of Rio de Janeiro
IOM Forum on Fungal diseases
2010 Nelson Lecture, Bozeman, Montana
2010 Theobald Smith Lecture at Albany
2010 Arthur White Lecture, U Indiana

2011 Scripps Institute, La Jolla
Stanford University
Naval Research Laboratory, Washington DC
GRC Immunology of Fungal Infections (Galveston)
Mark Wilson Conference, San Juan
Keystone Symposia on Lung Immunity
University of Pennsylvania, Philadelphia
Keynote Speaker, Annual Pew Scholars Meeting, Cozumel
Keynote Speaker, GRC on Chemical and Bioterrorism Threats
Department of Microbiology and Immunology, Loyola University
Inter Urban Clinical Club
National Biodefense RCE Meeting, Denver
Cryptococcus and cryptococcosis meeting
Weinstein Lecture, Tufts
Keynote Speaker, Brazilian Microbiology Society
Keynote Speaker, Australian Microbiology Society
Bacterial Toxins Meeting, Oslo Norway
Brown University
Massachusetts General Hospital
Merck Vaccine Symposium (Toronto)
ICAAC Boston
Brown University
University of North Carolina

National Plant Diagnostic Network
Harvard University

2012 Bard College
Keystone meeting on Fungal pathogenesis and drug discovery, Santa Fe
University of Calgary
University of Tennesse
University of Puerto Rico
Pasteur Institute
2012 Pugwash Conference
Symposium on fungal pathogenesis, Oviedo, Spain
ICAAC Lecture 2012
Translational Sciecne 2012 Meeting, Washington DC
University of Arkansas
International Conference of Emerging Infectious Diseases (Emerging Fungal Diseases) Atlanta
Keynote speaker, 8th National Symposium on Recent Advances in Carborhydrate Sci. Banff, Alberta
Vanderbilt University
Duke Mycology Symposium
NYAS Symposium 'Discovering antibacterial and anticancer therapeutics in unexpected places'
Keynote speaker – Tularemia meeting, Breckenridge CO
Keynote Speaker – U Cleveland Immunology retreat
Health Research Alliance, Washington DC
Jenner Lecture, St. Georges Hospital, London

2013 Human Fungal Pathogens 2013 Nice, France
NIH Immunology Program, Bethesda MD
GRC Fungal Infections – Galveston, TX
Ohio State University, Columbus, OH
ASM Biodefense and Emerging Infectious Meeting, Washington, DC
Virginia Commonwealth University, Richmond, VA
Columbia University (Responsible conduct of research course)
Texas A&M, College Station, TX
University of Texas at San Antonio
University of Texas at Austin
University of Jena
American Society for Microbiology General Meeting, Denver, CO
BWF Meeting in Calgary, Canada
Swiss Society for Microbiology, Interlaken
Capetown, South Africa
Human Fungal Pathogens Course, Nice, France
Keynote Speaker, Donaghue Foundation
Rheumatology Division, Beth Israel Medican Center
Snowmass Microbial Pathogenesis Meeting
Kynnoun Lecture, NIAID

2014 Association of American Law Schools (AALS) Annual Meeting, New York
Bridging Lecture, International Union of Microbiological Societies 2014 meeting, Montreal, Canada

Departmet of Microbiology and Immunology, UC Davis
2014 Keystone Symposium on Prophylactic and Therapeutic Antibodies
Keynote Speaker, Israeli Society of Microbiology 2014 meeting
Keynote Speaker 17th Upstate NY Immunology Conference
Keynote Speaker International Life Sciences Institute Annual meeting, Bermuda
Keynote Speaker, The 2nd Annual Infection, Inflammation, and Immunity Summer Symposium, U Utah
Benard Fields Memorial Lecture, The Scripps, La Jolla
2014 American Association of Immunology Minority Affairs Guest Lecturer
Student Invited Speaker, Graduate Biosciences Society at the University of Virginia, Charlottesville
Invited speaker, GRC Cellular and Molucular Fungal Biology
Group on Research Advancement and Development (GRAND), AAMColleges
San Antonio Vaccine Development Center Conference titled "Infections, Immunity and Vaccines
Keynote Speaker Department of Microbiology and Molecular Genetics Retreat, UTHSCenter, Houston
Keynote Speaker Upstate NY Immunology Conference, Lake George
Keynote Speaker ASM Eastern NY Branch, Albany, NY
Symposium on Microbes in Health and Disease at Weill Medical College
Keynote Speaker XII International Meeting on Paracoccidioidomycosis, Brasilia, Brasil.

2015 14th Annual St. Jude/PIDS Pediatric Infectious Diseases Research Conf., Memphis, TN
Invited Speaker, Icahn School of Medicine at Mount Sinai, New York, NY
Invited Speaker, Albert Einstein, New York, NY
Invited Speaker, Princeton University, Princeton, NY
Invited Speaker, Baylor College, Houston, TX
Invited Speaker and Organizer, Model Host Conference, Crete, Greece
Invited Speaker, Universidad de la RepAblica, Montevideo, Uruguay
Invited Speaker, North Dakota State University, Fargo, ND
Invited Workshop Speaker, National Diversity Equity Workshop, Arlington, VA
Invited Speaker, Merck, East Brunswick, NJ
Invited Speaker, University of Kentucky, Lexington, KY
Invited Speaker, University of Maryland, Baltimore, MD
Invited Speaker, Nationwide Children's Hospital, Columbus, Ohio
Invited Speaker, ASM Maryland Branch, Hunt Valley, MD
McCollum Colloquim, Dartmouth, Hanover, NH
Columbia University ethics course, New York, NY
NIH Director's Wednesday Afternoon Lecture Series, NIH, Bethesda, MD
Invited Speaker, East Tennessee University, Johnson City, TN
Keynote Speaker, New York Hospital Queens, New York, NY
Douglas McGregor Keynote Address, Cornell University, Ithaca, NY
McGinnis Memorial Lecture, Duke University, Durham, NC
Annual Microbial Sciences Symposium, Harvard University, Cambridge, MA
Keynote Speaker, University of California Irvine, Lake Arrowhead, CA
3rd Conference on Model Hosts, Crete, Greece

2016 Plenary Speaker, ASM Biodefense Conference, Arlington VA
Microbiology 2016, Liverpool, UK
Medoff Lecture, Washington University, St. Louis
Department of Biomedical Sciences, East Tenesse University, TN

Naff Lecture, Case Western Reserve
McGhee Lecture, University of Arkansas
National Library of Medicine
Keynote Speaker, Canadian Society of Microbiology, Toronto
Microbe 2016, American Society of Microbiology, Boston, NY
Karling Lecture, The Mycological Society of Americas, Berkeley, CA.
Emerging Infectious Disease Workshop, Madrid, Spain
15th CRG-Centre for Genomic Regulation Symposium, Barcelona, Spain
Keynote Speaker, MSGERC Meeting, Asilomar, CA
Society for Glycobiology, New Orleans
Retreat Keynote Speaker, Department of Microbiology, U Maryland
Student Invited Speaker, McMaster University, Ontario, Portland
Reed College, Portland, Oregon
Merck Sharp and Dohme
Keynote Speaker (student invited), McMaster University, Ontario, Canada
Reed College, Portland, Oregon
Merck Sharp and Dohme
Boston University, Boston, MA
Plenty Speaker, 2016 Society for Glycobiology, New Orleans, LA
University of Pittsburgh, Pittsburgh, PA

2017

Westmere Lecture, Birmingham UK
Harry Smith Lecture, Birmingham UK
Boston University, Boston, MA
Queens College, New York, NY
University of Wisconsin-Madison, Madison, WI
University of Kansas, Manhattan, KS
Plenary Speaker, 2017 International Mtg of Microbiological Society of Korea, Seoul
5th International Symposium of the Collaborative Research Centre, Tubingen, Germany
GAP Summit 2017, Georgetown University, Washington, DC
Food & Drug Administration, Silver Spring, MD
Keynote Speaker, 2017-2018 Icahn SOM at Mount Sinai Annual Retreat, Ellenville, NY
Mahmoud Ghannoum 20th Anniversay Symposium, University Hospitals Cleveland Medical Ctr, Ohio
Middle Tennessee State University, Murfreesboro, TN
National Research Council of the Swiss Nation, Berne, Switzerland
Columbia Law School, New York, New York

2018

SPRIG Speaker, National Institutes of Health, Bethesda, MD
Columbia Law School, New York, New York
Plenary Speaker, 14th European Conference on Fungal Genetics, Haifa, Israel
Speaker, Biosecurity Luncheon, The National Academies of Science, Engineering and Medicine, Washington, DC
Speaker, Israel Society for Medical Mycology, Tel Aviv, Israel
Speaker, United States Uniformed Health Services, Bethesda, MD
Speaker, University of Connecticut, Storrs, CT
Speaker, Signals of Trust Science Communicaiton, Cold Spring Harbor, Lloyd Harbor, NY
Speaker, University of Nebraska Medical Center, Omaha, NE
Speaker, Broad Institute, Cambridge, MA
Keynote Speaker, Kelsey Lecture, The University of Texas MD Anderson Cancer Center, Houston, Texas

Keynote Speaker, Van Andel Institute, Grand Rapids, MI
Speaker, Gordon Research Conference Extracellular Vesicles, Newry, ME
Speaker, Duke University MGM annual retreat, Durham, NC
Speaker,8th BMMC Conference, Dublin, Ireland
Speaker Fungal CIFAR Workshop, Toronto, Canada
Speaker, Center for Valley Fever Symposium, Sacramento, California
Speaker, Tulane University School of Medicine, New Orleans, LA
Speaker, University of Pittsburgh, Pittsburgh, PA
Speaker, Columbia Law, New York, NY
Speaker, Albert Einstein College of Medicine, New York, NY

2019 Speaker, University of Alabama, Birmingham, Alabama
Speaker, University of Maryland Baltimore, Baltimore, Maryland
Speaker, Johns Hopkins School of Medicine, Baltimore, Maryland
Speaker, Columbia Law, New York, NY
Speaker, University of Arizona, Tucson, Arizona
Speaker, Baruch College CUNY, New York, NY
Speaker, APSA, Chicago, Il
Speaker, World Vaccine Congress, Washington, DC
Speaker, University of Buffalo, Buffalo, New York
Speaker, UT Southwestern Medical Center, Dallas, TX
Speaker, Merck Research Laboratories, Boston, MA
Speaker, Rocky Mountain Laboratories, Hamilton, MT
Speaker, Melanin Workshop, Silver Spring, MD
Speaker, Cancer Biology Training Consortium, Baltimore, MD
Keynote Speaker, Queen's University of Belfast, Belfast
Speaker, Cornell University, New York, New York
Speaker, NASA Glenn Research Center, Cleveland, Ohio
Speaker, National Academies of Sciences, Engineering and Medicine, Washington, DC
Speaker, Rockefeller University, New York, New York

Appendix B

APPENDIX B

Exh. No.	Description
AMG1001	U.S. Patent 9,725,504 to Bell et al.
AMG1002	Declaration of Joseph P. Balthasar, Ph.D.
AMG1003	Curriculum Vitae of Joseph P. Balthasar, Ph.D.
AMG1004	Hillmen, P., et al., "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria," N. Engl. J. Med. 350:552-559 (2004) ("Hillmen '04")
AMG1005	Bell, L. and Rother, R., "Method of Treating Hemolytic Disease," U.S. Patent Application Publication No. 2005/0191298 A1 (filed February 3,2005; published September 1, 2005)
AMG1006	Bowdish, K., et al., "Rationally Designed Antibodies," U.S. Patent Application Publication No. 2003/0232972 A1 (filed December 2, 2002; published December 18, 2003)
AMG1007	Evans, M., et al., "C5-Specific Antibodies for The Treatment of Inflammatory Diseases," U.S. Patent No. 6,355,245 B1 (filed June 7, 1995; issued March 12, 2002)
AMG1008	Mueller, J., et al., "Porcine Cell Interaction Proteins," International Patent Application Publication No. WO 97/11971 A1 (filed September 27, 1996; published April 3, 1997)
AMG1012	Hillmen, P., et al., "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria," N. Engl. J. Med. 355:1233-1243 (2006)
AMG1014	File History for U.S. Patent No. 9,725,504 B2
AMG1015	File History for U.S. Patent No. 9,732,149 B2
AMG1016	File History for U.S. Patent No. 9,718,880 B2
AMG1018	Harlow and Lane, Chapter 2: Antibody Molecules, in Antibodies, A Laboratory Manual (1988)
AMG1019	Brekke, O. and Sandlie, I., "Therapeutic antibodies for human diseases at the dawn of the twenty-first century," Nature Reviews Drug Discovery 2: 52-62 (2003)
AMG1020	Pierangeli, S., et al., "Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia," Arthritis & Rheumatism 52: 2120-2124 (2005)
AMG1021	Kaplan, M., "Eculizumab (Alexion)," Curr. Opin. Investig. Drugs 3:1017-1023 (2002)

Samsung Bioepis Exhibit No. 1002
Page 13296

Exh. No.	Description
AMG1023	Thomas, T., et al., "Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv.," Molecular Immunology, 33: 1389- 1401 (1996)
AMG1028	Wang, Y., "Nebulization of Monoclonal Antibodies for Treating Pulmonary Diseases," U.S. Patent Application Publication No. 2005/0271660 A1 (filed May 11, 2005; published December 8, 2005)
AMG1029	Wang, W., et al., "Antibody Structure, Instability, and Formulation," Journal of Pharmaceutical Sciences 96: 1-26 (2007)
AMG1031	Mueller, P., et al., "Humanized Porcine VCAM-Specific Monoclonal Antibodies With Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding To Porcine Endothelial Cells," Molecular Immunology 34: 441 -452 (1997)
AMG1032	Rother, R., et al., "Antibodies and Fusion Proteins That Include Engineered Constant Regions," International Patent Application Publication No. WO 2005/007809 A2 (filed May 28 2004; published January 27, 2005)
AMG1033	Rother, R., et al., "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," Nature Biotechnology 25: 1256-1264 (2007)
AMG1034	Tacken, P., et al., "Effective induction of naive and recall T-cell responses by targeting antigen to human dendritic cells via a humanized anti–DC-SIGN antibody," Blood 106: 1278-1285 (2005)
AMG1039	Matis, L. and Rollins, S., "Complement-specific antibodies: Designing novel anti-inflammatories," Nature Medicine 1: 839-842 (1995)
AMG1042	Hillmen, P., et al., "Eculizumab, a C5 complement blocking antibody, is the first therapy to reduce transfusion requirements in patients with paroxysmal nocturnal haemoglobinuria (PNH)," British Journal of Haematology - Supplement 121:87, Abstract 257 (2003)
AMG1047	Hill, A., et al., "Sustained response and long-term safety of eculizumab in paroxysmal nocturnal Hemoglobinuria," Blood 106: 2559-2565 (2005) ("Hill '05")
ALXN2005	Original SOLIRIS® Label (2005-2007)
ALXN2006	Dmytrijuk et al., FDA Report: Eculizumab (SOLIRIS®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, THE ONCOLOGIST, 13:993-1000 (2008)
ALXN2007	Janeway and Travers, Immunobiology: The Immune System in Health and Disease (Garland Science, 6th ed. (2005))

