UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner

U.S. Patent No. 10,590,189 B2
Issue Date: March 17, 2020

Title: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

DECLARATION OF JEFFREY V. RAVETCH, M.D., PH.D.

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I, Jeffrey V. Ravetch, declare as follows:

I. INTRODUCTION AND QUALIFICATIONS

A. Qualifications and Experience

1. My Curriculum Vitae, which contains information pertaining to my education, experience, and qualifications in the field of immunology, microbiology, cellular biology, and molecular genetics, as well as a list of my publications within at least the preceding 10 years, and publications on relevant subject matter is attached as **Exhibit A**.

2. I reside in New York, New York.

3. I have been retained by counsel for Petitioner to provide my expert opinion in connection with the above-captioned proceeding as set forth herein.

4. I am an M.D. / Ph.D. specializing in molecular genetics and immunology and particularly the structure and function of antibodies and the interactions between antibodies and their receptors on immune cells. My research has focused on the mechanisms by which antibodies generate diversity and the translation of that diversity into physiological responses. As a result of my work on antibody diversification of effector responses novel therapeutic antibodies have been developed and approved for the treatment of inflammatory and neoplastic diseases.

I have over 40 years of academic and research experience in the area of immunology. Currently, I am the Theresa and Eugene M. Lang Chair and head of the Leonard Wagner Laboratory of Molecular Genetics and Immunology at The Rockefeller University ("Rockefeller").

5. I earned a Bachelor of Science degree at Yale University in 1973 in molecular biophysics and biochemistry. In 1978, I earned a Ph.D. at Rockefeller, where I completed my research in the Laboratory of Genetics under Norton Zinder and Peter Model. In 1979, I completed my M.D. at Cornell University Medical College.

6. From 1979 to 1982, I completed postdoctoral training in the Laboratory of Molecular Genetics at the National Institutes of Health under Philip Leder. Dr. Leder was a pioneering researcher in molecular genetics, helping to determine the genetic code and elucidate genes underlying immune proteins and genes involved in cancer. During my postdoctoral studies, I characterized genes for human antibodies and genetic elements involved in producing variability in the variable domains and heterogeneity in the constant domain of antibodies. Those studies established the genetic elements involved in diversification of the variable domains and the mechanisms by which effector domains are diversified

7. In 1982, I established my own laboratory at Memorial Sloan-Kettering

Cancer Center ("MSKCC"). I was an Assistant Faculty Member of the Division of Molecular Biology at MSKCC from 1982 to 1986, an Associate Faculty Member from 1986 to 1990, and a Full Faculty Member from 1990 to 1996. My laboratory researched the genetics of the immune system with a particular focus of understanding how effector functions are triggered by antibodies. Under my leadership, the laboratory characterized the structure and function of the "Fc" domains of antibodies as well as the Fc receptors ("FcRs") that recognize them. We further characterized the regulation of the expression of antibodies and different domains of antibodies, including in response to signaling molecules like interferon-γ. Our studies resulted in a new paradigm to account for the inflammatory properties of antibodies that are triggered by the engagement of specific Fc domains to Fc receptors. These interactions underlie the basis for inflammatory diseases caused by autoantibodies, as are found in autoimmune diseases like lupus and rheumatoid arthritis and form the basis for the therapeutic activity of anti-tumor antibodies like Herceptin and Rituximab.

8. From 1986 to 1990, I served as the Associate Attending in the Division of Medical Oncology, Hematology-Lymphoma Service, Department of Medicine, at MSKCC. From 1990 to 1996, I served as an Attending in the Division of Hematologic Oncology in the Department of Medicine at Memorial Hospital for

Cancer and Allied Diseases.

9. In 1996, I returned to Rockefeller as a Professor and was named the Theresa and Eugene M. Lang Chair in 1997. Since 1996 and continuing today, my laboratory studies the mechanisms of Fc and FcR interactions as well as the role these interactions play in coordinating immune system responses and treatments for disease. We have advanced novel therapeutic antibodies into clinical trials, optimized for their activity by selective modification of the Fc domain to engage specific Fc receptors.

10. I have published over 250 peer-reviewed scientific articles and book chapters, the vast majority of which are related to immunoglobulin G ("IgG") antibodies, Fc and FcR structure and function, and regulation of the immune system. I have published several articles and book chapters over the past 30 years studying Fc structure, Fc function, and modifications of the Fc domain to alter the function of antibodies in disease and treatment of disease. (*See, e.g.*, EX1038, Stylianos Bournazos et al., *Fc-optimized antibodies elicit CD8 immunity to viral respiratory infection*, 588 Nature 485 (2020) ("Bournazos 2020"); EX1039, Stylianos Bournazos et al., *Human IgG Fc domain engineering enhances antitoxin neutralizing antibody activity*, 124 J. Clinical Investigation 725 (2014) ("Bournazos 2014"); EX1040, Lucie Baudino et al., *Impact of a Three Amino Acid Deletion in*

the CH2 Domain of Murine IgG1 on Fc-Associated Effector Functions, 181 J. Immunology 4107 (2008); EX1041, Toshiyuki Takai et al., *FcR γ Chain Deletion Results in Pleiotropic Effector Cell Defects*, 76 Cell 519 (1994).) I further published two highly cited reviews on FcRs including a review in Nature Reviews Immunology titled "Fcγ Receptors as Regulators of Immune Responses" (cited over 2750 times) and a review in Annual Review of Immunology titled "Fc receptors" (cited over 2190 times). (*See* EX1042, Falk Nimmerjahn & Jeffrey V. Ravetch, *Fcγ receptors as regulators of immune responses*, 8 Nat. Rev. Immunol. 34 (2008); EX1043, Jeffrey V. Ravetch & Jean-Pierre Kinet, *Fc Receptors*, 9 Annu. Rev. Immunol. 457 (1991).)

11. For my work, I have been recognized with several international awards. In 2006, I was elected a member of the National Academy of Sciences in the section of Immunology and Inflammation. In 2008, I was elected a Fellow of the American Academy of Arts and Sciences. In 2012, I received both the Gairdner International Award and the Sanofi-Institut Pasteur Award. The Gairdner International Award recognizes "outstanding researchers whose unique scientific contributions have increased the understanding of human biology and disease" while the Sanofi-Institut Pasteur Award recognizes "scientists for their past or ongoing research demonstrating real scientific progress in the life sciences." Most recently, I received

the Wolf Prize in Medicine (2015), the Ross Prize (2017), the Robert Koch Award (2018) and the William Paul Memorial Award (2021) for my contributions to dissecting the mechanisms of antibody effector function and its role in antibody therapeutics. For my work in immunology, I received an honorary doctorate from the Friedrich-Alexander-University Erlangen-Nürnberg in 2013.

12. I am a consultant and a member of the scientific advisory boards for a variety of biotechnology and pharmaceutical companies in the area of antibody design and their therapeutic applications. I have founded several biotechnology companies in the area of therapeutic antibody discovery.

13. I am a frequent lecturer at academic conferences and university seminars and have served on the advisory boards of several philanthropic organizations focused on biomedical research.

14. I am being compensated at my usual consulting rate of $1,250 per hour for my work on this matter. I also am being reimbursed for reasonable and customary expenses associated with my work and testimony in this investigation. My compensation is not dependent upon my opinions or testimony or the outcome of this proceeding.