Exh. No.	Description
ALXN2008	McCloskey et al., Human Constant Regions Influence the Antibody Binding Characteristics of Mouse-Human Chimeric IgG Subclasses, IMMUNOLOGY, 88: 169-173 (1996)
ALXN2009	Torres et al., The Immunoglobulin Heavy Chain Constant Region Affects Kinetic and Thermodynamic Parameters of Antibody Variable Region Interactions with Antigen, J. OF BIOL. CHEM., 282(18): 13917–27 (2007)
ALXN2010	Janda et al., Ig Constant Region Effects on Variable Region Structure and Function, FRONT.MICROBIOL., 7(22): 1-10 (2016)
ALXN2011	Pritsch et al., Can Immunoglobulin CH1 Constant Region Domain Modulate Antigen Binding Affinity of Antibodies?, J. CLIN. INVEST., 98(10): 2235-43 (1996)
ALXN2012	Pritsch et al., Can Isotype Switch Modulate Antigen-Binding Affinity and Influence Clonal Selection?, EUR. J. IMMUNOL., 30: 3387-95 (2000)
ALXN2013	McLean et al., Isotype Can Affect the Fine Specificity of an Antibody for a Polysaccharide Antigen, J. OF IMMUNOLOGY, 169: 1379–86 (2002)
ALXN2014	Greenspan et al., Complementarity, Specificity and the Nature of Epitopes and Paratopes in Multivalent Interactions, IMMUNOL. TODAY, 16(5): 226-30 (1995)
ALXN2015	Radbruch, et al., Drastic Change in Idiotypic but Not Antigen-Binding Specificity of an Antibody by a Single Amino-Acid Substitution, NATURE, 315(6): 506-508 (1985)
ALXN2017	Hawkins et al., The Contribution of Contact and Non-contact Residues of Antibody in the Affinity of Biding to Antigen: The Interaction of Mutant D1.3 Antibodies with Lysozyme, J.MOL. BIO., 234: 958-964 (1993)
ALXN2019	Ricklin & Lambris, Complement-Targeted Therapeutics, NATURE BIOTECHNOLOGY, 25(11); 1265-1275 (2007)
ALXN2020	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, available at https://news.alexion.com/press-release/company-news/alexions-soliris-receives-2008-prix-galien-usa-award-best-biotechnology-p (last visited May 15, 2019)

Exh. No.	Description
ALXN2021	BusinessWire, Alexion's Soliris® Receives 2009 Prix Galien France for Most Innovative Drug for Rare Disease, June 10, 2009, available at https://www.businesswire.com/news/home/20090610005826/en/Alexions-Soliris®-Receives-2009-Prix-Galien-France (last visited May 15, 2019)
ALXN2023	Curriculum Vitae of Arturo Casadevall
ALXN2028	Hill, et al., Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria, THE HEMATOLOGY JOURNAL, 31-33, 2007
ALXN2029	Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, U.S. Dept. of Health and Human Services, Food and Drug Admin., 1997
ALXN2030	3/16/2007 FDA Approves Alexion's Soliris™ for all Patients with PNH
ALXN2031	Janeway, et al.,Immunobiology, The Immune System in Health and Disease, Appendix I: Immunologists' Toolbox, 6th ed. 2005
ALXN2032	Deposition Transcript of Joseph P. Balthasar, Ph.D., Amgen, Inc. v. Alexion Pharmaceuticals, Inc., IPR No. 2019-00740 (Oct. 23, 2019)
ALXN2033	Kim, et al., Antibody Engineering for the Development of therapeutic Antibodies, MOLECULES AND CELLS, Vol. 20, No. 1, pp. 17-29, 2005
ALXN2034	Hwang, et al., Immunogenicity of engineered antibodies, SCIENCE DIRECT, 17 Jan. 2005
ALXN2035	Shepherd, et al., Monoclonal Antibodies, Oxford University Press, pp. 58-5 (Appendix) 2000
ALXN2036	Lo, Benny K., Antibody Engineering Methods and Protocols, METHODS IN MOLECULAR BIOLOGY, Vol. 248 2004
ALXN2037	Welt, et al., Phase I Study of Anticolon Cancer Humanized Antibody A33, CLINICAL CANCER RESEARCH, 2003
ALXN2038	Haller, et al., Safety Issues Specific to Clinical Development of Protein Therapeutics, NATURE PUBLISHING GROUP, 2008
ALXN2039	Torres, et al, Exchanging Murine and Human Immunoglobulin Constant Chains Affects the Kinetics and Thermodynamics of Antigen Binding and Chimeric Antibody Autoreactivity, PLOS ONE, 2007
ALXN2040	Torres, et al., Variable-Region-Identical Antibodies Differing in Isotype Demonstrate Differences in Fine Specificity and Idiotype, JOURNAL OF IMMUNOLOGY, 2005

Exh. No.	Description
ALXN2042	Mathieu, Barbara G., Clinical Testing of Biologically Derived Therapeutics, Biologics Development: A Regulatory Overview, 3d ed., 2004
ALXN2043	Andersen, et al,, Production technologies for monoclonal antibodies and their fragments, SCIENCE DIRECT, 2004
ALXN2044	Chadd, et al., Therapeutic antibody expression technology, 2001
ALXN2045	2007 USP Dictionary of USAN and International Drug Names
ALXN2046	Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances, 1997
ALXN2047	McClean, et al., A point mutation in the CH3 domain of huan IgG3 inhibits antibody secretion without affecting antigen specificity, MOLECULAR IMMUNOLOGY, 2005
ALXN2049	HemOnc Today, Eculizumab's triumph over PNH, https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh (Aug. 25, 2008)
ALXN2050	Fatimah Al-Ani et al., "Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations, Ther. Clin. Risk Manag.; 12: 1161–1170 (2016)
ALXN2051	Foote, Jefferson and Winter, Greg, "Antibody Framework Residues Affecting the Coformation of the Hypervariable Loops," J. Mol. Biol., 224:487-449 (1992)
ALXN2052	Xiang, Jim et al., Framework Residues 71 and 93 of the Chimeric B72.3 Antibody are Major Determinants of the Conformation of Heavy-chain Hypervariable Loops," J. Mol. Biol. 253:385-390 (1995)
ALXN2053	June 2019 Soliris Label
ALXN2054	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris(TM) (eculizumab)," (Sept. 20, 2006)
ALXN2055	Alexion Press Release, "Alexion Submits Market Authorization Application for Soliris(TM) (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency," (Sept. 26, 2006)
ALXN2075	GenScript, "Final Report – Antibody Full Length Sequencing of Hybridoma 5G1.1 T175," Order Number: U856UEK140-1 (Nov. 15, 2019)
ALXN2086	Stebbings, R., *et al.*,"After TGN1412: Recent developments in cytokine release assays," J. of Immunotoxicology, 10(1):75-82 (2013)
ALXN2088	Amgen Biosimilar Pipeline Approved Products (2019)

Exh. No.	Description
ALXN2089	Generium Pharmaceutical, "Elizaria" Product (2019)
ALXN2090	Samsung Bioepis - Biosimilar candidates and Novel biologic (2019)
ALXN2091	Harlow and Lane, Chapter 15: Antibody Molecules, in Antibodies, A Laboratory Manual, 622-25 (1988)

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00739
Patent: 9,725,504

DECLARATION OF BERNHARDT L. TROUT, Ph.D.

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Patent Trial and Appeal Board
U.S. Patent and Trademark Office
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Alexandria, VA 22313-1450

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND AND QUALIFICATIONS 3

III. SUMMARY OF OPINIONS 7

IV. LEGAL PRINCIPLES PROVIDED BY COUNSEL 8

V. PERSON OF ORDINARY SKILL IN THE ART AS OF MARCH 15, 2007 9

VI. STATE OF THE ART REGARDING FORMULATION OF THERAPEUTIC ANTIBODIES AS OF MARCH 15, 2007 11

- A. Monoclonal Antibodies for Human Therapeutic Use 11
- B. Challenges to Formulation of Therapeutic Monoclonal Antibody Products as of March 15, 2007 14

VII. THE '504 PATENT 23

VIII. BELL (AMG1005) AND WANG (AMG1028) DID NOT MOTIVATE A POSA TO MAKE THE CLAIMED COMPOSITIONS OF THE '504 PATENT, OR GIVE A POSA A REASONABLE EXPECTATION OF SUCCESS IN DOING SO 28

- A. A POSA Prior to March 15, 2007 Would Not Have Been Motivated to Make, or Reasonably Expected Success in Making, a Pharmaceutical Composition of an Unstudied Antibody Comprising SEQ ID NOs: 2 and 4 33
- B. Bell (AMG1005) and Wang (AMG1028) Would Not Have Motivated a POSA Prior to March 15, 2007 to Make the Pharmaceutical Composition of '504 Patent Claim 6, or Given a POSA a Reasonable Expectation of Success in Doing So 39

Samsung Bioepis Exhibit No. 1002
Page 13303

I, Bernhardt L. Trout, Ph.D., hereby declare and say as follows:

I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this declaration.

2. I understand that the Patent Trial and Appeal Board has granted Amgen Inc.'s ("Amgen") petition to institute this *Inter Partes* Review ("IPR") regarding claims 1-10 of U.S. Patent No. 9,725,504 ("the challenged claims of the '504 patent"). (AMG1001.) I understand from counsel that the '504 patent is owned by Alexion Pharmaceuticals Inc. ("Alexion").

3. This Declaration sets forth my opinions with respect to the challenged claims of the '504 patent, including the documents I considered, and my response to certain opinions set forth in the Declaration of Dr. Joseph P. Balthasar, Ph.D. (AMG1002) as they relate to issues of pharmaceutical formulation and pharmaceutical compositions of monoclonal antibodies.

4. I have been asked whether, from the perspective of a person of ordinary skill in the art ("POSA") prior to March 15, 2007, the pharmaceutical compositions recited in claims 4 and 5 of the '504 patent would have been obvious in view of Hillmen (2004) (AMG1004) and Bell (AMG1005) as asserted in Amgen's Ground 2.

Samsung Bioepis Exhibit No. 1002
Page 13304

5. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical composition recited in claim 6 of the '504 patent would have been obvious in view of Hillmen (2004), Bell, and Wang (AMG1028) as asserted in Amgen's Ground 3.

6. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical compositions recited in claims 1-5 and 7-10 of the '504 patent would have been obvious in view of Bell, Bowdish (AMG1006), and Evans (AMG1007) as asserted in Amgen's Ground 4.

7. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical composition recited in claim 6 of the '504 patent would have been obvious in view of Bell, Bowdish, Evans, and Wang as asserted in Amgen's Ground 5.

8. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical compositions recited in claims 1-5 and 7-10 of the '504 patent would have been obvious in view of Bell, Evans, and Mueller as asserted in Amgen's Ground 6.

9. I have also been asked whether, from a POSA's perspective prior to March 15, 2007, the pharmaceutical composition recited in claim 6 of the '504 patent would have been obvious over Bell, Evans, Mueller, and Wang as asserted in Amgen's Ground 7.

10. Below is a complete Table of the Grounds upon which I will opine in this declaration.

Ground	Claims	Basis	Asserted References
2	4,5	35 U.S.C. § 103(a)	Hillmen (2004) and Bell
3	6	35 U.S.C. § 103(a)	Hillmen (2004), Bell, and Wang
4	1-5, 7-10	35 U.S.C. § 103(a)	Bell, Bowdish, and Evans
5	6	35 U.S.C. § 103(a)	Bell, Bowdish, Evans, and Wang
6	1-5, 7-10	35 U.S.C. § 103(a)	Bell, Evans, and Mueller
7	6	35 U.S.C. § 103(a)	Bell, Evans, Mueller, and Wang

11. I am being compensated at my usual rate for consultation on patent matters of $ 900/hr, plus any additional reasonable expenses. My compensation is in no way dependent on the outcome of this proceeding.

II. BACKGROUND AND QUALIFICATIONS

12. I am currently a Professor of Chemical Engineering at the Massachusetts Institute of Technology (MIT). I am also Director of the Society, Engineering and Ethics (SEE) Program at MIT.

13. I received my B.S. and M.S. degrees from MIT (1990) and my Ph.D. from the University of California at Berkeley (1996), all in chemical engineering. I performed post-doctoral research at the Max-Planck Institute for Solid-State Physics in Stuttgart. In 1998, I became an Assistant Professor of Chemical Engineering at MIT. I was promoted to Associate Professor of Chemical Engineering in 2003, and I was promoted to Full Professor of Chemical

Engineering at MIT in 2008. Since 2014, I have held the Raymond F. Baddour, ScD, (1949) Chair as Professor of Chemical Engineering.

14. I am a member of various scientific societies including the American Institute of Chemical Engineers, the American Association of Pharmaceutical Scientists, and the American Chemical Society.

15. I have been a reviewer for several journals including mAbs, Proceedings of the National Academy of Sciences, The Journal of Physical Chemistry, Chemical Physics Letters, Pharmaceutical Research, Journal of the American Chemical Society, Biochemistry, Journal of Pharmaceutical Sciences, Biophysical Journal, The Journal of Organic Chemistry, Analytical Biochemistry, Research Letters in Physical Chemistry, Nature Materials, Molecular Pharmaceutics, Chemical Physics Letters, and Angewandte Chemie.

16. I have given more than 150 invited talks on pharmaceuticals including difficulties associated with antibody formulation and stability, including at the FDA, the American Association of Pharmaceutical Sciences, the Industrial Society of Pharmaceutical Engineering, the American Chemical Society, PEP Talk, and many companies.

17. I have published more than 200 papers in refereed journals and have 18 patents pending or issued.

18. I have over 20 years' experience working with protein formulation and have focused my research on monoclonal antibody formulation since 2004.

19. My current research group at MIT consists of approximately 5 Masters or Ph.D. students, Post-Doctoral Associates, and technical research staff, most of whom focus on antibody formulation research. My research consists of a wide range of areas in pharmaceutical and biopharmaceutical (protein and antibody) development and manufacturing, including formulation and stabilization. Target formulations and manufacturing approaches include both liquid and lyophilized final dosage forms. My research investigates the underlying science of pharmaceutical and biopharmaceutical development and manufacturing and aims to develop new technologies in those areas.

20. My work includes developing approaches to antibody stabilization, developing tools to mitigate antibody aggregation, evaluating monoclonal antibody aggregation, and developing stable antibody formulations. Since starting as a professor at MIT in 1998, I have worked on about 50 or more biologic therapeutics, most of them monoclonal antibodies. The vast majority of this work has been sponsored by industry and includes characterization, formulation, and design of antibodies. My laboratory has elucidated mechanisms of degradation, including aggregation, oxidation, deamidation, and hydrolysis. Current research includes developing approaches for the rational formulation of monoclonal

antibodies and determining key molecular descriptors responsible for various degradation routes in addition to enhanced viscosity.

21. Since 2010, I have been the lead instructor (with a colleague from the FDA and a colleague from industry) of an MIT professional short course entitled, "Formulation and Stabilization of Biotherapeutics." This course is offered annually and mainly consists of professionals in the area of formulation who want to enhance their knowledge in the subject.

22. I also consult and have given invited talks and plenary lectures on topics including stabilizing proteins and antibodies for industry, including for Amgen and Biogen-Idec. I have also lectured at the Biomanufacturing Summit, Cambridge, MA., and have been a consultant for the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. Overall, my consulting consists of a range of endeavors from technical problem solving to strategy. Much of this consulting is related to formulation of biopharmaceuticals, including mAbs to be commercialized. At least one monoclonal antibody that I have consulted on is now a commercial product, and several others are being commercialized.

23. A full description of my background, awards, and qualifications can be found in my curriculum vitae attached as an appendix to this declaration. My curriculum vitae is attached hereto as Appendix A (ALXN2025.).

Samsung Bioepis Exhibit No. 1002
Page 13309

III. SUMMARY OF OPINIONS

24. In forming my opinions contained in this Declaration, I have relied on my education, background and experience in antibody formulation. I have also reviewed the '504 patent, the Balthasar Declaration (AMG1002), the transcript for the October 23, 2019 Deposition of Dr. Joseph Balthasar (ALXN 2032); the Institution Decision (Paper No. 15), and the publications, patents, patent applications and other documents cited in this Declaration.

25. In connection with the opinions and conclusions contained within this Declaration, I have reviewed and considered the documents listed in Appendix B attached to this Declaration, as well as any other documents cited throughout this Declaration.