B. Materials Considered

15. The analysis that I provide in this Declaration is based on my education, research, and experience, as well as the documents I have considered. In forming my opinions, I have read and considered U.S. Patent No. 10,590,189 B2 ("'189 patent") **[EX1001]** and its prosecution history **[EX1002]**. I also considered the expert declaration of Dr. Cindy Ippoliti, Pharm.D, regarding the conventional claim limitations that relate to dose forms and formulation **[EX1062]**. I have cited to or considered the following documents in my analysis below:

Exhibit No.	Description of Document
1001	U.S. Patent No. 10,590,189 B2 issued to Leonard Bell et al. (filed July 5, 2017, issued Mar. 17, 2020) ("'189 patent")
1002	Prosecution History for U.S. Patent No. 10,590,189 B2
1004	U.S. Patent Application Publication No. 2003/0232972 A1 issued to Katherine S. Bowdish et al. (filed Dec. 2, 2002, published Dec. 18, 2003) ("Bowdish")
1005	U.S. Patent No. 6,355,245 B1 issued to Mark J. Evans et al. (filed June 7, 1995, issued Mar. 12, 2002) ("Evans")
1006	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 Molecular Immunology 441 (1997) ("Mueller 1997")

Exhibit No.	Description of Document
1007	U.S. Patent Application Publication No. 2005/0191298 A1 issued to Leonard Bell et al. (filed Feb. 3, 2005, published Sept. 1, 2005) ("Bell")
1008	Paul J. Tacken 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*, 106 Blood 1278 (2005) ("Tacken")
1009	World Intellectual Property Organization International Publication No. WO 97/11971 issued to John P. Mueller et al. (filed Sept. 27, 1996, published Apr. 3, 1997) ("Mueller PCT")
1010	Thomas C. Thomas et al., *Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv*, 33 Molecular Immunology 1389 (1996) ("Thomas")
1011	Peter Hillmen et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350 N. Engl. J. Med. 552 (2004) ("Hillmen 2004")
1012	Anita Hill et al., *Abstract# 2823: Sustained Control of Hemolysis and Symptoms and Reduced Transfusion Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy*, 104 Blood 772a (2004) ("Hill 2004")
1013	Anita Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 Blood 2559 ("Hill 2005")
1014	Peter Hillmen et al., *The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria*, 355 N. Engl. J. Med. 1233 (2006) ("Hillmen 2006")
1015	Neal S. Young et al., *Abstract# 971: Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal*

Exhibit No.	Description of Document
	Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study, 108 Blood 290a (2006) ("Young")
1016	Peter Hillmen et al., *Abstract# 154: Eculizumab, a C5 Complement-Blocking Antibody, Abolishes Hemolysis and Renders Hemolytic Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Transfusion Independent*, 100 Blood 44a (2002) ("Hillmen 2002")
1017	Peter Hillmen et al., *Abstract# 1858: Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained Over a Prolonged Period of Therapy*, 102 Blood 509a (2003) ("Hillmen 2003")
1018	Excerpts from *Recommended INN List 49, International Nonproprietary Names for Pharmaceutical Substances*, 17 WHO Drug Information 115, World Health Organization (2003)
1019	*Guidelines on the Use of International Nonproprietary Names (INNs) for Pharmaceutical Substances*, Programme on International Nonproprietary Names (INN), Division of Drug Management & Policies, World Health Organization, Geneva (1997)
1020	Alexion Press Release, *Alexion Issued Key C5 Complement Inhibitor Patent for Inflammatory Diseases* (Mar. 15, 2002), https://web.archive.org/web/20030621141230/http://www.alxn.com/products/index.cfm
1021	World Intellectual Property Organization International Patent Publication No. WO 2005/007809 A2 issued to Russell P. Rother et al. (filed May 28, 2004, published Jan. 27, 2005)
1022	World Intellectual Property Organization International Patent Publication No. WO 2005/110481 A2 issued to Russell P. Rother et al. (filed May 16, 2005, published Nov. 24, 2005)

Exhibit No.	Description of Document
1023	Mariana Kaplan, *Eculizumab Alexion*, 3 Curr. Opin. Investig. Drugs 1017 (2002)
1024	*Amgen Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, Paper 15, Decision – Institution of *Inter Partes* Review (PTAB Aug. 30, 2019)
1025	*Amgen Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, Paper 22, Patent Owner Response Pursuant to 37 C.F.R. § 42.120 (PTAB Nov. 22, 2019)
1027	Opposition File History for European Patent No. 1 720 571 B1
1028	File History for European Patent No. 3 167 888
1029	Excerpt from the File History for U.S. Patent Application No. 11/127,438, Amendment in Response to Non-Final Office Action (Aug. 2, 2011)
1030	Application for Extension of Patent Term under 35 U.S.C. § 156 and 37 CFR § 1.740, U.S. Patent No. 6,355,245, Alexion Pharmaceuticals (May 11, 2007)
1031	Certificate Extending Patent Term, U.S. Patent No. 6,355,245 (June 11, 2010)
1033	Esther M. Yoo et al., *Human IgG2 Can Form Covalent Dimers*, 170 J. Immunol. 3134 (2003) ("Yoo 2003")
1037	Jette Wypych et al., *Human IgG2 Antibodies Display Disulfide-mediated Structural Isoforms*, 283 J. Biol. Chem. 16194 (2008) ("Wypych")
1038	Stylianos Bournazos et al., *Fc-optimized* antibodies *elicit CD8 immunity to viral respiratory infection*, 588 Nature 485 (2020) ("Bournazos 2020")

Exhibit No.	Description of Document
1039	Stylianos Bournazos et al., *Human IgG Fc domain engineering enhances antitoxin neutralizing antibody activity*, 124 J. Clinical Investigation 725 (2014) ("Bournazos 2014")
1040	Lucie Baudino et al., *Impact of a Three Amino Acid Deletion in the CH2 Domain of Murine IgG1 on Fc-Associated Effector Functions*, 181 J. Immunology 4107 (2008)
1041	Toshiyuki Takai et al., *FcR γ Chain Deletion Results in Pleiotropic Effector Cell Defects*, 76 Cell 519 (1994)
1042	Falk Nimmerjahn & Jeffrey V. Ravetch, *Fcγ receptors as regulators of immune responses*, 8 Nat. Rev. Immunol. 34 (2008)
1043	Jeffrey V. Ravetch & Jean-Pierre Kinet, *Fc Receptors*, 9 Annu. Rev. Immunol. 457 (1991)
1044	U.S. Patent Application Publication No. 2005/0271660 A1 issued to Yi Wang (filed May 11, 2005, published Dec. 8, 2005) ("Wang")
1045	Charles A. Janeway, Jr. et al., *Chapter 1: Basis Concepts in Immunology*, and *Chapter 3: Antigen Recognition by B-cell and T-cell Receptors*, Immunobiology: the immune system in health and disease, pp. 1-34, 93-122 (5th ed. 2001)
1046	Excerpts from Pei-Show Juo, Ph.D., Concise Dictionary of Biomedicine and Molecular Biology (2nd ed. 2001)
1047	Tina Völkel et al., *Optimized linker sequences for the expression of monomeric and dimeric bispecific single-chain diabodies*, 14 Protein Engineering 815 (2001) ("Völkel")
1048	Evelyn D. Lobo et al., *Antibody Pharmacokinetics and Pharmacodynamics*, 93 Journal of Pharmaceutical Sciences 2645 (2004) ("Lobo 2004")

Exhibit No.	Description of Document
1049	Neil S. Lipman et al., *Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information Resources*, 46 ILAR Journal 258 (2005) ("Lipman 2005")
1050	Benny K.C. Lo, *Chapter 7: Antibody Humanization by CDR Grafting*, Methods in Molecular Biology, Vol. 248: Antibody Engineering: Methods and Protocols, pp. 135-159 (2004) ("Lo 2004")
1051	Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 Nature 323 (1988) ("Riechmann")
1052	Janice M. Reichert, *Marketed therapeutic antibodies compendium*, 4 mAbs 413 (2012) ("Reichert")
1053	Bruce Alberts et al., *Chapter 12: Intracellular Compartments and Protein Sorting*, Molecular Biology of the Cell, pp. 551-98 (1994)
1054	Elisabeth E. Adderson et al., *Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to Haemophilus influenzae Type b Capsular Polysaccharide Are Dominated by a Limited Number of V_κ and V_λ Segments and VJ Combinations*, 89 J Clin. Invest. 729 (1992)
1055	Genentech, Inc., Avastin 2004 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125085lbl.pdf
1056	Millennium, Campath 2001 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/alemmil050701LB.htm
1057	ImClone Systems, Inc., Erbitux 2004 Package Insert, https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125084lbl.pdf

Exhibit No.	Description of Document
1058	Genentech, Inc., Herceptin 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/trasgen092598lb.pdf
1059	Centocor, Inc., Remicade 1998 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/inflcen082498lb.pdf
1060	Genentech, Inc., Rituxan 1997 Package Insert, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-lab.pdf
1061	Ann L. Daugherty & Randall J. Mrsny, *Formulation and delivery issues for monoclonal antibody therapeutics*, 58 Advanced Drug Delivery Reviews 686 (2006)
1062	Declaration of Cindy Ippoliti, Pharm.D.
1066	Excerpt from the File History of U.S. Patent No. 9,718,880, Response to Non-Final Office Action Under 37 C.F.R. § 1.111, dated May 12, 2017

II. PERSON OF ORDINARY SKILL IN THE ART

16. I am informed by counsel that, under the patent laws in effect before the America Invents Act ("AIA") of 2011, an assessment of claims of a patent filed before the AIA took effect should be undertaken from the perspective of a person of ordinary skill in the art as of the earliest claimed priority date (i.e., the "time the invention was made"). For purposes of the '189 patent, I have assumed that date to

be March 15, 2007, which is the date the earliest application in the patent family from which the '189 patent issued (Appl. Ser. No. 12/225,040) was filed. I am not aware of any claim by the patent owner that the claims of the '189 patent are entitled to an earlier date of invention, but I reserve the right to supplement this opinion if the patent owner were to later claim that the '189 patent was entitled to an earlier priority date.

17. I have been advised that to determine the appropriate level of a person having ordinary skill in the art, I may consider the following factors: (1) the types of problems encountered by those working in the field and prior art solutions thereto; (2) the sophistication of the technology in question, and the rapidity with which innovations occur in the field; (3) the educational level of active workers in the field; and (4) the educational level of the inventor. I am also informed that a person of ordinary skill in the art is presumed to be aware of all of the pertinent prior art.

18. The '189 patent relates to "[t]reatment of [PNH] patients by an inhibitor of complement," namely, eculizumab. (EX1001, Cover.) More specifically, the '189 patent discloses sequences for the heavy and light chains of eculizumab, methods of treatment of disorders such as paroxysmal nocturnal hemoglobinuria ("PNH") using eculizumab, and clinical trials such as the "TRIUMPH" and "SHEPHERD" trials in which eculizumab was evaluated in humans as a treatment

for PNH. I provide a more complete overview of the '189 patent in Part V below. As noted above, I have extensive education and experience in the field of therapeutic antibodies, including antibodies targeting complement, and in the design and modification of therapeutic antibodies. Having been active as a researcher and educator in this field for more than 40 years, I am familiar with the relevant skill set that would have been possessed by a hypothetical person of ordinary skill in the art ("POSA") at the time of the invention of the '189 patent (March 2007).

19. In my opinion and based on the subject matter of the '189 patent, the level of ordinary skill in the relevant art was high. Specifically, a POSA as of March 2007 would have knowledge of the scientific literature and have skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics before March 15, 2007. Such a person also would have knowledge of laboratory techniques and strategies used in immunology research, including practical applications. A POSA would have possessed an advanced degree in the biological sciences, such as an M.D. or a Ph.D., in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, and at least two years of experience in the discovery, development, and design of therapeutic antibodies for use as potential treatment in human disease. A POSA could have also worked as part of a multidisciplinary team and drawn upon not only his or her own

skills, but also upon specialized skills of team members, for example, a clinician, a doctor of pharmacy, and a formulation chemist who are part of a team may help solve a given problem.

20. Although my qualifications and experience may be viewed as exceeding those of the hypothetical person having ordinary skill in the art defined above, my analysis and opinions regarding the '189 patent have been based on the perspective of a person of ordinary skill in the art as of March 2007.

III. STATEMENT OF LEGAL PRINCIPLES

A. Claim Construction

21. I understand that a purpose of claim construction is to determine what a person of ordinary skill in the art would have understood the claim terms to mean. Claim terms are generally given 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 as of the earliest claimed priority date.

22. I understand that, in Inter Partes Review (IPR) proceedings, a claim of a patent shall be construed using the same claim construction standard that would be used to construe the claim in a civil action filed in a U.S. district court (which I understand is called the "*Phillips*" claim construction standard), including

construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent. I have been instructed by counsel to apply the "*Phillips*" claim construction standard for purposes of interpreting the claims in this proceeding, to the extent they require an explicit construction. I have interpreted all the claim terms in accordance with the ordinary and customary meaning of such terms as understood by one of ordinary skill in the art in 2007.

B. Anticipation

23. I understand that a claim is anticipated if its subject matter was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention. I understand that in an IPR proceeding such as this, anticipation arguments are only permitted to the extent they are based on patents and/or printed publications.

24. I understand that one reference may incorporate another "by reference," and when this occurs the combined disclosures of the multiple documents are treated as a single integrated document for prior art purposes. Whether a document incorporates another by reference is judged from the perspective of a POSA, and requires that the incorporated document identify what material from the incorporated

document is being incorporated. One document can incorporate the entire disclosure of another document into itself, in such case the complete teachings of both documents are treated as one single integrated document for prior art purposes.

25. I also understand that a prior art reference can anticipate a claim "inherently." I understand that an inherent disclosure is that which necessarily discloses the claimed subject matter. I also understand that a reference provides an enabling disclosure of inherently disclosed subject matter when a POSA can make the claimed subject matter based on the description of the invention in the reference, in the context of his or her own knowledge of the particular art. I understand that evidence from after the priority date of the invention can be relevant as proof of inherency, and that a POSA need not have recognized the inherent disclosure as of the time of the invention.

C. Obviousness

26. I understand that a patent claim is obvious if, as of the earliest claimed priority date, the invention recited in view of the claims would have been obvious to a person having ordinary skill in the field of the technology to which the claimed subject matter belongs.