26. I understand that the documents Bell (AMG1005), or Bell in combination with Wang (AMG1028) are cited in Amgen's asserted Grounds 2-7 for *inter partes* review of the '504 patent. Based on my experience and expertise, and the documents and information I have reviewed and considered, I disagree with Dr. Balthasar's positions that Bell (AMG1005), or Bell in combination with Wang (AMG1028) disclosed the pharmaceutical compositions recited in claims 1-10 of the '504 patent. I further disagree with Dr. Balthasar's opinions that a person of ordinary skill in the art ("POSA") would have been motivated to make and use

the pharmaceutical compositions claimed in the '504 patent, or that a POSA would have had a reasonable expectation of success in doing so.

IV. LEGAL PRINCIPLES PROVIDED BY COUNSEL

27. I am not an attorney. However, I have been advised of the following legal principles, and they have helped to form my conclusions in this report. I understand that Petitioner has asserted that the challenged claims of the '504 patent are unpatentable under 35 U.S.C. § 103 as obvious in view of the various prior art combinations I listed in paragraphs 4-9, above.

28. I understand that it is Amgen's burden to show that the challenged claims are obvious, and that to do this Amgen must show, without the benefit of hindsight, that the claimed invention as a whole would have been obvious to a POSA prior to the date of invention or "priority date."

29. I understand the Board will consider the following factors when assessing whether Amgen has met its burden to show obviousness: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness. I have been informed by counsel that objective evidence of non-obviousness can include: that the invention satisfied a long-felt but unmet need that existed at the time of the invention; commercial success of products

embodying the claimed invention; teaching away from the invention in the prior art; copying of the invention; and industry praise.

30. I understand that, when considering obviousness, I must not use hindsight knowledge of the invention claimed in the '504 patent. I understand that I must consider only documents or information that would have been available before the priority date. I further understand that I must consider the full scope and content of the prior art that would have been available to a POSA as of March 15, 2007, and that I may not use hindsight to select references from the prior art to be considered in the obviousness analysis. I understand that I must consider the prior art as a POSA would have viewed it as of March 15, 2007, without the benefit of knowing how the invention was successfully achieved.

31. I understand that Amgen must show that, without the benefit of hindsight, a POSA would have been motivated to combine a particular set of prior art references, and that in doing so a POSA would have had a reasonable expectation of success in achieving the claimed invention.

V. PERSON OF ORDINARY SKILL IN THE ART AS OF MARCH 15, 2007

32. I understand from counsel that, for purposes of this proceeding, the '504 patent is to be read from the perspective of a person of ordinary skill in the art ("POSA") at the time of invention. I further understand that a POSA is a

hypothetical person who is presumed to know the relevant art at the time of the invention.

33. I understand that the Board has accepted a definition of POSA as a person with an M.D. and/or Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry. (Institution Decision, '504 Paper 15 at 20-21.) I agree with this definition, and I provide my opinions from the perspective of a POSA of March 15, 2007, with a focus on issues pertaining to antibody formulation.

34. I also understand that Dr. Balthasar proposed that "a POSA may have worked as part of a multidisciplinary team and drawn upon not only her or her own skills, but also taken advantage of certain specialized skills of others on the team," including "a clinician and a formulation chemist." (AMG1002 ¶ 20.) I agree that a POSA with respect to the '504 patent could have – and in the context of drug development, would have – consulted with others having specialized skill and experience concerning the formulation of pharmaceutical compositions of monoclonal antibodies, as well as others having specialized skill and experience in clinical therapy.

35. I understand from counsel that, for purposes of this proceeding, the '504 patent and other pertinent information is to be considered from the

Samsung Bioepis Exhibit No. 1002
Page 13313

perspective of a POSA **prior to March 15, 2007**, which counsel informs me is the earliest filing date for the '504 patent.

VI. STATE OF THE ART REGARDING FORMULATION OF THERAPEUTIC ANTIBODIES AS OF MARCH 15, 2007

A. Monoclonal Antibodies for Human Therapeutic Use

36. As of March 15, 2007, a POSA would have known that antibodies[1] are large, roughly Y-shaped protein molecules. Figure 1 below, adapted from Dr. Balthasar's declaration, is a simplified two-dimensional illustration of the general structure of an antibody. (AMG1002 ¶ 26.) As seen in the figure, antibody structure can be divided into two regions: the "variable" region at the top of the Y-shaped structure, and the "constant" regions that start below the variable regions

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[1] Unless otherwise noted, I use the term "antibodies" to refer to intact, full-length antibody structures. A POSA would have also known of various antibody-related molecules that are structurally different from full-length, intact antibodies. These would have included "Fab" fragments, each consisting of one antigen-binding "arm" of an IgG antibody – *i.e.*, the variable and constant regions from a light chain, and the variable and first part of the constant region from a heavy chain – and "single-chain variable fragments," or "scFv," each consisting of the variable region of a heavy chain linked by a synthetic peptide to the variable region of a light chain. (AMG1029 at 8; *see also* AMG1030 at 699-700.)

through the stem of the Y structure. The variable regions at the top of the "Y" were understood to include the sites that bind to certain target compounds, known as "antigens," and were also referred to as the "antigen binding region."

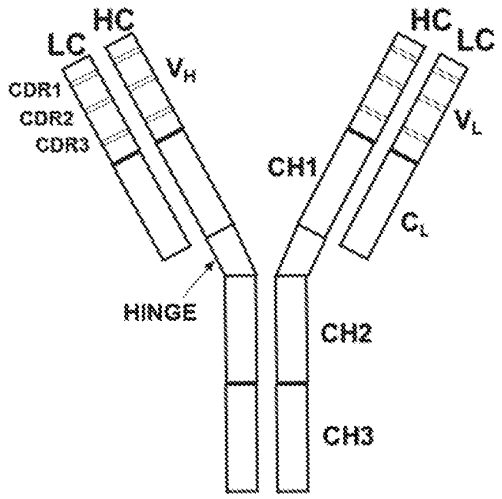


Figure 1: General structure of an IgG-class antibody

37. Following the creation of "monoclonal" antibody technology that (if successfully carried out) could potentially result in the development of highly selective antibodies directed only against a specific target antigen, monoclonal antibodies became an area of interest of pharmaceutical development. (AMG1030 at 686-87.) As Dr. Balthasar notes, and I do not dispute, there were at least 23 monoclonal antibody products (including partial antibody structures ("Fab") and conjugates) approved for commercial marketing in the United States as of March 15, 2007. (AMG1002 ¶¶ 28, 98 fn 7, Appendix I; AMG1029 at 2-4 (Table 1).)

38. The majority of commercial monoclonal antibody products were full-length antibodies of the IgG class. (AMG1029 at 2-4 (Table 1).) Of "humanized" antibodies – *i.e.*, antibodies made from the combination of human variable and constant regions with mouse CDRs – the IgG1 subclass was most common, followed by IgG4. (*Id.*; AMG1030 at 688.) All of the approved antibodies used naturally-occurring isotypes – there were no approved antibodies with a non-naturally occurring, engineered (*e.g.*, "hybrid") constant region isotype. (*Id.*)

39. These 23 commercial monoclonal antibody products were developed for a variety of therapeutic and diagnostic applications in humans, including treatment of cancer (*e.g.*, Avastin (bevacizumab)) and chronic inflammatory conditions (*e.g.*, Humira (adalimumab)). (AMG1029 at 2-4 (Table 1).) A POSA as of March 15, 2007 would have known that, to be marketed commercially in the United States, the makers of these 23 products had to demonstrate to the U.S. Food and Drug Administration ("FDA") that these products were safe and effective for their indicated use. (ALXN2032 at 46:20-48:2; ALXN 2079 at 19.)

40. A POSA would have further known that, to obtain the FDA's authorization to even study these monoclonal antibody products in human clinical trials prior to their approval for commercial marketing, the FDA would have required the submission of extensive information characterizing the product to be administered to humans – including information regarding the monoclonal

antibody in the form of the pharmaceutical composition to be used in clinical trials. (ALXN2029 at 12-13, 23, 31-33; ALXN2079 at 19.) As a POSA understood, the purpose of this FDA review was to ensure that human subjects would not be put at undue risk when receiving the antibody product in experimental clinical trials. (*See* ALXN2032 at 46:20-48:2.)

B. Challenges to Formulation of Therapeutic Monoclonal Antibody Products as of March 15, 2007

41. A POSA would have understood that, for a monoclonal antibody to be made available for therapeutic use in humans, a "formulation" or "pharmaceutical composition" would need to be developed, which would include the monoclonal antibody itself as the active ingredient, as well as additional, "inactive" ingredients. (AMG1029 at 14; AMG1030 at 701; ALXN2080 at 163-64, 175-76, 178.) But, as of March 15, 2007, developing suitable pharmaceutical compositions of new, previously-unformulated monoclonal antibodies was not a straightforward task. In particular, a POSA would have understood that a suitable formulation for one antibody might not be suitable for another antibody – even if the two were closely related in sequence and structure. In fact, a POSA would understand that the approach to formulating a given antibody was to develop a formulation from scratch, not plug the antibody into formulations that were developed for other antibodies. (*See, e.g.*, AMG1029 at 5 ("[T]he behavior of antibodies [in pharmaceutical compositions] seems to vary, even though they have similar

structures."); AMG1030 at 690 ("Each antibody seems to have a unique personality related to its requirements for stability. . . . [T]he interfacial surface of each antibody drug is unique and thus requires specific formulation components to provide maximal stability and retention of activity.").)

42. In my 20-plus years of experience working in conjunction with pharmaceutical companies on the development of pharmaceutical formulations, I have personally seen on many occasions that an antibody that appeared to be promising from studies in the "discovery" phase of development could not move forward into clinical development because it was not capable of being made into a suitable pharmaceutical composition.

43. As discussed below, there were a variety of issues that a POSA would have needed to address in formulating a monoclonal antibody, with numerous options for addressing them. For example, a POSA would have needed to consider the intrinsic stability of the monoclonal antibody, and the effects of a formulation on its rates of chemical and physical degradation. (AMG1029 at 15-17; AMG1030 at 689-90; ALXN2080 at 163-64, 175-76, 178.) Formulation development – including the concentration of an antibody formulation – could be influenced by the desired route of administration (*e.g.*, intravenous or subcutaneous) and type of formulation (liquid vs. lyophilized), and, vice versa, the desired route of administration and chosen formulation type could be influenced by the outcome of

studies during formulation development. (ALXN2079 at 2, 4 (Table 2), 10-12; *see also* ALXN2080 at 178; AMG1029 at 14-15; AMG1030 at 694-95.) As of March 15, 2007, monoclonal antibody formulation development was not a linear process, but instead involved significant empirical testing, and rounds of decisions made based on the results of formulation development studies.

44. Overall, a POSA as of March 15, 2007 would have understood that a primary goal of developing an antibody formulation was to achieve sufficient **stability** so that the product could be **stored and transported**, and thereafter, **safely and effectively** administered to human patients. As one major 2007 review cited by Dr. Balthasar explained, "The **major purpose** of formulating antibodies as therapeutic agents [was] to **control the rate of antibody degradation** to provide an acceptable shelf life for worldwide shipping and storage."[2] (AMG1029 at 14 (emphases added); *see also* ALXN2079 at 19 ("[T]he formulation should maintain the safety and efficacy profile of the protein drug during all the handling and uses specified on the label."); ALXN2080 at 178 ("In the development of a protein formulation, the most challenging task is the stabilization of a protein to achieve an acceptable shelf life.").)

[2] Unless otherwise noted, all emphases are added.

45. In general, a POSA understood "stability" in the context of monoclonal antibody pharmaceutical compositions to refer to a variety of types of physical or chemical degradation, resulting in unwanted "degradants" or "degradation products." (*See* AMG1029 at 8-14; AMG1030 at 690-94; ALXN2080 at 137-45; *see also* ALXN2082 at 300-01.)

46. A POSA developing an antibody for therapeutic use would have been particularly concerned about the effects on patients resulting from administering an insufficiently stable formulation containing such degradation products. For example, a POSA understood that the degradation products may have reduced therapeutic activity relative to the therapeutic antibody itself. (AMG1029 at 14; AMG1030 at 690; ALXN2079 at 9; ALXN2080 at 137; *see also* ALXN2082 at 300-01.) A POSA would have also understood that administering an insufficiently stable formulation could result in safety risks, such as increased immunogenicity – which could lead to "neutralization" of the therapeutic antibody by the patient's immune system, as well as immune reactions against a patient's own endogenous proteins. (ALXN2083 at E503; ALXN2082 at 300-01; AMG1029 at 14; *see also* ALXN2081 at 897, 901; ALXN2080 at 137; ALXN2079 at 9.)

47. As of March 15, 2007, a POSA would have understood that multiple pathways could contribute to antibody physical and chemical degradation. For example, types of physical instability included denaturation (misfolding of the

protein) and partial denaturation, which could be caused by temperature change, shear-stress, certain processing steps, or time; and aggregation, which can be impacted by antibody concentration, temperature, storage, shaking, viscosity, ionic strength, pH, and lyophilization process parameters, amongst other factors. (AMG1029 at 8-9; AMG1030 at 689-90, 692-95; *see also* ALXN2080 at 137-40; ALXN2079 at 13 (Table 6).)

48. A POSA would have also been aware of various potential pathways for chemical instability of antibody formulations, including, for example, cross-linking (potentially resulting in chemical aggregation); deamidation, isomerization, and oxidation (resulting in changes to certain amino acids of the primary amino acid sequence); formation of acidic or basic species; C-terminal clipping (removal of certain lysine amino acids); fragmentation; and sugar adduct formation. (AMG1029 at 11-14; AMG1030 at 690-92; *see also* ALXN2080 at 140-145; ALXN2079 at 13 (Table 6).) Chemical instability was known to be influenced by factors such as storage, temperature, pH, and (for oxidation) light exposure. (AMG1029 at 11-14.) It was understood that, generally speaking, both physical and chemical instability tended to increase with increased temperature and storage time. (*See* AMG1029 at 8-14; ALXN2079 at 15-16.)

49. Aggregation in particular was a prevalent stability issue for antibody formulations. It was one of the more commonly experienced physical instability

issues and could potentially limit the concentration of an antibody formulation. (AMG1029 at 8, 14-15; *see also* AMG1030 at 692-93; ALXN2080 at 137-140.) Antibody aggregates were generally known to have reduced activity and greater potential to cause immune reactions due to the aggregates' altered conformation and interaction with epitopes. (AMG1029 at 9; ALXN2080 at 137; ALXN2079 at 9; *see also* ALXN2082 at E503; ALXN2081 at 901 (describing aggregation as a concern for immunogenicity of even fully human proteins).) Due to aggregates' potential to impact safety and efficacy, even low levels could be unacceptable for a pharmaceutical composition to be administered to human patients. (ALXN2079 at 9 ("[E]ven at levels of a few percent or less of the total protein population, non-native aggregates can cause adverse reactions in patients such as immune responses and even anaphylactic shock."); ALXN2080 at 137.)

50. A POSA would also have understood that development of liquid formulations was especially challenging. This was because liquid formulations were known to have more stability issues than lyophilized formulations, including concentration-dependent aggregation, physical instability due to shaking/shear-stress, and increased potential for chemical instability due to storage in water-based formulations, which could facilitate the chemical reactions known to cause antibody degradation. (AMG1029 at 14-17; AMG1030 at 694; ALXN2080 at 150, 152; ALXN2079 at 10.) Although liquid formulations were generally preferred

because they were easier to administer and less expensive to manufacture, as of 2007 many commercial antibody products could not be stabilized as a liquid formulation. (AMG1029 at 2-4 (Table 1), 14; *see also* AMG1030 at 694; ALXN2079 at 10-11 ("Because lyophilized products have less stability-related issues and have a much greater potential tolerance for room-temperature storage, many biopharmaceutical industries consider the lyophilized formulation as a default option.").) Lyophilized formulations were often used where stability issues prevented development of a liquid formulation. (ALXN2079 at 10.)