27. I understand that the following factors should be considered in

analyzing obviousness: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; and (3) the level of ordinary skill in the pertinent art. I also understand that certain other facts known as "secondary considerations" such as commercial success, unexplained results, long felt but unsolved need, industry acclaim or praise, simultaneous invention, copying by others, skepticism by experts in the field, and failure of others may be utilized as indicia of nonobviousness. I understand, however, that secondary considerations evidence must be connected, or have a "nexus," with the novel aspects of the invention claimed in the patent at issue in order to be relevant to the obviousness inquiry.

28. I understand that a reference qualifies as prior art for obviousness purposes when it is analogous to the claimed invention. The test for determining what art is analogous is: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved.

29. I understand that a person of ordinary skill in the art is assumed to have knowledge of all prior art. I understand that one skilled in the art can combine various prior art references based on the teachings of those prior art references, the general knowledge present in the art, or common sense. I understand that a

motivation to combine references may be implicit in the prior art, and there is no requirement that there be an actual or explicit teaching to combine two references. Thus, one may take into account the inferences and creative steps that a person of ordinary skill in the art would employ to combine the known elements in the prior art in the manner claimed by the patent at issue. I understand that one should avoid "hindsight bias" and ex post reasoning in performing an obviousness analysis. But this does not mean that a person of ordinary skill in the art for purposes of the obviousness inquiry does not have recourse to common sense.

30. I understand that when determining whether a patent claim is obvious in light of the prior art, neither the particular motivation for the patent nor the stated purpose of the patentee is controlling. The primary inquiry has to do with the objective reach of the claims, and if those claims extend to something that is obvious, then the patent claim is invalid.

31. I understand one way that a patent can be found obvious is if there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims. I understand that a motivation to combine various prior art references to solve a particular problem may come from a variety of sources, including market demand or scientific literature. I understand that a need or problem known in the field at the time of the invention can also provide

a reason to combine prior art references and render a patent claim invalid for obviousness. I understand that familiar items may have obvious uses beyond their primary purpose, and that a person of ordinary skill in the art will be able to fit the teachings of multiple prior art references together like the pieces of a puzzle. I understand that a person of ordinary skill is also a person of at least ordinary creativity. I understand when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this finite number of predictable solutions leads to the anticipated success, I understand that the invention is likely the product of ordinary skill and common sense, and not of any sort of innovation. I understand that the fact that a combination was obvious to try might also show that it was obvious, and hence invalid, under the patent laws. I understand that if a patent claims a combination of familiar elements according to known methods, the combination is likely to be obvious when it does not yield more than predictable results. Thus, if a person of ordinary skill in the art can implement a predictable variation, an invention is likely obvious. I understand that combining embodiments disclosed near each other in a prior art reference would not ordinarily require a leap of inventiveness.

32. I understand that obviousness may be shown by demonstrating that it

would have been obvious to modify what is taught in a single piece of prior art to create the patented invention. Obviousness may also be shown by demonstrating that it would have been obvious to combine the teachings of more than one item of prior art. I understand that a claimed invention may be obvious if some teaching, suggestion, or motivation exists that would have led a person of ordinary skill in the art to combine the invalidating references. I also understand that this suggestion or motivation may come from the knowledge of a person having ordinary skill in the art, or from sources such as explicit statements in the prior art. I understand that when there is a design need or market pressure, and there are a finite number of predictable solutions, a person of ordinary skill may be motivated to apply common sense and his skill to combine the known options in order to solve the problem.

33. I understand the following are examples of approaches and rationales that may be considered in determining whether a piece of prior art could have been combined with other prior art or with other information within the knowledge of a person having ordinary skill in the art:

(1) Some teaching, motivation, or suggestion in the prior art that would have led a person of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention;

(2) Known work in one field of endeavor may prompt variations of it for use in the same field or a different field based on design incentives or other market forces if the variations would have been predictable to a person of ordinary skill in the art;

(3) Combining prior art elements according to known methods to yield predictable results;

(4) Applying a known technique to a known device, method, or product ready for improvement to yield predictable results;

(5) Applying a technique or approach that would have been "obvious to try" (choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success);

(6) Simple substitution of one known element for another to obtain predictable results; or

(7) Use of a known technique to improve similar products, devices, or methods in the same way.

34. I understand that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference. The test for obviousness, in other words, is not whether the references

could necessarily be physically combined but whether the claimed inventions are rendered obvious by the teachings of the prior art as a whole.

IV. TECHNOLOGY AND FACTUAL BACKGROUND

A. Antibody Structure and Humanization of Antibodies

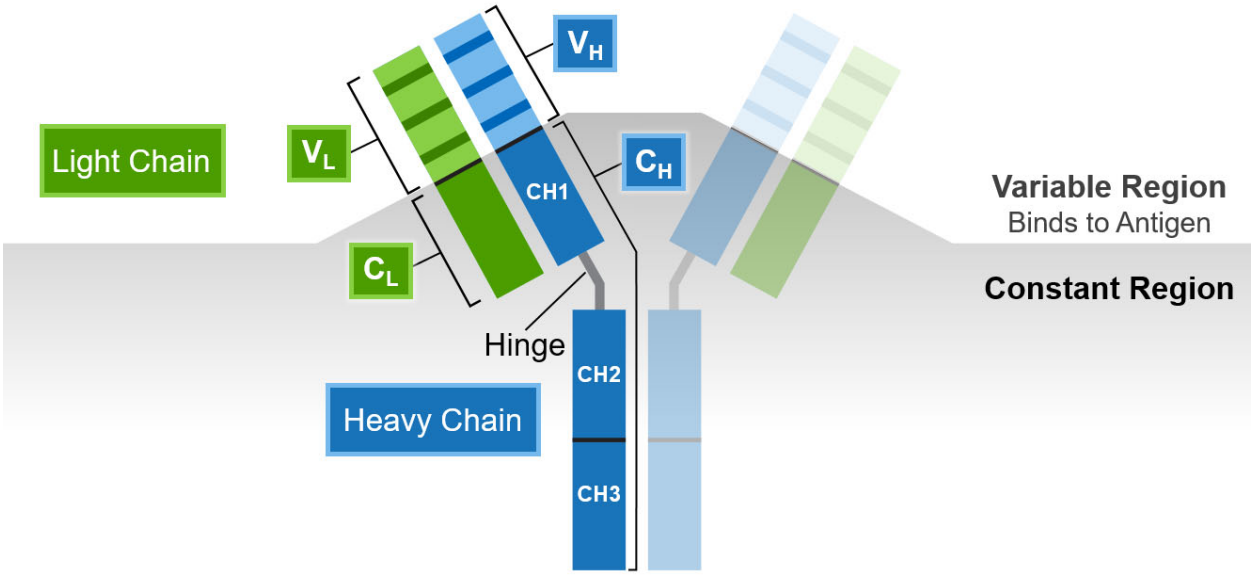
35. Antibodies may be described by their particular amino acid sequences. Mammals have twenty different amino acids, and each of these twenty amino acids has its own unique structure. Biologists commonly refer to the different amino acids using either the full name of the amino acid, the three letter code, or the one letter code. For example, the '189 patent provides the amino acid sequences in SEQ ID NOS:2 and 4 using their one letter code and three letter code. (EX1001, Cols. 30-37.)

36. In general, antibodies have four polypeptide chains that ultimately assemble into the final three-dimensional shape of the antibody: two identical chains of, on average, 450-550 amino acids in length known as the heavy (H) chains; and two identical chains of, on average, 200 amino acids in length known as the light (L) chain. Together, the two heavy chains and two light chains form a canonical Y-shaped structure of an antibody, discussed in more detail in the following sections. (EX1045, Charles A. Janeway, Jr. et al., Immunobiology: the immune system in

health and disease (5th ed. 2001), 030, Fig. 1.17.) The amino acid sequences of antibodies are further organized as distinct regions or domains that have specialized functions as I discuss further below.

1. "Variable" Region of an Antibody

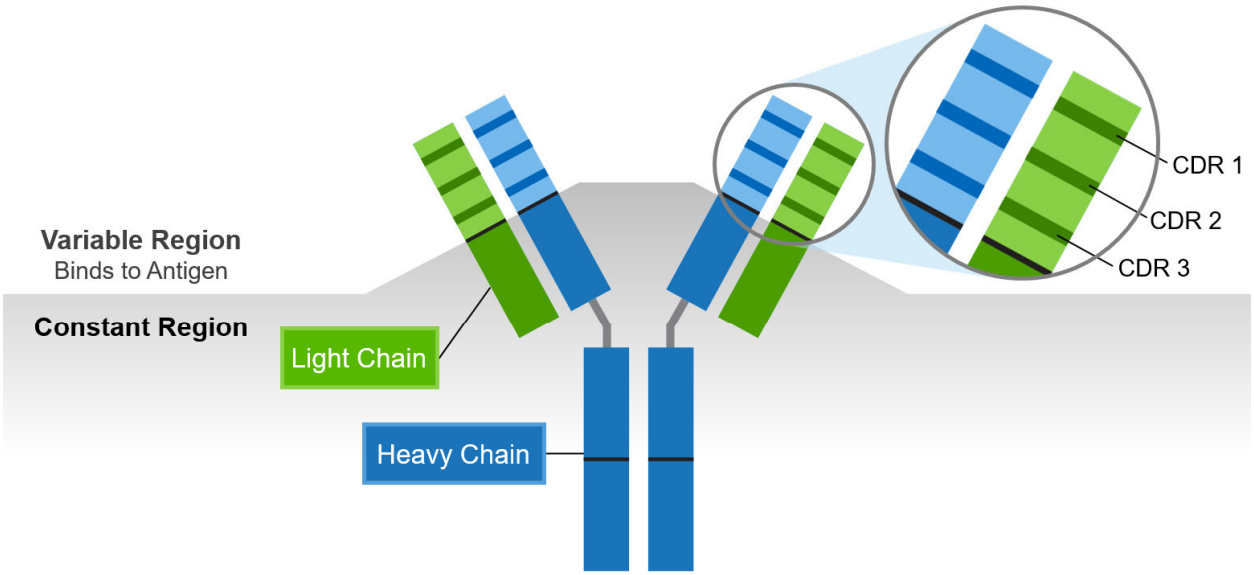
37. One region, known as the "variable region," binds the antigen recognized by the antibody. This variable region functions to dictate which antigen an antibody binds to and is highly selective for a particular antigen. As indicated by its name, the variable region varies considerably across antibodies and is what accounts for the ability of different antibodies to selectively bind to different targets. (*See* EX1046, Pei-Show Juo, Ph.D., Concise Dictionary of Biomedicine and Molecular Biology (2nd ed. 2001), 006.) Thus, any individual antibody can selectively recognize a specific antigen while "the total repertoire of antibodies made by a single individual is large enough to ensure that virtually any [substance] can be recognized." (EX1045, 048.) As shown in the figure I prepared below, in the area near the ends of each of the heavy and light chain, an antibody has two variable regions formed by parts of the two light chains and parts of the two heavy chains:



Basic domain structure of antibody

(*See* EX1045, 030, 052, Figs. 1.17, 3.1c.) As shown in the figure above, the variable region for the heavy chain is denoted as V_H, and the variable region for the light chain is denoted as V_L.

38. The variable regions V_H and V_L are further subdivided into "complementarity determining regions" (or "CDRs") and "framework regions." (EX1045, 055-56.) As shown in the figure I prepared below, each V_H and V_L contains three CDRs, each comprised of a unique amino acid sequence, interspersed between four framework regions. The CDRs play a key role in antigen binding as they form the primary binding interface between the antibody and the antigen. (*Id.*, 056-57.)



Basic domain structure of antibody

39. Antibody researchers and engineers sometimes create and study so-called antibody "fragments" that typically contain variable regions of at least one chain of an antibody. One such antibody fragment known in 2007 (and today) is single chain variable fragment or "scFv" fragment. An scFv fragment corresponds to V_L and V_H domains of an antibody joined by a short peptide linker. By the early 2000s, most scFvs were generated using the 15 amino acid linker sequence, "GGGGSGGGGSGGGGS," also known as a $(Gly_4Ser)_3$ linker. (EX1047, Tina Völkel et al., *Optimized linker sequences for the expression of monomeric and dimeric bispecific single-chain diabodies*, 14 Protein Engineering 815 (2001), 006.) An scFv fragment is often used as a surrogate for full-length antibodies because it

includes the antigen-binding sites of an antibody.

2. "Constant" Region of an Antibody

40. Other regions, known as the constant regions, do not bind to antigen but instead provide a structural framework for the antibody, facilitate the assembly of the heavy and light chains into a 4 chain structure, and coordinate the antibody's interactions with other immune cells and effector molecules. These other cells in turn function, for example, to recruit white blood cells to dispose of or neutralize antigen once it is bound by the antibody. Other functions of the constant region include its ability to determine the half-life of an antibody in the serum and ability to cross epithelial barriers.

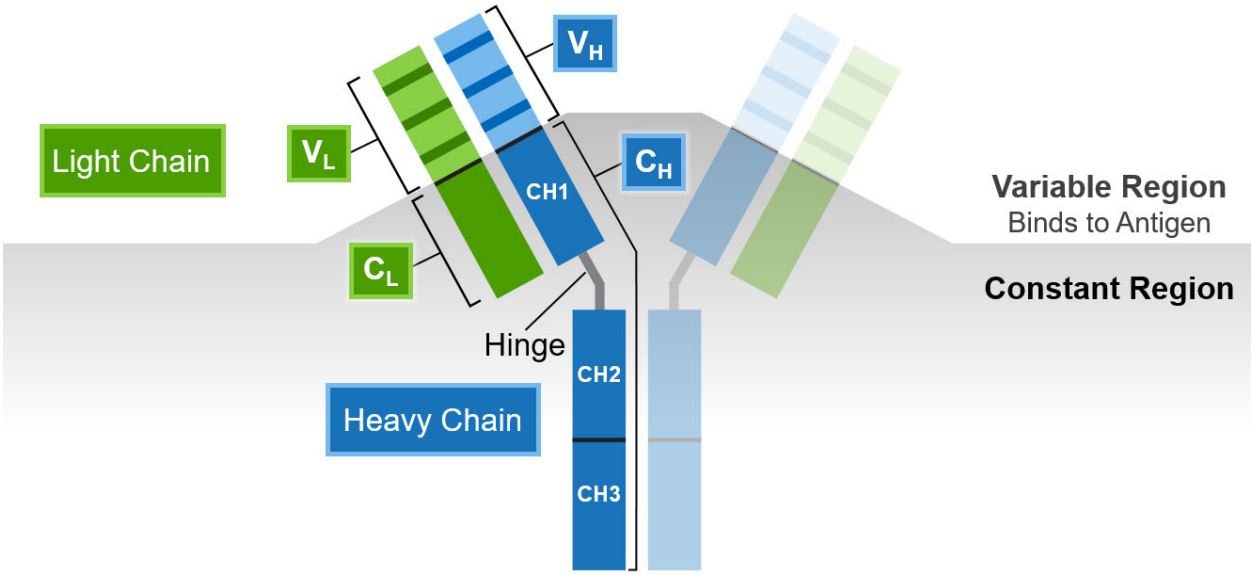
41. As its name suggests, in contrast to the extensive variability of the variable region, the constant region is generally highly conserved between different antibodies depending on the class. (*See* EX1046, 004-05.) The constant region for the light chain is denoted as CL, and the constant region of for the heavy chain is denoted as CH.