51. Although generally considered more stable than liquid formulations, a POSA would still have understood that lyophilized formulations were associated with their own set of potential instabilities and development challenges. (*See* ALXN2080 at 175 ("[F]reeze-dried solid protein formulation is generally more stable [than liquid formulation], although lyophilization often causes significant protein instability.").) For example, a POSA would have understood that design of a lyophilized formulation would require selection of an acceptable bulking agent and stabilizers to form a solid "cake," and that lyophilization came with a risk of aggregation and other degradation processes during lyophilization, reconstitution and storage. (AMG1029 at 18-20; AMG1030 at 694-95.) Such risk could be exacerbated depending on the moisture content. (AMG1029 at 18-20; AMG1030 at 694-95.)

52. A POSA would have been aware of antibody stability issues related to the concentration of antibody formulations. Sufficiently high antibody concentration was understood to be desirable for formulations to be administered by subcutaneous injection, to achieve low enough injection volume required for patient administration. (AMG1029 at 14; AMG1030 at 688, 692.) However, in liquid formulations higher antibody concentration was generally thought to increase the risk of antibody aggregation by increasing the frequency of protein-protein interactions. (AMG1029 at 14; AMG1030 at 692; ALXN2080 at 152.)

53. Accordingly, a POSA as of March 15, 2007 would have understood that antibody formulation development would encompass significant empirical work to develop a formulation with sufficient stability for therapeutic use, and still might not succeed. (ALXN2029 at 23; ALXN2084 at 2; AMG1029 at 21; ALXN2080 at 175; ALXN2079 at 2, 4-5, 10.) A POSA would have generally understood that stability testing was to reflect the various "external conditions which can affect the [antibody] product's potency, purity and quality." (ALXN2084 at 2.) Stability testing typically would include, among other things, studies of the integrity of the antibody and its degradation under various conditions over time, to account for stability in storage and shipment. (ALXN2085 at 2; *see also* ALXN2079 at 5-7, 15-16.)

54. Typically, testing would be done early in the development process to assess an antibody's susceptibility for various forms of degradation, identify likely formulation challenges, and develop relevant analytical methods for assessing stability. (ALXN2079 at 5.) These tests would include accelerated stability studies, in which an antibody's stability was assessed under stress conditions to try to predict instability that could develop over its shelf-life. (ALXN2079 at 5; ALXN2080 at 177; ALXN2084 at 7; ALXN2085 at 17; ALXN2029 at 23; *see also* AMG1029 at 17-18, 20.) Stress conditions could include exposing an antibody formulation to high temperature, mechanical stress such as agitation (shaking / stirring), light, multiple freeze/thaw cycles, oxidation, or exposure to denaturants. (ALXN2079 at 5-6; ALXN2080 at 177.)

55. A POSA would have known to examine various product characteristics to assess stability. These included biologic activity, rate of antibody degradation and identity of degradants, formation of aggregates / precipitation (antibody coming out of solution – typically due to formation of aggregates), solution color, pH, viscosity, and sterility. (ALXN2080 at 177; ALXN2079 at 7; *see also* ALXN2084 at 5-6; ALXN2029 at 23.) Analytical methods used to assess these characteristics could have included various forms of chromatography (*e.g.*, HPLC), electrophoresis (*e.g.*, SDS-PAGE), spectroscopy, thermal analysis, and light scattering / turbidity. (ALXN2079 at 7.) It was understood that a variety of

analytical methods were necessary to accurately assess antibody stability, due to the complex nature and multiple pathways for antibody degradation. (ALXN2079 at 6; ALXN2080 at 178 ("[N]o single technique can satisfactorily provide sufficient information about a protein. Thus, a combination of analytical methods needs to be used to characterize a protein and to monitor protein instability.").)

56. As development progressed, additional studies would need to be performed to further progress development of candidate formulations, and to assess the impact of transportation and handling and process scale-up on antibody stability. (ALXN2079 at 13-16.) Further, a POSA would have understood that real-time storage studies, lasting months to years, would need to be performed to assess the actual stability of an antibody over the course of its shelf-life, as accelerated studies were known to be not entirely predictive. (ALXN2079 at 16; ALXN2080 at 178; ALXN2084 at 2; ALXN2085 at 4, 10; ALXN2029 at 23.)

VII. THE '504 PATENT

57. In forming my opinions in this case, I have reviewed and considered the '504 patent, including its specification and claims. I understand from counsel that the '504 patent was not available to a POSA prior to March 15, 2007, and that analysis of whether the claims of the '504 patent would have been obvious to a POSA prior to March 15, 2007 must be done from the perspective of a POSA without hindsight knowledge of the '504 patent or its claims.

58. Claims 1-10 of the '504 patent read as follows:

> **1.** A method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to the patient a pharmaceutical composition comprising an antibody that binds C5, wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.
>
> 2. The method of claim 1, wherein the pharmaceutical composition is administered by intravenous infusion.
>
> 3. The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.
>
> 4. The method of claim 1, wherein the pharmaceutical composition is in a single unit dosage form.
>
> 5. The method of claim 4, wherein the single unit dosage form is a 300 mg single unit dosage form.
>
> 6. The method of claim 1, wherein the pharmaceutical composition comprises a 300 mg

Samsung Bioepis Exhibit No. 1002
Page 13327

single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.

7. The method of claim 1, wherein the patient is anemic.

8. The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7+1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7+1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14+2 days.

9. The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

10. The method of claim 9, wherein the immediate decrease occurs within one week of administration of the antibody.

59. The specification of the '504 patent includes a description of a randomized, multi-center, double-blind, placebo controlled clinical trial ("TRIUMPH") assessing the efficacy of eculizumab to treat paroxysmal nocturnal hemoglobinuria ("PNH"). (AMG1001 at 19:51-28:38.) Eculizumab, or placebo,

was administered by intravenous infusion, at 600 mg every 7 days for 4 doses, followed by 900 mg (or placebo) by IV infusion 7 days later, followed by a maintenance dose of 900 mg (or placebo) by IV infusion every 14 days, for a total of 26 weeks of treatment. (AMG1001 at 20:39-50.) The results of the study showed that eculizumab was a "safe and effective therapy for patients with the rare disorder PNH." (AMG1001 at 28:21-24.) Patients in the study experienced an improvement in PNH symptoms, including reduced intravascular hemolysis, stabilized hemoglobin levels, reduced fatigue, and a reduction in the need for blood transfusions such that most patients became transfusion independent, and an improved quality of life. (AMG1001 at 28:25-30.)

60. The '504 patent identifies "eculizumab" as an antibody comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4. (AMG1001 at 30:22-31, 30:38-44.)

61. The '504 patent describes the invention as including "a method of treating a patient suffering from [PNH] by administering a pharmaceutical composition comprising an antibody that binds C5," and, more specifically, eculizumab. (AMG1001 at 3:13-19.) The '504 patent further states that the antibody can be administered in a "300 mg single-use dosage form, comprising 30 ml of a 10 mg/ml sterile, preservative free solution." (AMG1001 at 4:15-18, 4:22-24.)

62. I understand that there is a dispute between Amgen and Alexion as to, among other things, (1) whether an antibody comprising the heavy and light chain sequences SEQ ID NO: 2 and 4 was disclosed by, or obvious in view of, the prior art available prior to March 15, 2007, and (2) whether, prior to March 15, 2007, a POSA would have known that "eculizumab" was an antibody comprising the heavy and light chain sequences SEQ ID NO: 2 and 4. For purposes of this proceeding, I am not offering an opinion on what was known prior to March 15, 2007 regarding the claimed amino acid sequence, except to say that in my review of Bell (AMG1005) and Wang (AMG1028), I did not see **any** disclosure of the specific amino acid sequence recited in claims 1-10 of the '504 patent, or **any** disclosure that "eculizumab" had the specific amino acid sequence recited in claims 1-10 of the '504 patent.

63. I further understand that there is a dispute between Amgen and Alexion as to whether it was known prior to March 15, 2007 that "eculizumab" had a hybrid IgG2/IgG4 constant region structure. I understand that it is known **today** that, eculizumab, as used the commercial product SOLIRIS®, contains a non-naturally occurring, engineered heavy chain constant region including a specific combination of sequences from human "IgG2" and human "IgG4" constant regions. I further understand it is known **today** that the heavy chain consisting of SEQ ID NO: 2 in claims 1-10 of the '504 patent reflects the sequence of the non-

naturally occurring heavy chain constant region in SOLIRIS® (eculizumab). For purposes of this proceeding, I am not offering an opinion on what was known prior to March 15, 2007 regarding the identity of the constant region or isotype of "eculizumab." It is my opinion, however, that prior to March 15, 2007, there were no FDA-approved or commercially marketed products in the United States containing any non-naturally occurring, engineered "hybrid" isotypes, let alone the specific hybrid isotype of SOLIRIS® reflected in SEQ ID NO: 2 of the '504 patent. (*See* AMG1029 at 2-4 (Table 1).)

VIII. BELL (AMG1005), OR BELL AND WANG (AMG1028), DID NOT MOTIVATE A POSA TO MAKE THE CLAIMED COMPOSITIONS OF THE '504 PATENT, OR GIVE A POSA A REASONABLE EXPECTATION OF SUCCESS IN DOING SO

64. In my opinion, nothing in the Bell (AMG1005) and Wang (AMG1028) documents, alone or in any combination, would have motivated a POSA as of March 15, 2007 to make the pharmaceutical compositions recited in claims 1-10 of the '504 patent, or would have given a POSA a reasonable expectation of success in doing so.

65. I have reviewed and considered Dr. Balthasar's arguments regarding the teachings of Bell (AMG1005) and Wang (AMG1028) as they relate to the claims of the '504 patent, and I disagree. In my opinion, Dr. Balthasar uses his hindsight knowledge of the claimed invention of the '504 patent to make assumptions about Bell and Wang that are not supported by the text available to a

POSA prior to March 15, 2007, and misconstrues how a POSA without hindsight would have understood the teachings of those documents.

66. While both Bell (AMG1005) and Wang (AMG1028) refer to the antibody "eculizumab," I have seen nothing in either document that discloses the complete amino acid sequence for "eculizumab," or in any way associates "eculizumab" with an antibody comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4, the sequence that is recited in the claims of the '504 patent. I also did not see anything in my review of Bell or Wang that identified "eculizumab" as having a hybrid IgG2/IgG4 isotype. I understand Dr. Balthasar agrees with me that Bell and Wang (AMG1028) did not disclose the specific amino acid sequence of the '504 patent claims. (*See, e.g.*, AMG1002 ¶ 139 ("Bell does not provide the amino acid sequence of eculizumab . . . ."); ALXN2032 at 146:15-25, 256:15-257:20.)

67. Despite his admissions regarding the limits of Bell and Wang, Dr. Balthasar contends a POSA would have connected the "eculizumab" antibody of Bell and Wang with the '504 patent's specific claimed amino acid sequence, based on information he combines from other documents outside of Bell and Wang. (*See, e.g.*, AMG1002 ¶¶ 120, 130 ("Bowdish and Evans together"); AMG1002 ¶ 172 (citing "Evans and Mueller").) I understand that Alexion disagrees that Dr. Balthasar's cited combinations of documents disclosed the claimed amino acid

sequence of the '504 patent, or that a POSA as of March 15, 2007 would have known the "eculizumab" antibody of the Bell (AMG1005) or Wang (AMG1028) to have the claimed amino acid sequence of the '504 patent.

68. Regardless of whether Alexion or Amgen is correct on what a POSA as of March 15, 2007 knew, if anything, about the specific amino acid sequence of the "eculizumab" antibody referenced in Bell (AMG1005) and Wang (AMG1028), it is my opinion that a POSA would **not** have been motivated by Bell and Wang to make the claimed pharmaceutical compositions of the '504 patent, and would not have reasonably expected success in doing so. Specifically:

- **If Bell's and Wang's "eculizumab" was *not* known to be an antibody with the claimed sequence of the '504 patent:** A POSA as of March 15, 2007 would not have been motivated by Bell (for claims 1-5 and claims 7-10) or Bell and Wang (for claim 6) to make the claimed pharmaceutical compositions of the '504 patent, and would not have reasonably expected to succeed in doing so, because, among other things, a POSA would have had no evidence that an antibody with the sequence claimed in the '504 patent had **ever** been successfully formulated for therapeutic use. In view of the challenges regarding therapeutic antibody formulation (*see* Section VI.B above), a POSA would not have reasonably assumed that any particular new, previously-unformulated

antibody could be made into a pharmaceutical composition suitable for human therapeutic use, let alone the specific composition recited in claim 6 of the '504 patent. And even if, hypothetically, a POSA had understood generally that eculizumab had a hybrid IgG2/IgG4 isotype, but did not know that "eculizumab" corresponded to the specific claimed amino acid sequence, a POSA would not have been motivated by Bell and Wang to create the claimed compositions with a reasonable expectation of success. In particular, there were no commercial antibodies with a non-natural IgG2/IgG4 isotype available as of March 15, 2007, and Bell and Wang do not provide guidance as to a suitable formulation for an antibody with an IgG2/IgG4 isotype. Even if there were, knowledge of a suitable formulation for a given antibody with an IgG2/IgG4 isotype would not motivate a POSA to formulate another antibody with an IgG2/IgG4 isotype, nor would it give the POSA a reasonable expectation of success.

- **Even under Amgen's theory that Bell's and Wang's "eculizumab" was known to be an antibody with the claimed sequence of the '504 patent:** It is my opinion that, in this scenario, a POSA as of March 15, 2007 would not have been motivated by Bell and Wang to make the specific claimed pharmaceutical composition of at least claim 6 of the

'504 patent, (*i.e.*, "a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution"), and would not have reasonably expected success in doing so. Nothing in Bell (AMG1005) provided a POSA with any specific guidance towards the pharmaceutical composition of claim 6. And Wang (AMG1028) – which described various antibodies for inhalation administration with nebulizers – neither disclosed the specific pharmaceutical composition of claim 6, nor would it have motivated a POSA to make such a composition, or provided a POSA with a reasonable expectation of success in doing so. Further, as stated above, Bell and Wang would not have provided a POSA with motivation to create a formulation for an antibody with a non-natural, IgG2/IgG4 isotype, because there were no commercial antibodies at the time with this isotype, and Bell and Wang did not provide any guidance as to a suitable formulation for an antibody with an IgG2/IgG4 isotype. . Even if they did, knowledge of a suitable formulation for a given antibody with an IgG2/IgG4 isotype would not motivate a POSA to formulate another antibody with an IgG2/IgG4 isotype, nor would it give the POSA a reasonable expectation of success.

Samsung Bioepis Exhibit No. 1002
Page 13335

A. A POSA Prior to March 15, 2007 Would Not Have Been Motivated to Make, or Reasonably Expected Success in Making, a Pharmaceutical Composition of an Unstudied Antibody Comprising SEQ ID NOs: 2 and 4

69. If it were the case that a POSA as of March 15, 2007 did not know that the "eculizumab" antibody described in Bell (AMG1005) and Wang (AMG1028) was the claimed antibody comprising SEQ ID NOs: 2 and 4 recited in the '504 patent, then in my opinion, a POSA would not have been motivated to make, and would not have reasonably expected to succeed in making, the pharmaceutical compositions recited in claim 6 of the '504 patent. In this scenario, neither Bell nor Wang would have taught a POSA that **any** pharmaceutical composition of an antibody comprising SEQ ID NOs: 2 and 4 had ever been created or even attempted. With no evidence that an antibody comprising SEQ ID NOs: 2 and 4 even **could** be formulated into a pharmaceutical composition suitable for therapeutic use, and understanding the complexity of antibody formulation development as of March 15, 2007, a POSA would not have been motivated to make such a composition, or reasonably expected success in doing so.