42. There are two classes of light chain constant region (CL) in antibodies – kappa (κ) or lambda (λ) chains based on small differences in their amino acid sequences. (EX1045, 050.) The sequence for each class of CL is highly conserved

between different antibodies.

43. There are five classes of heavy chain constant region (CH) in antibodies –immunoglobulin M (IgM), immunoglobulin D (IgD), immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin E (IgE). (EX1045, 050.) The heavy chain constant region defines the class or isotype of an antibody.

44. The IgG class is the most abundant in humans and the only class pertinent to the opinions I express in this declaration. (EX1045, 050.) The IgG class has four subclasses, IgG1, IgG2, IgG3, and IgG4. (*Id.*) The heavy chain constant region (CH region) of the IgG class of antibodies is divided into four parts, referred to as CH1, CH2, CH3, and a hinge region between CH1 and CH2. These are shown in the figure I prepared in ¶37 above, reproduced here:



Basic domain structure of antibody

45. The constant regions of an antibody play a crucial role in signaling the immune system to respond when the antibody binds to an antigen. (EX1045, 048, 050-51, 055.) Specifically, the "fragment crystallizable" region or the Fc region of the antibody formed by the constant regions of the two heavy chains, mediates interactions with Fc receptors that initiate immunological responses. (*Id*., 051.) The Fc region also mediates antibody pharmacokinetic properties, such as antibody metabolism, through interactions with the Fc receptor, FcRn. (EX1048, Evelyn D. Lobo et al., *Antibody Pharmacokinetics and Pharmacodynamics*, 93 Journal of Pharmaceutical Sciences 2645 (2004), 013-14.)

46. The amino acid sequence of a constant region of an antibody is often

unique to the animal species in which the antibody was generated, meaning that, for example, the heavy chain constant region of a human IgG will be different than the heavy chain constant region of a mouse IgG. Because the constant regions are involved in effectuating an immune response in the body, antibody engineers by 2007 (and today) routinely seek to optimize the nature of this response by making adjustments to the amino acid sequence of the constant regions (particularly those of the heavy chains) by selecting specific IgG subclass constant domains (for example, IgG1, IgG2, IgG3 or IgG4), either alone or in combination, and by substituting one or more amino acids for another, or by combinations of these strategies.

47. Each IgG subclass displays unique properties based on their affinities for specific Fc receptors, and therefore, induces different effector responses. Antibody engineers utilize these unique naturally occurring features in the design of the therapeutic antibody under construction. For example, IgG2 and IgG4 have reduced binding affinities to the activating receptors on effector cells. Therefore, if a therapeutic antibody is being developed to minimize activation of effector responses, then IgG2 or IgG4 are selected. Finally, because of the distinctive properties of the hinge regions of each IgG subclass, antibody engineers can replace these regions as well in the final design, creating chimeric constant domains with

features of different subclasses, such as hybrid IgG2/G4 constant regions.

48. By 2007, it was known that IgG2 does not generally activate the complement system or bind Fc receptors to an appreciable degree. (EX1006, 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 Molecular Immunology 441 (1997) ("Mueller 1997"), 011.) It was also known that IgG4 has low propensity to activate the complement system. (*Id*.) Therefore, antibody engineers used the overall similarity in the human IgG2 and IgG4 primary sequences to design a chimeric IgG2/G4 constant region that did not activate the complement system or bind to Fc receptors. (*Id*., 011, 013.) This IgG2/G4 constant region has the CH1 and hinge regions of IgG2 joined with the CH2 and CH3 regions of IgG4. The resulting antibody with the IgG2/G4 constant region does not contain antibody sequences that generally bind Fc receptors to an appreciable degree nor any regions that would likely be immunogenic. If antibodies for therapeutic use in humans are designed using this hybrid IgG2/G4 constant region, the amino acid sequence of that constant region would typically be conserved between antibodies.

3. Humanization of Antibodies

49. As described above, antibodies identify and bind to potentially harmful foreign antigens and then trigger an immune response to eliminate the threat. The role of therapeutic antibodies (i.e., antibody drugs), however, is somewhat different. Antibodies used in human therapeutics are typically designed to target a naturally occurring antigen within the human body itself. Among the most common targets for antibody drugs are human proteins that play a key role in cellular processes that can contribute to disease, such as the complement cascade pathway for PNH. (*See* ¶¶56-58 (Part IV.C).)

50. At a high level, to generate an IgG antibody in a laboratory or clinical setting, the antigen of interest is injected into a subject, for example, a mouse, which will recognize the antigen as foreign and then produce or "raise" antibodies against it. The antibodies can then be isolated for use in medicines.

51. Antibodies that are raised in response to an antigen can be either "polyclonal" or "monoclonal." Polyclonal antibodies are a mixture of many different antibodies with different amino acid sequences that are produced against the same antigen, and can often be directly collected from the blood of the inoculated animal. (*See* EX1049, Neil S. Lipman et al., *Monoclonal Versus Polyclonal Antibodies: Distinguishing Characteristics, Applications, and Information*

Resources, 46 ILAR Journal 258 (2005) ("Lipman 2005"), 005-07.) Monoclonal antibodies are, in contrast, antibodies with identical amino acid sequences that are produced, for example, by cloning a single cell extracted from an inoculated animal. (*See* EX1049, 006.) These antibodies (sometimes referred to as "mAbs") do not occur naturally and can only be produced in a laboratory setting. (*See* EX1049, 005-06.) The vast majority of therapeutic antibodies (i.e., those used as drugs) are based on or derived from monoclonal antibodies.

52. For practical and safety reasons, one approach to produce antibodies for therapeutic use in humans is to immunize animals, such as mice with the antigen of interest. This is particularly useful when the antigen of interest is of human origin because, unlike a healthy human immune system, a mouse immune system will treat the human antigen as a foreign substance and generate antibodies against it. In this approach, the antibodies that are generated have non-human variable regions, including CDRs, derived from mouse variable region genes that will bind to the antigen of interest, and non-human (e.g., mouse) constant regions.

53. It is problematic to give the non-human or mouse antibodies to humans because they may provoke an immune response in the patient (called a "Human Anti-Murine Antibody" or "HAMA" response), which significantly reduces the intended therapeutic effect and can result in adverse reactions. (EX1050, Benny K.C. Lo,

Chapter 7: Antibody Humanization by CDR Grafting, Methods in Molecular Biology, Vol. 248: Antibody Engineering: Methods and Protocols, 135-59 (2004), 010.) Well before 2007, a known solution to this problem was to "humanize" the non-human antibody by replacing its constant regions (and some or all of its framework regions) with those of a human antibody while retaining the original non-human CDRs involved in target binding. (EX1050, 011-12.) Functionally, this is accomplished by starting with a completely human antibody sequence and then replacing its variable regions, in whole or in part, by the variable regions of the non-human antibody generated against the chosen antigen. The goal is for the resulting hybrid "humanized" antibody to have the same binding activity against the chosen antigen as its non-human counterpart (due to the presence of the original non-human CDRs) but have fewer therapeutic limitations because its regions based on human amino acid sequences protect it from attack by the patient's immune system. Most commonly, humanized antibodies contain only non-human CDRs (and, on occasion, minimal sequences from the non-human framework), but have human constant regions and framework regions.

54. As of 2007, humanized antibodies and the basic techniques for making them were well-known. The first humanized antibodies were prepared in the late 1980s by a British research group headed by Sir Greg Winter. (EX1050, 010, 012.)

Since this work was first published in an early 1988 Nature paper, the methods and technology for humanizing antibodies have advanced substantially. (*See* EX1051, Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 Nature 323 (1988).)

B. By 2007, Therapeutic Antibodies Were Routinely Used as Pharmaceutical Compositions

55. By 2007, the FDA has already approved more than a dozen antibodies, including several humanized antibodies, for therapeutic use in humans. (*See* EX1052, Janice M. Reichert, *Marketed therapeutic antibodies compendium*, 4 mAbs 413 (2012), 002-03.) These antibodies were commonly manufactured as pharmaceutical compositions that were formulated in sterile, preservative-free single use dosage forms and administered by intravenous ("IV") infusion.

C. By 2007, the Anti-C5 Antibody Eculizumab Was Known as a Treatment for PNH

56. Paroxysmal Nocturnal Hemoglobinuria, commonly known as PNH, is a disease in which a genetic mutation causes red blood cells to become more susceptible to destruction by the human complement system. (EX1007, U.S. Patent Application Publication No. 2005/0191298 issued to Leonard Bell et al. ("Bell"), [0005]; EX1013, Anita Hill et al., *Sustained response and long-term safety of*

eculizumab in paroxysmal nocturnal hemoglobinuria, 106 Blood 2559 (2005) ("Hill 2005"), 009.) Patients who suffer from PNH have sudden attacks in the night ("paroxysmal nocturnal") and have hemoglobin in the urine, causing dark coloring ("hemoglobinuria"). (EX1007, [0007]; EX1013, 009.) PNH patients also have other known clinical symptoms, such as anemia, fatigue, thrombosis and pain. (EX1007, [0007]; EX1013, 009; EX1011, Peter Hillmen et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350 N. Engl. J. Med. 552 (2004) ("Hillmen 2004"), 004.)

57. By 2007, it was recognized that PNH symptoms can be reduced by inhibiting the complement cascade pathway at the step at which the complement protein C5 is converted to C5a and C5b. C5 is the first protein of "terminal complement assembly." (EX1013, 009.) Preventing its cleavage at this stage results in complement inhibition that blocks the generation of C5a and formation of C5b-9, while also preserving the upstream complement system activity critical for the clearance of microorganisms and immune system function. (EX1013, 009; EX1011, 004.) By 2007, three references – Bell, Hillmen 2004 and Hill 2005 – taught the use of pharmaceutical compositions with antibody formulations that are delivered intravenously to treat PNH patients. (EX1007, [0062], [0082]; EX1013, 010; EX1011, 005.)

58. Before March 15, 2007, it was known that an anti-C5 antibody, also called "eculizumab," targets the complement protein C5 and prevents its cleavage, thereby inhibiting C5 conversion. (EX1013, 009.) For example, the Bell reference discloses results from a trial that showed the successful treatment of PNH patients using anti-C5 antibody. (EX1007, [0082].) Hillmen 2004 also reported results from the same trial, and further stated that "[e]culizumab is safe and well tolerated in patients with PNH." (EX1011, 003.) Hill 2005 reported the results of a one-year follow-up extension study designed to evaluate the long-term safety and efficacy of eculizumab in PNH patients. (EX1013, 009.) Thus, several years before March 15, 2007, at least three separate publications—Bell, Hillmen 2004, and Hill 2005—reported that eculizumab was a useful treatment for PNH. Several other prior art references also report clinical trial results relating to the use of the anti-C5 antibody eculizumab as a treatment for PNH. (EX1014, Peter Hillmen et al., *The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria*, 355 N. Engl. J. Med. 1233 (2006) ("Hillmen 2006"); EX1015, Neal S. Young et al., *Abstract# 971: Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study*, 108 Blood 290a (2006) ("Young"); EX1012, Anita Hill et al., *Abstract# 2823: Sustained Control of Hemolysis and Symptoms and Reduced Transfusion*

Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy, 104 Blood 772a (2004) ("Hill 2004"); EX1017, Peter Hillmen et al., *Abstract# 1858: Eculizumab, a C5 Complement-Blocking Antibody, Controls Hemolysis in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Responses Maintained Over a Prolonged Period of Therapy*, 102 Blood 509a (2003) ("Hillmen 2003"); EX1016, Peter Hillmen et al., *Abstract# 154: Eculizumab, a C5 Complement-Blocking Antibody, Abolishes Hemolysis and Renders Hemolytic Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Transfusion Independent*, 100 Blood 44a (2002) ("Hillmen 2002").) Table 1 below lists several publications published before March 15, 2007 that reported clinical trials with eculizumab for treating PNH. This list is not exhaustive and there may be further clinical trials and publications discussing clinical trials with eculizumab that are not listed here:

Table 1 – Publications Reporting Clinical Trials with Eculizumab to Treat PNH

Prior Art Publication	Reported Clinical Trial Details	Dosing Regimen	Reported Outcome with Eculizumab
Bell (EX1007)	Phase 2 Pilot Study and Extensions with 11 patients	"weekly 600 mg intravenous infusion of [eculizumab] …. Patients received 900 mg of eculizumab 1	"reduction in adverse symptoms associated with PNH" (EX1007, [0096].)

		week later then 900 mg on a biweekly basis." (EX1007, [0082].)	
Hillmen 2004 (EX1011)	Phase 2 Pilot Study with 11 patients	"infusions of 600 mg of eculizumab weekly for four weeks, followed one week later by a 900-mg dose and then by a dose of 900 mg every other week through week 12" (EX1011, 005.)	"safe and well tolerated in patients with PNH" "improvement in the quality of life in patients with PNH" (EX1011, 003 (Abstract).)
Hill 2005 (EX1013)	Phase 2 Pilot Study Extension #1 with 11 patients	"maintenance dose of 900 mg intravenously every 14 days" for 52 weeks (64 weeks total) (EX1013, 010.)	"sustained reductions in hemolysis and blood transfusions and continued improvement in quality of life." (EX1013, 015.)
Hill 2004 (EX1012)	Phase 2 Pilot Study Extension #2 with 10 patients	"10 of the 11 patients from the initial 3 month study have continued to receive 900 mg eculizumab every other week for 2 years." (EX1012, 009 (Abstract).)	"eculizumab is well tolerated and has persisting efficacy … as well as improvement in the symptoms of PNH, for over 2 years of therapy." (EX1012, 009