70. With respect to motivation, Dr. Balthasar argues that a POSA would have combined the references cited in Amgen's Grounds 2 and 3 because these references, according to Dr. Balthasar, all relate to therapeutic treatment with eculizumab. (AMG1002 ¶¶ 98 (stating Hillmen (2004) and Bell both teach methods of treating PNH), 117 (describing Ground 3 references as related to

"therapeutic use of eculizumab").) Dr. Balthasar also argues that a POSA would have combined the references in Amgen's Grounds 5-7 based on a POSA's desire to create eculizumab compositions "to treat a patient suffering from PNH" and because the cited references "relate to therapeutic use of an anti-C5 antibody." (*Id.* at ¶¶ 139, 169, 189, 208.) Further, Dr. Balthasar argues Wang taught that, at concentrations of 1 to 30 mg/mL, eculizumab could be formulated so that it would be "sufficiently stable to be used as a therapeutic." (*Id.* at ¶ 113; *see also id.* at ¶ 113 ("Wang disclosed that eculizumab could be stably formulated at a concentration between 1 and 30 mg/mL"), ¶ 138 (same).) While I agree with Dr. Balthasar that developing a formulation that would be sufficiently stable for therapeutic use was an important aspect of antibody formulation development, I disagree that the disclosures of Bell and Wang would have motivated a POSA to prepare a stable formulation of an antibody with the amino acid sequence claimed in the '504 patent – which is not disclosed in Bell or Wang and which, under this first scenario, I assume would not have been understood by a POSA to correspond to "eculizumab." Moreover, I disagree with Dr. Balthasar that Bell and Wang, read alone or in combination, would have taught a POSA that "eculizumab" would be stable when formulated as in the claimed compositions.

71. As discussed above in Section VI.B, the pharmaceutical formulation development of a new, previously-unformulated monoclonal antibody required

many experiments the results of which were unpredictable as of March 15, 2007. A POSA as of March 15, 2007 knew that, even for closely-related antibody sequences, the formulation that is suitable for one antibody could not be assumed to be suitable for another.[3] (*See* Section VI.B; AMG1029 at 5; AMG1030 at 690.) For that reason, a POSA having no information about whether an antibody comprising SEQ ID NOs: 2 and 4 had ever been attempted to be formulated into a pharmaceutical composition, or whether that antibody had ever been administered to humans to test its clinical effects, would not have reasonably expected that the antibody was even capable of being used in a suitable pharmaceutical formulation. Without significant empirical testing, a POSA would not have known whether an antibody comprising SEQ ID NOs: 2 and 4 could be formulated into a sufficiently stable product using known antibody formulation approaches, including those in Wang (AMG1029) and Daugherty (AMG1030), as of March 15, 2007. (*See*

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[3] For this reason, even assuming hypothetically that a POSA would have known that an antibody comprising SEQ ID NOs: 2 and 4 was related in sequence to the "eculizumab" antibody described in Bell (AMG1005) and Wang (AMG1028), a POSA would not have reasonably expected any formulation used for Bell and Wang's "eculizumab" to also work for antibody comprising SEQ ID NOs: 2 and 4.

ALXN2029 at 23; ALXN2084 at 2; AMG1029 at 21; ALXN2080 at 175; ALXN2079 at 2, 4-5, 10.)

72. If, as Dr. Balthasar argues, a POSA had known that an antibody comprising SEQ ID NOs: 2 and 4 had a hybrid IgG2/IgG4 constant region (*e.g.*, AMG1002 ¶ 56), that further supports my opinion that a POSA would not have been motivated to make, and would not have reasonably expected to succeed in making, any pharmaceutical compositions of that antibody suitable for therapeutic use. As of March 15, 2007, there were no commercially marketed antibodies demonstrating that an antibody with a hybrid IgG2/IgG4 constant region was capable of pharmaceutical formulation.[4] (AMG1029 at 2-4 (Table 1); ALXN2032 at 251:3-7.) Furthermore, nothing in Bell (AMG1005) or Wang (AMG1028)

[4] And hypothetically, even if a different IgG2/IgG4 isotype antibody had been previously formulated, it was still the case that a POSA could not assume from the formulation of one antibody construct to a particular concentration in liquid that a different antibody could be formulated to a given concentration, if at all, because even slightly different antibodies could have markedly different formulation properties. (*See* Section VI.B above.)

stated that an antibody with a hybrid IgG2/IgG4 constant region was capable of pharmaceutical formulation or had been used in any human clinical studies.[5]

73. A POSA would have been particularly concerned about whether a new, previously-unformulated and untested antibody comprising SEQ ID NOs: 2 and 4 could be formulated as a single-use dosage form in **solution**, as claim 6 of the '504 patent requires. A POSA as of March 15, 2007 would have known that, even "[a]mong all the **commercial antibody products**," only "**about half** are stable enough to be formulated in a liquid form" (which a solution is). (AMG1029 at 14.) For a previously-unformulated and unstudied antibody, a POSA would have had an even lower expectation of success in making a solution formulation

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[5] Dr. Balthasar also asserts that Evans (AMG1007) "provided information regarding how to prepare pharmaceutical compositions comprising eculizumab." (AMG1002 ¶¶ 80, 91 (citing AMG1007, 18:30-43.) I have reviewed Evans (AMG1007), as well as Dr. Balthasar's deposition testimony regarding Evans, and it is my understanding that Evans does not disclose "eculizumab," an antibody with SEQ ID NOs: 2 and 4, or any other full-length humanized antibodies, and thus does not provide any information on pharmaceutical compositions of such antibodies. (ALXN2032 at 163:5-15, 163:25-164:19, 169:13-18, 199:15-17.)

than what was known for the products that had already been commercially marketed.

74. I note that Dr. Balthasar's "Appendix I" is misleading with respect to the number of FDA approved formulations in solution as opposed to lyophilized form. While all the products he lists were injectables, many of them were formulated as single-unit dosage forms of **lyophilized powders** – a **solid** form, not a solution.[6] (AMG1029 at 2-4 (Table 1); AMG1059 at 1; AMG1061 at 1;

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[6] While lyophilized (solid) formulations are eventually reconstituted into a solution just prior to administration by injection, a POSA as of March 15, 2007 would have understood that does not make the **pharmaceutical composition** itself (*i.e.*, the product of manufacture) a "solution." (*See* AMG1029 at 2-4 (Table 1) (containing entries for formulations described as "solution[s]" and, separately, entries for formulations with a specific concentration "on reconstitution"), 14; AMG1030 at 694; ALXN2079 at 10-11.) As a POSA would have known, there were potential advantages to making a liquid (solution) composition for injection versus a lyophilized composition – but obtaining the benefit of these potential advantages was dependent on the unpredictable question of whether a suitable solution formulation was even possible. (AMG1029 at 14; AMG1030 at 694; ALXN2079 at 10-11.)

Samsung Bioepis Exhibit No. 1002
Page 13341

AMG1066 at 1; AMG1067 at 1; 1070 at 1; 1071 at 1; AMG1074 at 1.) For example, while the product Remicade® (infliximab) was administered by intravenous infusion, its pharmaceutical composition was "a sterile, white, **lyophilized powder**." (AMG1067 at 1.) As discussed above, lyophilization was a formulation approach that generally leads to a more stable formulation than a solution formulation. (*See* Section VI.B above.)

75. Accordingly, if a POSA as of March 15, 2007 had no information regarding the pharmaceutical formulation or clinical use of an antibody comprising SEQ ID NOs: 2 and 4, it is my opinion that a POSA would not have been motivated to make the pharmaceutical compositions recited in claims 1-10 of the '504 patent, and would not have reasonably expected to succeed in doing so.

B. Bell (AMG1005) and Wang (AMG1028) Would Not Have Motivated a POSA Prior to March 15, 2007 to Make the Pharmaceutical Composition of '504 Patent Claim 6, or Given a POSA a Reasonable Expectation of Success in Doing So

76. Assuming, hypothetically, that a POSA prior to March 15, 2007 would have identified the "eculizumab" antibody of Bell (AMG1005) and Wang (AMG1028) as an antibody comprising SEQ ID NOs: 2 and 4 of the '504 patent,[7]

[7] As noted throughout my Declaration, I have not seen any evidence in my review of Bell (AMG1005) or Wang (AMG1028) that a POSA prior to March 15,

it is my opinion that a POSA prior to that date would not have been motivated by Bell and Wang to make a "300 mg single-use formulation of 30 ml of a 10 mg/mL sterile, preservative free solution" of the antibody comprising SEQ ID NOs: 2 and 4, as recited in claim 6 of the '504 patent, or a "300 mg single unit dosage form" of such an antibody as recited in claim 5 of the '504 patent, and that a POSA prior to that date would not have reasonably expected to succeed in doing so. Nothing in Bell or Wang, alone or in any combination, disclosed a pharmaceutical composition of "eculizumab" featuring a 300 mg single-use dosage form a 10 mg/ml solution of "eculizumab," or would have motivated or given a POSA a reasonable expectation of success in making such a pharmaceutical composition of "eculizumab."

77. First, nothing in Bell (AMG1005), Wang (AMG1028) or Dr. Balthasar's other cited documents would have motivated a POSA prior to March 15, 2007 to specifically make a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single-use dosage form. Neither Bell nor Wang

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2007 would have known the specific, complete amino acid sequence of the "eculizumab" antibody they disclose, or that a POSA would have connected an antibody comprising SEQ ID NOs: 2 and 4 to the "eculizumab" antibody of Bell and Wang.

disclosed such a pharmaceutical composition, or would have given a POSA any confidence that a 10 mg/ml concentration of "eculizumab" in solution would have been suitable for a pharmaceutical composition as claimed in the '504 patent.

78. Bell (AMG1005) discloses nothing about a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" (or any other concentration of "eculizumab") in a single use dosage form. Bell described, among other things, the results of an 11-patient, 12 week clinical trial (and 52-week and 2-year extensions of that clinical trial), where "eculizumab" was administered to PNH patients by "intravenous infusion," in 600 mg weekly doses for four weeks, followed by 900 mg for all successive doses, and was shown to alleviate their symptoms. (AMG1005 ¶¶ [0081]-[0096].) A POSA reading Bell would have understood that "eculizumab" could in fact be formulated as some kind of pharmaceutical composition suitable for therapeutic use (including for use in treating patients with PNH). But a POSA would **not** have known from Bell any of the details regarding that pharmaceutical composition, including, for example, whether the composition was in solution or was a solid, lyophilized composition; and if the composition was in solution, what was the specific **concentration** of "eculizumab" in that solution.

79. Dr. Balthasar's suggestion that Bell provided information for "formulating eculizumab" or "prepar[ing] pharmaceutical compositions

comprising eculizumab" is thus misleading. (*E.g.*, AMG1002 ¶¶ 80, 91 (citing AMG1005 ¶ [0062]); AMG1002 ¶ 130 (citing AMG1005 ¶¶ [0060], [0062]).) A POSA prior to March 15, 2007 would have seen that paragraphs [0060] and [0062] of Bell were very general statements discussing, for example, all conceivable routes of administration (whether feasible or not), and reference to a general reference book for the concept of "[f]ormulations suitable for injection." Nothing in Bell suggested specifically making a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single use dosage form, or would have given a POSA a reasonable expectation that such a composition would have been suitable as a pharmaceutical formulation, for the treatment of patients with PNH or otherwise.

80. Further, even if Bell were combined with the information in Wang (AMG1028), a POSA prior to March 15, 2007 would not have envisioned or been motivated to make a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single use dosage form, and would not have reasonably expected success in making or using such a composition.

81. First, I disagree with Dr. Balthasar's premise that a POSA prior to March 15, 2007 would have had any motivation to combine Bell (AMG1005) with Wang (AMG1028). (AMG1002 ¶ 149.) While Bell described clinical studies showing that "eculizumab" safely and effectively treated **PNH** when administered

by **intravenous infusion** (AMG1005 ¶ [0082]),[8] Wang (AMG1028) had an entirely different focus – "treating **pulmonary diseases**" (*i.e.*, respiratory diseases such as asthma) by "**nebulization**" (dispersing into small particles for inhalation) of various different monoclonal antibodies (AMG1028 at, e.g., ¶¶ [0004]-[0009], [0058]-[0066]; ALXN2032 at 256:24-258:9.) A POSA would have had no reason to disregard the clinically proven intravenous route for "eculizumab" in treating PNH – a systemic blood condition – and instead use Wang's "nebulization" technology intended to deliver drugs locally to the respiratory tract. (*See* AMG1004 at 553-54; AMG1012 at 1234-35; AMG1047 at 2559-60; ALXN2032 at 258:10-16.)

82. As Dr. Balthasar concedes, nothing in Wang (AMG1028) disclosed a 10 mg/ml composition of "eculizumab" for intravenous infusion. (ALXN2032 at 260:5-13.) And even if a POSA were to have combined Bell with Wang, it is my opinion that nothing in that combination disclosed a pharmaceutical composition containing a 10 mg/ml solution of "eculizumab" in a single use dosage form.

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[8] I understand that the other reported clinical trials of "eculizumab" in treating PNH prior to March 15, 2007 likewise administered the drug by intravenous infusion. (AMG1004 at 554; AMG1012 at 1235; AMG1047 at 2560.)

83. While I agree with Dr. Balthasar that ensuring adequate stability is an important part of formulation development, contrary to Dr. Balthasar's assertions, nothing in Wang "disclose[d] that eculizumab is stable when formulated at a range of concentrations between 1 mg/ml and 30 mg/ml." (*E.g.*, AMG1002 ¶ 16.) First, the range of "1 to 30 mg/ml" that Dr. Balthasar cites from paragraph [0170] and Figure 10 of Wang (AMG1028) is **not a range for eculizumab**, but refers to a broad range that can include different possible antibodies, including at least the anti-mouse C5 antibody "BB5.1." (*See* AMG1028 ¶ [0170], Figure 10; *see also id.* at ¶ [0067] (describing "an antibody of the present application" as including antibodies specific to various targets, full-length antibodies and fragments, amongst others).) Neither paragraph [0170] nor Figure 10 use the term "eculizumab"; instead, paragraph [0170] refers to "examples for nebulization of **an antibody**," and Figure 10 provides two "Example" formulations with no specific antibody identified.[9] (*Id.* at ¶ [0170], Figure 10.) While Wang (AMG1028) contains some examples of a **30 mg/ml solution** of "eculizumab" (which, as

[9] In Formulation 1 in Figure 10, only a generic "mAb" is listed with no names or indication of any specific mAb, and certainly not "eculizumab"; and in Formulation 2, there is no monoclonal antibody listed, not even a generic one. (AMG1028, Fig. 10.)

explained below, was **not** shown to be stable), there is simply nothing in Wang disclosing a 10 mg/ml solution composition of "eculizumab," for nebulization or any other use.

84. Nor does anything in Wang (AMG1028) state that "eculizumab could be stably formulated at a concentration between 1 and 30 mg/ml," as Dr. Balthasar further asserts. (*E.g.*, AMG1002 ¶ 113 (citing AMG1028 at Fig. 10 and ¶¶ [0170]-[0172]).) Rather, all that Wang showed with respect to "eculizumab" was that a 30 mg/ml solution of "eculizumab" could be "effectively and efficiently nebulized" by a nebulizer. (AMG1028 at Fig. 10 and ¶¶ [0170]-[0172].) Nothing in Wang provided any of the standard data that a POSA as March 15, 2007 would have expected to see in establishing the stability of an antibody formulation, including, for example, data **over time** and under various **storage conditions** to establish that the composition is sufficiently stable to be stored for a reasonable time prior to human administration. (ALXN2085 at 2; ALXN2084 at 2, 5-6; ALXN2029 at 23; ALXN2080 at 177-78; ALXN2079 at 6-7, 15-16.)

85. For example, paragraph [0170] and Figure 10 of Wang, which Dr. Balthasar cites for the range of "1-30 mg/ml," does not state anything about the stability of eculizumab formulations within that range. Paragraph [0170] merely says that "[e]xamples of formulations suitable for nebulization of an antibody are shown in FIG. 10." Furthermore, paragraph [0170] mentions "BB5.1," but not

"eculizumab." (AMG1028 ¶ [0170]; *see also* AMG1028 ¶ [0025] ("FIG. 10 shows exemplary formulations suitable for nebulization of an antibody.") Figure 10 of Wang, in turn, lists a "Formulation 1," with 1-30 mg/ml of an unspecified antibody, and a "Formulation 2," with 40-200 mg/ml of an unspecified antibody. (AMG1028, Fig. 10.) Nothing in these statements would have indicated to a POSA that **eculizumab** "could be stably formulated at a concentration between 1 and 30 mg/ml," let alone in a 10 mg/ml solution specifically.

86. The **only** statement in Wang (AMG1028) actually mentioning "stability" states: "The antibody may be stable in a formulation at a concentration ranging from 1 mg/ml to 200 mg/ml." (AMG1028 ¶ [0067].) First, in the context of this statement, a POSA would have understood that "[t]he antibody" refers to a wide variety of possible antibodies, fragments and other compounds "specific to C5" (including even different antibodies for different epitopes). (AMG1028 ¶ [0067].) Second, in light of the use of the term "may," a POSA would not have viewed this isolated statement as teaching that every possible anti-C5 antibody and fragment within its scope would necessarily be stable at all concentrations within the broad recited range. Accordingly, a POSA would have understood that this statement was, at best, hypothetical, with no specific consideration of "eculizumab" or any other antibody, and that it did not reflect the results of any actual stability testing performed on any specific antibody at any specific

concentration – including a 10 mg/ml solution of "eculizumab." With no understanding that Wang provided any specific guidance for a stable "eculizumab" formulation, a POSA would not have looked to Wang to make such a composition, as Dr. Balthasar contends.

87. Figures 11-15 referenced in paragraphs [0170]-[0172] of Wang (AMG1028) also provide no evidence that, as Dr. Balthasar contends, "eculizumab could be stably formulated" in a 10 mg/ml solution composition. (AMG1002 ¶ 113.) Figure 11, described further in Wang paragraph [0170], is a test of a **different** antibody ("BB5.1") in a mouse respiratory model.[10] (AMG1028 at Fig. 11, ¶ [0170].) Figure 12, using 30 mg/ml eculizumab in "Formulation 1," likewise did not test for stability pertinent to developing a single-use dosage form of a solution for intravenous infusion (*e.g.*, degradation over time and under potential storage conditions). Instead Figures 12 and 13 rather looked at whether the composition could be "effectively and efficiently delivered through a nebulizer" – using *in vitro* tests designed to measure the size of particles being delivered by the nebulizer and the efficiency of nebulizer delivery. (AMG1028 at Fig. 12-13, ¶¶ [0171]-[0172]; ALXN2032 at 259:6-9.) Figures 12 and 13, referenced in

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[10] I note that Wang (AMG1028) does not disclose the administration of any "eculizumab" composition even to animals, let alone to humans.

paragraphs [00171-0172], only disclose data related directly to the testing of the nebulization process, do not include any stability information, and neither in Figure 13 nor in the description of it in [0172] and [0028] is the specific tested concentration of "eculizumab" disclosed.

88. I also disagree with Dr. Balthasar that Figures 14 and 15 of Wang (AMG1028) "indicate[] that eculizumab is sufficiently stable to be used as a therapeutic when formulated at a concentration of 1 to 30 mg/ml." (AMG1002 ¶ 113.) Figures 14 and 15 of Wang only studied one type of stress very specific to formulations for use in nebulization: "the integrity of the nebulized antibody through various sizes of the spray mouth piece." (AMG1028 ¶ [0173].) Further, there is nothing in Wang indicating exactly what concentration of eculizumab was used in the experiments reported in Figs. 14 and 15, just identifying it as "[e]culizumab in a suitable formulation." (AMG1028 ¶ [0173].) Figures 14 and 15 do not report the stability of their undefined "suitable formulation" over time, or under any stresses or conditions that a POSA would have understood to be pertinent to assessing the stability of a single use dosage form containing a monoclonal antibody solution.

89. Without suitable information disclosed in Wang (AMG1028) or elsewhere regarding the stability of a single use dosage form containing 10 mg/ml eculizumab formulated in solution, a POSA would not have reasonably expected

success with the pharmaceutical compositions recited in claim 6 of the '504 patent. As discussed above in Section VI.B, an insufficiently stable antibody formulation could lack efficacy and result in serious safety issues. A POSA prior to March 15, 2007 would not have had a reasonable expectation of success in making the claimed pharmaceutical composition of claim 6 of the '504 patent without evidence that a 10 mg/ml eculizumab solution composition was suitably stable" – particularly given that the claims require use of the pharmaceutical composition in "[a] method of treating a patient suffering from [PNH]." (*See* Section [ ], *supra*.)

90. A POSA prior to March 15, 2007 also could not have reasonably predicted from any of the commercialized products as of that date that a single-use dosage form containing a 10 mg/ml solution of "eculizumab" could be used in a suitable pharmaceutical composition. (*See* AMG1029 at 5 (antibody formulation development not straightforward due to antibodies' variable behavior, despite similar structures); AMG1030 at 690 (each antibody presents unique requirements for stability).) Dr. Balthasar is mistaken that 5 out of 23 commercially marketed antibodies as of March 15, 2007 were 10 mg/ml antibody solutions (AMG1002 ¶ 114), because one of the five products that he identifies was not even a solution composition (Remicade®). (AMG1002 ¶ 114, Appendix I; AMG1029 at 2-4 (Table 1); AMG1067 at 1.) And even counting Remicade®, only **one** of the 23 commercialized antibodies as of March 15, 2007 was a **full-length humanized**

antibody formulated as a 10 mg/ml solution (Campath®)[11] – and that product had an IgG1 isotype, not the "hybrid" isotype that Dr. Balthasar attributes to "eculizumab." (AMG1002 ¶ 114, Appendix I; AMG1029 at 2-4 (Table 1); AMG1058 at 13; AMG1063 at 4; AMG1067 at 1; AMG1069 at 1; AMG1073 at 1.) Further, a POSA would have seen that many commercialized full-length humanized antibodies appeared unsuitable for solution compositions, and instead were produced as solid, lyophilized compositions. (AMG1029 at 2-4 (Table 1), 14; AMG1056 at 1; AMG1071 at 1; AMG1074 at 1; AMG1061 at 1.) Having said all of that, even if were the case that 10 mg/ml were a common concentration for antibody formulations, that would have given a POSA no indication of whether or not a particular antibody (*e.g.*, eculizumab) could be formulated at 10 mg/ml without applying hindsight reasoning. (*See* VI.B above.)

91. I also disagree with Dr. Balthasar that it would have been obvious in view of Bell (AMG1005) to formulate "eculizumab" as a 300 mg single-use dosage form. (*E.g.*, AMG1002 at 102.) Dr. Balthasar asserts, with no support, that a POSA would have necessarily been motivated to make a 300 mg single-use dosage form to achieve the 600 and 900 mg doses described in Bell, rather than

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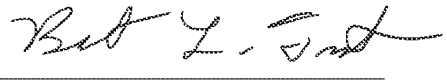
[11] The other products were a mouse Fab (Verluma®), mouse/human chimeric antibodies (Rituxan®, Remicade®), and a humanized IgG1 fragment (Lucentis®).

make 600 mg and 900 mg single use dosage forms, asserting that it would have been "the simplest, most efficient, and most convenient way." (AMG1002 ¶ 106.) I disagree. For example, it would be beneficial for ease and accuracy of administration for providers to use a single unit for each administration, rather than to use two or three. It is quite common for pharmaceutical products, including monoclonal antibody products, to be available in different dosage amounts, for the convenience of patients and health care providers. Dr. Balthasar's own references provide information on multiple antibody products that are available in difference doses. For example, bevacizumab was supplied in both 100 mg and 400 mg doses (AMG 1056, p. 2, 25); tositumomab was supplied in both 35 mg and 225 mg doses, and a given carton contains two 225 mg vials and one 35 mg vial (AMG 1057, p. 2,3); and rituximab was supplied in both 100 mg and 500 mg doses (AMG 1069, p. 1, 2).

Samsung Bioepis Exhibit No. 1002
Page 13354

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. I further declare that I made these statements with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: November 22, 2019



Bernhardt L. Trout, Ph.D.

Appendix A

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Director, Novartis-MIT Center for Continuous Manufacturing, June 2007 – May 2019
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Professor of Chemical Engineering, January 2008 – October 2014
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Associate Professor of Chemical Engineering, July 2003 – December 2007
Assistant Professor of Chemical Engineering, January 1998 – July 2003

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Page 13357

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Awards and Honors:

The Medicine Maker "Power List", 2019
ISCMP Co-Chair, 2018
The Medicine Maker "Power List", 2017
ISCMP Co-Chair, 2016
The Medicine Maker "Power List", 2016
AIChE Division 15 (FPBE) Plenary Speaking Award, 2015
Armenian Academy of Engineering, Foreign Member, elected 2015
The Medicine Maker "Power List", 2015
AIChE Excellence in Process Development Research Award, 2014
ISCMP Co-Chair, 2014
ISCMP Downstream Pharmaceutical Panel Chair, 2014
CCR Research Collaboration Award, 2014
Manufacturing Technology Runner-up for the Wall Street Journal Technology Innovation Award, 2012
Impact Award from the Computational Molecular Science and Engineering Forum of the AIChE (CoMSEF), 2011
ACS Plenary Lecture, 2011
AIChE Area 1A Program Chair, 2006
National Academy of Engineering participant in "Frontiers in Engineering," 2001
Henry L. and Grace Doherty Professorship, 2001 – 2003
Ford Motor Company Young Investigator Award, 2001
NSF CAREER Award, 2000 – 2004
Joseph R. Mares Junior Faculty Chair, 1998 – 2001
Max-Planck Institute Fellowship, 1996 – 1997
NSF Graduate Fellowship, 1991 – 1994

Committees/Memberships:

Samsung Bioepis Exhibit No. 1002
Page 13358

MIT Advisory Board for Social and Ethical Responsibilities of Computing (SERC), 2019-2020
MIT Schwarzman College of Computing Committee on Social Implications, 2019
MIT Task Force on Open Access, 2017 – 2019
Task Force on Open Access, Contracts subteam, 2017-2019
United States Pharmacopeia Expert Panel: Quality Standards for Pharmaceutical Continuous Manufacturing, 2016 – present
Molecular Systems Design & Engineering (MSDE), Royal Society of Chemistry Journal, Editorial Board Member, 2016 – present
FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, Consultant, 2015 – 2018
MIT Chemical Engineering Department Head Search Advisory Committee, 2015
FDA Coordination Group at MIT, 2014 – 2016
MIT Committee on Intellectual Property, 2011 – 2016
MIT Committee on the Undergraduate Program, 2006 – present
MIT Faculty Search Committee, 2006 – present
MIT Practice School Steering Committee, 2004 – 2015
ISPE Subcommittee on Pharmaceutical Manufacturing, 2010 – 2011
ISPE Subcommittee on Continuous Production, 2008
MIT Graduate Committee, 2006 – 2009
DuPont-MIT Advisory Committee, 2005 – 2007
Hottel Lecture Committee, 2004 – 2007
SMA Annual Report Committee, 2003 – 2012
Department Computer Committee, 2002 – 2007

Conferences Organization:

Co-Chair, International Symposium on Continuous Manufacturing, October 2018
Co-Chair, International Symposium on Continuous Manufacturing, September 2016
Chair, MIT Mastery of Nature Conference, May 2016
Organizing Committee, AIChE/FDA P2DM Workshop on Continuous Manufacturing, March 2016
Co-Chair, International Symposium on Continuous Manufacturing, May 2014

Scientific Publications:

203. Jensen, K., Xiang, A., Fitch, H., Alden, E., Myerson, A.S., and Trout, B.L., "Water-soluble Placebo Polymer Thin Films for Continuous Manufacturing of Tablets," *J. Appl. Polym. Sci., submitted.*

202. Badman, C., Cooney, C. L., Florence, A., Konstantinov, K., Krumme, M., Nasr, M. N., Mascia, S., Trout, B.L., "Why We Need Continuous Pharmaceutical Manufacturing and How to Make it Happen," *J. Pharm. Sci.,* **108**, 3521 (2019). **Featured Article**

Samsung Bioepis Exhibit No. 1002
Page 13359

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Samsung Bioepis Exhibit No. 1002
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4. Trout, B.L. and Parrinello, M., "The dissociation mechanism of H_2O in water studied by first-principles molecular dynamics," *Chem. Phys. Lett.*, **288**, 343 (1998).

3. Trout, B.L., Chakraborty, A.K. and Bell, A.T., "Diffusion and reaction in ZSM-5 studied by dynamic Monte Carlo," *Chem. Eng. Sci.*, **52**, 2276 (1997).

Samsung Bioepis Exhibit No. 1002
Page 13377

2. Trout, B.L., Chakraborty, A.K. and Bell, A.T., "Analysis of the thermochemistry of NO_x decomposition over CuZSM-5 based on quantum chemical and statistical mechanical calculations," *J. Phys. Chem.*, **100**, 17582 (1996).

1. Trout, B.L., Chakraborty, A.K. and Bell, A.T., "Local spin density functional theory study of copper ion-exchanged ZSM-5," *J. Phys. Chem.*, **100**, 4173 (1996).

Philosophical Publications:

2. Trout, B.L., "Quantum Mechanics and Political Philosophy" Minkov, S. Y. and Trout, Bernhardt L. (Eds.), *Mastery of Nature: Promises and Prospects* (pp. 220-232) Philadelphia, PA: University of Pennsylvania Press (2018).

1. Minkov, S. Y. and Trout, Bernhardt L. (Eds.), *Mastery of Nature: Promises and Prospects*, Philadelphia, PA: University of Pennsylvania Press (2018).

Non-Peer Reviewed Publications:

3. Livingston, A., et al. "Challenges and Directions for Green Chemical Engineering-- Role of Nanoscale Materials" in *Sustainable Nanoscale Engineering*, Elsevier, Amsterdam 2020.

2. Trout, B.L., "Foreword." *Developability of Biotherapeutics: Computational Approaches*, CRC Press, 2015.

1. Mascia, S., Trout, B.L., "Integrated Continuous Manufacturing," *Pharmaceutical Manufacturing*, December 2014, pp. 26-29.

Conference Publications:

6. Buck, P.M., Kumar, S., Wang, X., Agrawal, N.J., Trout, B.L., and Singh, S.K., "Computational Methods to Predict Biotherapeutic Protein Aggregation", *Therapeutic Proteins: Methods and Protocols, Second Edition*, Springer, Humana Press. pp. 425-451 (2012).

5. Agrawal, N.J., Lauer, T.M, Hernandez-Guzman, H., Helk, B. and Trout, B.L., "Novel computational tools could mitigate antibody aggregation", *Pharmaceutical Formulation and Quality*, (2012).

4. Radhakrishnan, R., Demurov, A., Herzog, H.J. and Trout, B.L., "Modeling the dissolution of liquid CO_2 in water under hydrate forming conditions," Proceedings of the Fourth International Conference on Gas Hydrates, Yokohama, Japan, May 2002, pp. 262- 266.

Samsung Bioepis Exhibit No. 1002
Page 13378

3. Cao, Z., Anderson, B., Tester, J.W. and Trout, B.L., "Computations of the thermodynamics of methane hydrates using *ab initio* data," Proceedings of the Fourth International Conference on Gas Hydrates, Yokohama, Japan, May 2002, pp. 315- 320.

2. Anderson, B., Bazant, M.Z. and Trout, B.L. "Application of an analytical method to extract molecular potentials from Langmuir curve data," Proceedings of the Fourth International Conference on Gas Hydrates, Yokohama, Japan, May 2002, pp. 418-423.

1. Radhakrishnan, R. and Trout, B.L., "Mechanism for the nucleation of CO_2 hydrate clathrates studied using a Monte Carlo based approach," Proceedings of the Fourth International Conference on Gas Hydrates, Yokohama, Japan, May 2002, pp. 494-497.

Patents:

18. "Continuous Freeze-drying Methods and Related Products." US 62/500,466, Filing Date: May 2, 2017

17. "Continuous Crystallization on Excipient Surface and Tablet Making." US 62/477253, Filing Date: 27.03.2017

16. "Core-Shell Particles for Controlled Release of Organic Material." US 62/348371, Filing Date: 23.09.2016

15. "Biocompatible Polymeric Hydrogels for Controlling Nucleation from Solution and Loading of Hydrophobic and Hydrophilic Pharmaceuticals." U.S. Patent Application: 14/575069, Filing Date: 18.12.2014

14. "Computer-Implemented Methods of Determining Protein Viscosity," U.S. Patent Application: 61/824680, PCT/US2014/038368, International Filing Date: May 16, 2014.

13. "Plasticity Induced Bonding," U.S. Patent No.: 10,213,**960**, Date of Patent: Feb. 26, 2019, PCT/US2015/031666, International Filing Date: May 20, 2015.

12. "Methods and Systems for Manufacturing a Tablet." U.S. Patent No.: 10,053,798, Date of Patent: Aug. 21, 2018, Filed: Apr. 30, 2015.

11. "Layer Processing for Pharmaceuticals." U.S. Patent No.: 9,205,089, Date of Patent: Dec. 8, 2015, Filed Apr. 27, 2012.

10. "Compositions, Methods, and Systems Relating to Controlled Crystallization and/or Nucleation of Molecular Species." U.S. Patent No.: 9,138,659, Date of Patent: Sept. 22, 2015, Filed: Aug. 23, 2011.

9. "Immunoglobulins with Reduced Aggregation.", U.S. Patent No.: 9,676,841, Date of Patent: Jun. 13, 2017, PCT/US2009/047948, International Filing Date: June 19, 2009.

Samsung Bioepis Exhibit No. 1002
Page 13379

8. "Immunoglobulins with Reduced Aggregation.", U.S. Patent No.: 8,747,848, Date of Patent: Jun. 10, 2014, PCT/US2009/047948, International Filing Date: June 19, 2009.

7. "HER2 and VEGF-A-binding Proteins with Enhanced Stability." U.S. Patent No.: 9,777,067, Date of Patent: Oct. 3, 2017, PCT/US2013/062108, International Filing Date: Sept. 27, 2013

6. "Methods to Identify Amino Acid Residues Involved in Macromolecular Binding and Uses Therefor." U.S Patent No.: 10,431,325, Date of Patent: Oct. 1, 2019, PCT/US2013/053499, International Filing Date: Aug. 2, 2013.

5. "Methods and Systems Relating to the Selection of Substrates Comprising Crystalline Templates for the Controlled Crystallization of Molecular Species," U.S. Patent No.: 9,822,467, Date of Patent: Nov. 21, 2017, Filing Date: Nov. 15, 2012.

4. "Dendrimer-Based Excipients for the Attenuation of Protein Aggregation," U.S. Patent No.: 9,410,142, Date of Patent: Aug. 9, 2016, PCT/US2011/060400, International Filing Date: Nov. 11, 2011.

3. "Methods for Identification of Sites for IgG Conjugation.", U.S. Patent No. 9,629,925, Date of Patent: Apr. 25, 2017, PCT/US2010/037517, International Filing Date: June 4, 2010.

2. "Methods for Identification of Sites for IgG Conjugation.", U.S. Patent No. 8,834,885, Date of Patent: Sept. 16, 2014, PCT/US2010/037517, International Filing Date: June 4, 2010.

1. "Methods to Identify Macromolecule Binding and Aggregation Prone Regions in Proteins and Uses Therefor,", U.S. Patent No.: 9,922,164, Date of Patent: Mar. 20, 2018, PCT/US2009/047954, International Filing Date: June 19, 2009.

Invited Talks and Plenary Lectures:

160. November 20, 2019, "Machine Learning for Developability and Formulation Design," CDD for Biologics, Boston, MA.

159. October 30, 2019, "Ethical Issues in AI and Implications for the Law," Artificial Intelligence Driving Life Sciences, Cambridge, MA.

158. October 23, 2019, "Continuous Lyophilization of Unit Doses," Lyophilization USA, Boston, MA.

Samsung Bioepis Exhibit No. 1002
Page 13380

157. September 26, 2019, "Continuous Manufacturing: State of the Art, Challenges, and Future Prospect," IMA conference "Can't Stop the Future: Spotlight on Continuous Manufacturing," Bologna, Italy.

156. June 11, 2019, "Formulation Starts in Discovery," Gordon Research Conference on Preclinical Form and Formulation, Waterville Valley, NH.

155. May 14, 2019, "Developability and Machine Learning for Formulation Design," Biovia Community Day, Dusseldorf, Germany (via webcast).

154. February 27, 2019, "Living a Life of Leisure While Teaching Science in a Classical Secondary School Education," Great Heats Academies, Sandra Day O'Connor College of Law, Phoenix, Arizona.

153. December 1, 2018, "Truths About Quantum Mechanics," St. John's College, Santa Fe, NM.

152. November 7, 2018, "Product and Process Development Start in Discovery," Takeda Pharmaceutical Company, Cambridge, MA.

151. October 25, 2018, "Product and Process Development Start in Discovery," Biovia Community Day, Boston, MA.

150. September 10, 2018, "Developability for Biologics and Approaches to Formulation Design," BioMan Process Intensification Conference, Cambridge, MA.

149. August 3, 2018, "Biomolecular Computational Methods for Protein Engineering Against Aggregation and Other Molecular Liabilities," Acceleron Pharma, Cambridge, MA.

148. May 30, 2018, "Continuous Lyophilization of Pharmaceutical Products in Unit Doses," Hudson Valley LyoMac Webinair.

147. December 7, 2017, "Enabling Developability via Molecular Modeling," CDD for Biologics, Boston, MA.

146. December 1, 2017, "The Significance of Quantum Mechanics," St. John's College, Annapolis, MD.

145. October 17, 2017, "Biomolecular Computational Methods for Protein Engineering Against Aggregation and Other Molecular Liabilities", Biovia Community Day, Cambridge, MA.

144. September 21, 2017, "Developability for Biologics and Approaches to Formulation Design," Biologics, Modeling, and Informatics (BMI) Discussion Group, Cambridge, MA.

Samsung Bioepis Exhibit No. 1002
Page 13381

143. July 19, 2017, "Biopharmaceuticals and Continuous Manufacturing," Senate Competitive Caucus, U.S. Senate, Washington D.C.

142. May 10, 2017, "New Continuous Crystallization Technologies for Small Molecule Pharmaceutical Manufacturing," Vertex Pharmaceuticals, Boston, MA.

141. April 13, 2017, "Ethics and Engineering: How to Think About the Ethics of AI," MIT Course 6 Super UROP, Cambridge, MA.

140. February 10, 2017, "New Technologies for Holistic Pharmaceutical Creation," United States Pharmacopeia, Rockville, MD.

139. February 1, 2017, "New Technologies for Holistic Pharmaceutical Creation: Focus on 3D Printing," Takeda, Zurich, Switzerland.

138. January 31, 2017, "Developability and Manufacturability in Pharmaceutical Creation," Roche, Basel, Switzerland.

137. January 31, 2017, "Developability and Manufacturability in Pharmaceutical Creation," Lonza, Basel, Switzerland.

136. December 15, 2016, "Enabling Developability Via Molecular Modeling," IBC Antibody Engineering & Therapeutics, San Diego, CA.

135. October 26, 2016, "Integrating Discovery, Development and Manufacturing in Pharmaceutical Creation," University of Pennsylvania Department of Chemical and Biomolecular Engineering, Philadelphia, PA.

134. May 13, 2016, "Quantum Mechanics and Political Philosophy," MIT Conference on Mastery of Nature, Cambridge, MA.

133. March 17, 2016, "Ethics in Engineering," MIT Course 6 Super-UROP, Cambridge, MA.

132. October 5, 2015, "New Technologies for Enabling Continuous Manufacturing," PQRI Meeting, Bethesda, MD (plenary lecture)

131. September 16, 2015, "Rational Approaches for the Developability of Biotherapeutics" Boston University Department of Physical Chemistry, Boston, MA

130. September 7, 2015, "MIT's Success at Teaching and Research," National Polytechnic University, Yerevan, Armenia

129. June 4, 2015 "Continuous Processing in (Bio)Pharmaceutical Manufacturing," Ipsen Corporation, Paris, FR

Samsung Bioepis Exhibit No. 1002
Page 13382

128. May 15, 2015 "Advanced Formulation, Stabilization, and Manufacturing of Therapeutic Antibodies" MassBiologics, Boston, MA

127. April 29, 2015 "Continuous Pharmaceutical Manufacture and Advances in Biopharmaceuticals Formulation" The Pall Corporation Technology Symposium, Cambridge, MA. (Keynote Address)

126. April 14, 2015 "Rational Approaches for the Development of Biotherapeutics,"4th International Symposium on Higher Order Structure of Protein Therapeutics, Boston, MA

125. March 27, 2015 "Molecular and Macroscopic Engineering of Small Molecular Crystallization," Department of Mechanical and Chemical Engineering, ETH, Zurich, Switzerland

124. March 24, 2015 "Holistic Pharmaceutical Process Development," Department of Mechanical and Chemical Engineering, ETH, Zurich, Switzerland

123. Sept. 16, 2014 "Enabling Technologies for the Continuous Manufacturing of APIs: Continuous Crystallization" at FDA/PQRI Conference, Silver Spring, MD

122. June 10, 2014 "How 'Continuous' Manufacturing will Transform Biotherapeutic Manufacturing" The Annual Bio Manufacturing & Process Innovation Leaders Summit USA 2014 (MANU-BIO), Boston, MA (Keynote Address)

121. June 6, 2014 "Strategic Approaches for Understanding and Hindering Aggregation" IBC's Protein Aggregation, Stability & Solubility Conference, San Francisco, CA (Keynote Address)

120. March 26, 2014 "Rational Approaches to Developability and Manufacturability" Accelyrs, Cambridge, MA

119. March 21, 2014 "Rational Approaches to Developability and Manufacturability" Bayer, Wuppertal, Germany

118. January 21, 2014 "Rational Approaches for Biologics and Small Molecule Pharmaceutical Development and Manufacturing" Columbia University, New York, NY

117. January 8, 2014 "Rational Approaches to Developability and Manufacturability" Pfizer, Cambridge, MA

116. December 16, 2013 "Rational Approaches to Developability and Manufacturability"BMS, Devens, MA

115. November 7, 2013, "Recent Updates at the Novartis-MIT Center for Continuous Manufacturing", FDA, Silver Spring, MD

Samsung Bioepis Exhibit No. 1002
Page 13383

114. November 5, 2013 "Transforming Manufacturing to "Continuous": Flexible API and Final Dosage Form" ISPE Meeting, Washington, DC

113. October 21, 2013 "Transforming Small Molecule Pharmaceutical Manufacturing to Continuous and the Potential for Continuous Biologics Manufacturing," Integrated Continuous Biomanufacturing, an ECI Conference, Barcelona, Spain (Keynote Address)

112. September 11, 2013 "Rational Approaches to Developability and Manufacturability," Biogen Idec, Cambridge, MA

111. September 10, 2013 "Rational Approaches to Developability and Manufacturability," Pfizer, Andover, MA

110. July 10, 2013 "What Molecular Modeling in Pharmaceutical Development Can Do for You," BMS Symposium on Modeling, New Brunswick, NJ (Keynote Address)

109. June 27, 2013 "Capitalizing on Continuous Manufacturing," 8th Global Pharma Manufacturing Summit, Boston, MA (Plenary Lecture)

108. June 12, 2013, "Transforming Small Molecule Pharmaceutical Manufacturing to Continuous and the Potential for Continuous Biologics Manufacturing," Biomanufacturing Leaders Summit, Boston, MA (Keynote Address)

107. April 24, 2013 "From Molecular Computations to Continuous Manufacturing and Their Role in Shaping a Sustainable Future," 9th European Congress of Chemical Engineering, The Hague, Netherlands (Plenary Lecture)

106. April 19, 2013 "Transforming Pharmaceutical Manufacturing Continuous: The Ultra Lean Way of Manufacturing," Pharmintech, Bologna, Italy (Keynote Address)

105. March 26, 2013, "Rational Approaches to Developability for Stabilization Against Aggregation and Other Routes," 6th Annual Proteins Conference, London, UK.

104. November 15, 2012, "Rational Approaches to Developability, Formulation, and Design of Biobetters," MIT Center for Biomedical Innovation: Biomanufacturing Summit, Cambridge, MA

103. November 14, 2012, "Advanced manufacturing for pharmaceuticals and the Novartis-MIT center for continuous manufacturing," MIT ILP R&D Conference, Cambridge, MA

102. August 21, 2012, "Technical Update for the FDA on the Downstream Continuous Manufacturing Toolbox," FDA, Cambridge, MA

101. May 5, 2012, "Rational Approaches to the Stabilization of Biologics: Incorporating Developability and Manufacturability," Ispen, Milford, MA.

Samsung Bioepis Exhibit No. 1002
Page 13384

100. November 18, 2011, "Protein Aggregation Modeling and Novel Excipients for Downstream Processing: Incorporating Rational Approaches to Developability and Manufacturability for Biotherapeutics," BioMan, Cambridge, MA.

99. November 9, 2011, "Predication of Aggregation Prone Regions in Proteins: Incorporating Rational Approaches to Developability and Manufacturability for Biotherapeutics," CASSS Symposium on Immunogenicity, Gaithersburg, MD

98. October 20, 2011, "Heterogeneous Crystallization of API's on Excipients for "Continuous" Process and Product Design," Peck Symposium at Purdue University, West Lafayette, IN

97. October 19, 2011, "Transforming Pharmaceutical Development and Manufacturing with Molecular Computations ," AIChE Annual Symposium, CoMSEF Award, Minneapolis, MN

96. September 15, 2011, "Transforming Pharmaceutical Manufacturing, Continuous: The Ultra Lean Way of Manufacturing," President Obama's Advanced Manufacturing Partnership, Cambridge, MA

95. August 4, 2011 "Rational Approaches to Stabilization: Incorporating Developability in Discovery through Development Phases," GSK, King of Prussia, PA

94. July 28, 2011 "Rational Approaches to Stabilization: Incorporating Developability in Discovery through Development Phases," Pfizer Research, Cambridge, MA

93. July 21, 2011, "Molecular Modeling Approaches for Predicting The Stability of Biotherapeutics, Antibodies in Particular," Colorado Protein Stability Conference , Breckenridge, CO

92. May 19, 2011, "Computational Approaches for Identifying Degradation "Hotspots": Spatial Aggregation Propensity and Implementation in Pipeline Pilot,"Accelrys North America-UGM Conference, Newark, NJ

91. March 29, 2011, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization," ACS, Anaheim, CA (Plenary Lecture)

90. March 15, 2011, "Transforming Pharmaceutical Manufacturing Continuous: The Ultra Lean Way of Manufacturing," ISPE-NJ

89. November, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," AAPS Annual Meeting, New Orleans, LA

Samsung Bioepis Exhibit No. 1002
Page 13385

88. October, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," PEGS Biotechnology conference, Hannover, Germany

87. September, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Ipsen Corporation, Milford, MA

86. September, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," IBC Protein Formulation Conference, Providence, RI

85. August, 2010, "Molecular Modeling for the Rational Control of Polymorphism and Morphology," Sepracor Corporation, Marlborough, MA

84. July, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," MedImmune Corporation, Gaithersburg, MD

83. July, 2010, "Continuous Manufacturing: The Ultimate in Quality by Design," Sepracor Corporation, Marlborough, MA

82. May, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Accelrys Annual International Conference, Boston, MA

81. April, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," ISPE Biotech Meeting, Cambridge, MA

80. April, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Merck, West Point, PA

79. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Genzyme, MA

78. March, 2010, "Molecular Modeling for the Rational Control of Polymorphism and Morphology," Gilead Corporation, Foster City, CA

77. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Genentech, South San Francisco, CA

Samsung Bioepis Exhibit No. 1002
Page 13386

76. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Amgen, Thousand Oaks, CA

75. March, 2010, "Modeling Protein Degradation Processes and the Development of Rational Approaches to Stabilization and Protein-Cosolute Interactions: A New Strategy of Molecular QbD," Biogen-Idec, Cambridge, MA

74. December, 2009, "Continuous Manufacturing of Small Molecule Pharmaceuticals," Leaders for Global Manufacturing, MIT, Cambridge, MA

73. November, 2009, "Order parameter methods for reactions in complex systems," Princeton Center for Theoretical Sciences, Department of Physics, Princeton, NJ

72. October, 2009, "Rational approaches to protein and antibody stabilization," Schering-Plough, Elizabeth, NJ

71. September, 2009, "Rational approaches to protein and antibody stabilization," Merck & Co., West Point, PA.

70. September, 2009, "Modeling of crystallization processes," Merck Research Laboratories, Rahway, NJ.

69. September, 2009, "Rational approaches to pharmaceutical manufacturing," Merck Research Laboratories, Rahway, NJ.

68. July, 2009, "Continuous manufacturing: the ultra lean way of manufacturing," Biochemical Engineering XVI, Burlington, VT.

67. June, 2009, "Rational approaches to protein and antibody stabilization," Bristol-Meyers Squibb, New Brunswick, NJ.

66. April, 2009, "Reactivity in complex systems," University of Washington.

65. March, 2009, "Reactivity in complex systems," North Carolina Theory Seminar.

64. February, 2009, "Reactivity in complex systems," UCLA.

63. September, 2008, "Continuous manufacturing of pharmaceuticals: the ultra lean way of manufacturing," Global Pharmaceutical Manufacturing Summit, Chicago.

62. June, 2008, "Rational design of solvent formulations via molecular computations," American Association of Pharmaceutical Science National Biotechnology Conference, Toronto, Canada.

Samsung Bioepis Exhibit No. 1002
Page 13387

61. March, 2008, "Frontiers in chemical reactivity and pharmaceutical manufacturing," Department of Chemical Engineering, University of Puerto-Rico.

60. March, 2008, "Frontiers in chemical reactivity and pharmaceutical manufacturing," Department of Chemical and Biomolecular Engineering, University of Illinois, Urbana-Champaign.

59. Oct., 2007, "Formulation approaches for the future," IBC Life Sciences on Formulation Strategies for Protein Therapeutics, Hynes Convention Center, Boston, Keynote Address.

58. July, 2007, "Understanding reaction processes in complex media such as liquids," Gordon Conference on the Chemistry of Liquids, Holderness School, New Hampshire

57. June, 2007, "Molecular Design of New Excipients for Large Molecule Stabilization," AAP National Biotechnology Conference, San Diego, CA.

56. March, 2007, "Finding reactions coordinates for complex processes via likelihood maximization," ACS Spring Meeting, Chicago, IL.

55. November, 2006, "Understanding complex reaction processes," Department of Chemical Engineering, University of Buffalo, Buffalo, New York.

54. July, 2006, "Molecular simulations of ice and gas hydrate nucleation," Physics and Chemistry of Ice Conference, Bremerhaven, Germany, Keynote Address.

53. June, 2006, "Reaction coordinates from likelihood maximization," U.S.-Poland Workshop on Nanoscience and Nanostructured Materials, Poznan, Poland.

52. June, 2006, "Understanding complex reaction processes with applications to pharmaceuticals and heterogeneous catalysis," Department of Chemistry, University of Western Ontario, London, Ontario, Canada.

51. February, 2006, "Statistical physics applied to the development of biopharmaceuticals," Department of Physics, University of Rome "La Sapienza," Rome, Italy.

50. February, 2006, "Statistical physics applied to the development of biopharmaceuticals," SISSA, International School for Advanced Studies, Trieste, Italy.

49. September, 2005, "Molecular engineering of chemical systems," Department of Chemical Engineering, Drexel University, Philadelphia, Pennsylvania.

48. September, 2005, "Molecular engineering of chemical systems," Department of Chemical Engineering, Texas A&M, College Station, Texas.

47. September, 2005, "Reactivity in complex systems," Meeting in honor of Michele Parrinello's 60th Birthday, Agno, Switzerland.

Samsung Bioepis Exhibit No. 1002
Page 13388

46. July, 2005, "Molecular computational engineering: mechanism of methionine oxidation and rational design of additives for hindering aggregation," Protein Stability Conference, Breckenridge, Colorado.

45. May, 2005, "Transition Path Sampling Calculations in Complex Systems or How Can We Find the Reaction Coordinate?" 2005 International Conference on Scientific Computation and Differential Equations (SciCADE), Nagoya, Japan.

44. March, 2005, "Molecular computations for predictions of clathrate-hydrate nucleation and phase-behavior of multi-component hydrates," Hydrate Symposium at the American Chemical Society Spring Meeting, San Diego, California.

43. March, 2005, "Water structuring in phase transitions and in chemical reactions at sulfur sites in proteins," Water: Structure, Dynamics and Reactions Across the Phase Diagram at the American Chemical Society Spring Meeting, San Diego, California.

42. July, 2004, "A unified approach for the nucleation of ice and ice-like systems in homogeneous and inhomogeneous environments," Telluride Workshop on Studies of ice, icy particles, ice surfaces, and ice-adsorbate interactions: a molecular view," Telluride, Colorado.

41. April, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Tufts University, Medford, Massachusetts.

40. April 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemistry, Boston University, Boston, Massachusetts.

39. March, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Cornell University, Ithaca, New York.

38. March, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Department of Chemical Engineering, University of Rochester, Rochester, New York.

37. February, 2004, "Molecular analyses and design for the stabilization of therapeutic proteins," Department of Chemical Engineering, Tsinghua University, Beijing, China.

36. February, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Department of Chemistry, Fudan University, Shanghai, China.

35. February, 2004, "Reactivity for phase transitions, zeolites, and biological systems," Center for Atomic-Scale Materials Physics (CAMP) and Department of Physics, Technical University of Copenhagen, Copenhagen, Denmark.

34. November, 2003, "Ordering of water in phase transitions and biological systems," Department of Chemistry, Washington University, St. Louis, MO.

Samsung Bioepis Exhibit No. 1002
Page 13389

33. November, 2003, "Ordering of water in phase transitions and biological systems," Department of Physics, University of Missouri, Columbus, MO.

32. October, 2003, "Nucleation and growth of clathrate-hydrates and ice and a new theoretical framework to address those," Dartmouth University, Thayer School of Engineering, Dartmouth, NH.

31. September, 2003, "Finding reaction pathways for industrial chemical problems," Statistical Mechanics of Rare Events, Paris, France.

30. September, 2003, "Analyses of reactions in acid zeolites and of proteins via nudged elastic band calculations and Car-Parrinello simulations," CECAM Workshop on Reactivity, Lyon, France.

29. May, 2003, "Reactivity of acidic zeolites via quantum chemical and Car-Parrinello molecular dynamical methods," Advances in the Understanding and Application of Catalysis, Moscow, Russia, *Plenary Lecture*.

28. April, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, Princeton University, Princeton, NJ.

27. April, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, University of Pittsburgh, Pittsburgh, PA.

26. March, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, University of Texas, Austin, TX.

25. March, 2003, "Reactivity of acidic zeolites via quantum chemical and Car-Parrinello molecular dynamical methods," invited talk in "Mechanistic Surface Chemistry," Spring Meeting of the American Chemical Society, New Orleans, LA.

24. March, 2003, "Effects of solvation on biological processes," invited talk in "Symposium in Honor of Professor Clayton J. Radke, recipient of the American Chemical Society Award in Colloid Chemistry," Spring Meeting of the American Chemical Society, New Orleans, LA.

23. March, 2003, February, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, Stanford University, Palo Alto, CA.

22. February, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, Tsinghua Univeristy, Beijing, China.

21. February, 2003, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, North Carolina State University, Raleigh, NC.

Samsung Bioepis Exhibit No. 1002
Page 13390

20. November, 2002, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, University of California, Berkeley, CA.

19. November, 2002, "Solvation effects in clathrate-hydrates and biological systems," Department of Chemical Engineering, California Institute of Technology, Pasadena, CA.

18. July, 2002, "Nucleation of and transport in clathrate-hydrates and ice," Physics and Chemistry of Ice Conference, New Foundland, Canada.

17. June 2002, "Quantum mechanical calculations applied to engineering problems," Steacie Institute of Molecular Sciences, National Research Council, Ottawa, Ontario, Canada.

16. April, 2002, "Molecular simulations for the stabilization of therapeutic proteins and the quantification of nucleation of clathrate-hydrates," Rensselaer Polytechnic Institute, Troy, NY.

15. April, 2002, "Quantification of reactive sites in zeolitic and transition metal catalysts via first-principles," ACS Meeting, Orlando, Fl.

14. February, 2002, "The identification and study of sites of varying activity in zeolites and transition metal catalysts," First-Principles Catalysis, Vienna, Austria.

13. February, 2002, "Order-disorder transitions on the surface of ice and in bulk ice and clathrate-hydrates," Swiss Center for Computational Sciences, Manno, Switzerland.

12. February, 2002, "Molecular simulations for the stabilization of therapeutic proteins and the quantification of nucleation of clathrate-hydrates," Colorado School of Mines, Golden, CO.

11. August, 2001, "Car-Parrinello simulations of the disordering of ice and dissociation of HCl, relevant to stratospheric chemistry," ACS Meeting, Chicago, IL.

10. July, 2001, "Insight into the stabilization of therapeutic proteins via molecular simulations," National University of Singapore, Singapore.

8. June, 2001, "Insight into the stabilization of therapeutic proteins via molecular simulations," Hong Kong University of Science and Technology, Hong Kong.

8. April, 2001, "Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics," University of Connecticut, Storrs, CT.

6. February, 2001, "Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics," Georgia Institute of Technology, Atlanta, GA.

6. January, 2001, "Multi-scale modeling of hydrate-clathrates from first-principles to macroscopic thermodynamics," National University of Singapore, Singapore.

Samsung Bioepis Exhibit No. 1002
Page 13391

5. November 1999, "Sustainable development," TBII Leonardo Lecture, MIT.

4. June, 1999, "Application of molecular modeling to automotive catalysis," Workshop held at Ford Motor Company, Dearborn.

3. March, 1999, "Defect structure and its relation to methanol activation", ACS Annual Conference, Annaheim, CA.

2. April, 1998, "Quantum mechanical methods in catalysis: a primer", New England Catalysis Society, Worchester, MA.

1. September, 1996, "Dynamic Monte Carlo study of reaction and diffusion sites in ZSM-5 Zeolites", Technical University of Athens, Athens, Greece.

Professional Affiliations:

AIChE, ACS, ASEE, AAPS

Languages:

French, German, Ancient Greek

Samsung Bioepis Exhibit No. 1002
Page 13392

Appendix B

APPENDIX B

Exh. No.	Description
AMG1001	U.S. Patent 9,725,504 to Bell et al.
AMG1002	Declaration of Joseph P. Balthasar, Ph.D.
AMG1003	Curriculum Vitae of Joseph P. Balthasar, Ph.D.
AMG1004	Hillmen, P., et al., "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria," N. Engl. J. Med. 350:552-559 (2004) ("Hillmen '04")
AMG1005	Bell, L. and Rother, R., "Method of Treating Hemolytic Disease," U.S. Patent Application Publication No. 2005/0191298 A1 (filed February 3,2005; published September 1, 2005)
AMG1006	Bowdish, K., et al., "Rationally Designed Antibodies," U.S. Patent Application Publication No. 2003/0232972 A1 (filed December 2, 2002; published December 18, 2003)
AMG1007	Evans, M., et al., "C5-Specific Antibodies for The Treatment of Inflammatory Diseases," U.S. Patent No. 6,355,245 B1 (filed June 7, 1995; issued March 12, 2002)
AMG1012	Hillmen, P., et al., "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria," N. Engl. J. Med. 355:1233-1243 (2006)
AMG1014	File History for U.S. Patent No. 9,725,504 B2
AMG1016	File History for U.S. Patent No. 9,718,880 B2
AMG1028	Wang, Y., "Nebulization of Monoclonal Antibodies for Treating Pulmonary Diseases," U.S. Patent Application Publication No. 2005/0271660 A1 (filed May 11, 2005; published December 8, 2005)
AMG1029	Wang, W., et al., "Antibody Structure, Instability, and Formulation," Journal of Pharmaceutical Sciences 96: 1-26 (2007)
AMG1030	Daugherty, A. and Mrsny, R., "Formulation and delivery issues for monoclonal antibody therapeutics," Advanced Drug Delivery Reviews 58: 686-706 (2006)
AMG1031	Mueller, P., et al., "Humanized Porcine VCAM-Specific Monoclonal Antibodies With Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding To Porcine Endothelial Cells," Molecular Immunology 34: 441 -452 (1997)

Samsung Bioepis Exhibit No. 1002
Page 13394

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AMG1047	Hill, A., et al., "Sustained response and long-term safety of eculizumab in paroxysmal nocturnal Hemoglobinuria," Blood 106: 2559-2565 (2005) ("Hill '05")
AMG1056	Genentech, Inc., Avastin 2004 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf
AMG1058	Millennium, Campath 2001 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm
AMG1059	Immunomedics, Inc., CEA-Scan 1999 Package Insert, available at https://pharmacyce.unm.edu/nuclear_program/neolibrary/libraryfiles/package_inserts/CEA-scan.pdf
AMG1061	Genentech, Inc., Herceptin 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/trasgen092598lb.pdf
AMG1063	Genentech, Inc., Lucentis 2006 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/125156lbl.pdf
AMG1066	Genentech, Inc., Raptiva 2009 Package Insert, available at https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM143346.pdf
AMG1067	Centocor, Inc., Remicade 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/inflcen082498lb.pdf
AMG1069	Genentech, Inc., Rituxan 1997 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-lab.pdf
AMG1070	Novartis Pharm. Corp., Simulect 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/basnov051298lb.pdf
AMG1071	MedImmune, Inc., Synagis 1999 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/palimed102302LB.pdf
AMG1073	Boehringer Ingelheim Int'l GmbH, Verluma 1996 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1996/nofedrk082096lb.pdf

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AMG1074	Genentech, Inc., Xolair 2007 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf
ALXN2005	SOLIRIS® Label (2007)
ALXN2025	*Curriculum Vitae* of Bernhardt L. Trout, Ph.D.
ALXN2029	Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use, U.S. Dept. of Health and Human Services, Food and Drug Admin., 1997
ALXN2032	Deposition Transcript of Joseph P. Balthasar, Ph.D., *Amgen, Inc. v. Alexion Pharmaceuticals, Inc.*, IPR No. 2019-00740 (Oct. 23, 2019)
ALXN2079	Chang, Byeong S. and Hershenson, Susan, "Practical Approaches to Protein Formulation Development," Pharmaceutical Biotechnology Vol. 13, 1-25 (2002)
ALXN2080	Wang, Wei, "Instability, stabilization, and formulation of liquid protein pharmaceuticals," International Journal of Pharmaceutics, 185:129-188 (April 28, 1999)
ALXN2081	Hermeling, S. et al., "Structure-Immunogenicity Relationships of Therapeutic Proteins, " Pharmaceutical Research, 12:6, 897-903 (June 2004)
ALXN2082	Frokjaer, Sven and Otzen, Daniel E., "Protein Drug Stability: A Formulation Challenge," Nature Reviews, Drug Discovery, 4:298-306 (April 2005)
ALXN2083	Rosenberg, Amy S., "Effects of Protein Aggregates: An Immunologic Perspective," AAPS Journal 8, Article 59, pp. E501-E507 (Aug. 4, 2006)
ALXN2084	ICH Topic Q5C, "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products," European Medicines Agency (July 1996)
ALXN2085	U.S. Depart of Health and Human Services, FDA, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products," ICH Rev. 2 (Nov. 2003)