			(Abstract).)
Hillmen 2006 (EX1014)	Phase 3 "TRIUMPH" Study with 87 patients	"infusions of 600 mg of eculizumab or placebo every week (±2 days) for 4 weeks, followed 1 week (±2 days) later by 900 mg of eculizumab or placebo, and then by a maintenance dose of 900 mg of eculizumab or placebo every 2 weeks (±2 days) through week 26." (EX1014, 003.)	"Eculizumab is an effective therapy for PNH." (EX1014, 001.)
Young (EX1015)	Phase 3 "SHEPHERD" Study with 97 patients	"Eculizumab was dosed as follows: 600 mg IV every 7 days x 4; 900 mg 7 days later; and then 900 mg every 14±2 days." (EX1015, 011 (Abstract).)	"eculizumab treatment markedly reduces intravascular hemolysis, thereby providing clinical benefit to treated [PNH] patients." (EX1015, 011 (Abstract).)

D. As of the 2007 Priority Date, Alexion Believed the Sequence of Eculizumab Had Been Publicly Disclosed

59. I understand that in 1999, Alexion submitted the full amino acid sequence for eculizumab in a submission to Chemical Abstracts Services ("CAS"). I am also informed that, in a submission to the European Patent Office, Alexion has

stated that "the sequence for eculizumab was publicly available [before Feb. 3, 2004]," and the "sequence for eculizumab was submitted to [CAS] and entered into their STN database on 14 February 1999[.]" (EX1027, 277, 291 (5.1.2.).) However, ten years later, in 2009, Alexion submitted another filing in an European counterpart patent application in this family that stated that Alexion "learned" that the eculizumab sequence had been "inadvertently" submitted with errors. (EX1028, 235-42, 280-81, 412-13, 522-23.)

60. However, as I explain and describe below, the prior art as of 2007 anticipated and rendered obvious the sequence of eculizumab.

E. Eculizumab Development and Naming History

61. Alexion scientists began the research program that eventually led to the eculizumab antibody by seeking to create an antibody that would bind the C5 protein of the complement system and inhibit its cleavage. When Alexion scientists first identified the mouse antibody that specifically binds C5, they gave it the name "5G1.1." (EX1010, Thomas C. Thomas et al., *Inhibition of Complement Activity By Humanized Anti-C5 Antibody and Single-Chain Fv*, 33 Molecular Immunology 1389 (1996) ("Thomas"), 006-07.) This 5G1.1 mouse antibody was then humanized using techniques that were well-developed by the mid-1990s. Specifically, the CDR

domains responsible for C5 binding were grafted into a human "framework" variable region. (*Id*., 007-08.) The resulting humanized antibody contained (1) fully mouse sequences in each of its six CDR domains that bind C5 and (2) human sequences for the variable "framework" region to varying degrees. Alexion called this humanized antibody "h5G1.1." (*Id*., 010-12; *see also* EX1005, U.S. Patent No. 6,355,245 issued to Evans et al. ("Evans"), 43:6-14, 43:62-45:4.) After Alexion scientists confirmed that the humanized antibody variable region still binds C5, they then used the human IgG4 isotype to assemble it into a full-length antibody, which they called "h5G1.1 HuG4." (EX1010, 013.)

62. Shortly after creating the h5G1.1 HuG4 antibody, Alexion scientists improved its therapeutic potential by modifying the IgG4 heavy chain constant region to a hybrid IgG2/IgG4 constant region. (EX1006, 013-14; *see also* EX1009, World Intellectual Property Organization International Publication No. WO 97/11971 issued to John P. Mueller et al. (filed Sept. 27, 1996, published Apr. 3, 1997) ("Mueller PCT"), at 014, 097 (referencing "h5G1.1 G2/G4").) As I discussed above, replacing parts of the IgG4 isotype with comparable IgG2 sequences was known to reduce or eliminate binding to other proteins, such as Fc receptors or C1q (another complement protein), that are involved in human immune responses and the complement system. (EX1006, 015-16.) The improved IgG2/G4 constant region

of the antibody contained the CH1 and hinge region from IgG2 and the CH2 and CH3 regions from IgG4. (*Id*.) In 1997, Alexion confirmed that this modification did not impact binding to C5, and called this antibody "h5G1.1 HuG2/G4." (*Id*.) Alexion disclosed the complete sequence of the constant regions of this antibody in the "Mueller PCT" companion patent application describing the same work published in the Mueller 1997 article. (EX1009, 014, 054-55, 058-59, 097.) In that patent application, Alexion called this antibody interchangeably "h5G1.1 G2/G4" and "h5G1.1 CO12 HuG2/G4." (EX1009, 014, 097.) Based on the name, a POSA would immediately recognize that this antibody contained the IgG2/G4 constant region.

63. Under the World Health Organization's guidelines for international nonproprietary names ("INNs") in place since the 1990s, antibodies are named as follows: A random prefix of a few letters chosen by the product sponsor for uniqueness (for example, "ecu-") is followed by a "sub-stem" indicating its function (immunomodulators use "-li-"). This in turn is followed by another sub-stem indicating humanization ("-zu-") and is finally followed by the ultimate stem "-mab," which is applied to all monoclonal antibodies. (EX1019, 031-32.) In 2002, Alexion obtained a nonproprietary name for its antibody following this protocol: ecu-li-zu-mab.

64. By 2007, several publications and statements by Alexion and others disclosed that the humanized 5G1.1 antibody with a hybrid G2/G4 constant domain was eculizumab. For example, the Tacken reference, published in 2005, referred to eculizumab as Alexion's "potential product" and identified eculizumab as the h5G1.1-mAb which contains the "human hybrid IgG2/IgG4 constant domain." (EX1008, Paul J. Tacken 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*, 106 Blood 1278 (2005) ("Tacken"), 010-011.) On this exact point, Tacken provides reference 17, citing to the Mueller 1997 article, which as I discussed above discloses the conversion of h5G1.1 to the HuG2/G4 form, and calls it "h5G1.1 HuG2/G4." (EX1008, 011, 017 (ref. 17 (citing EX1006)).) I note that Tacken has what a POSA would immediately recognize as an obvious typo in its spelling of eculizumab ("eculizamab"). Under the INN guidelines discussed above, the stem "-zamab" is not allowed for any antibody names, and thus there cannot be any antibody called eculizamab. Furthermore, Tacken and other references disclosed that Alexion's 5G1.1 antibody was humanized. Thus, a POSA would have known that a humanized antibody such as eculizumab must have the stem "-zumab," not "-zamab."

65. In 2002, Alexion also announced the issuance of the Evans patent,

which Alexion said "cover[s] the composition and use of Alexion's lead drug candidate[] eculizumab (formerly known as 5G1.1)." (EX1020, 001; *see also* EX1022, World Intellectual Property Organization International Publication No. WO 2005/110481 A2 issued to Russell P. Rother et al. ("Rother 2005 PCT"), 18:7-13.)

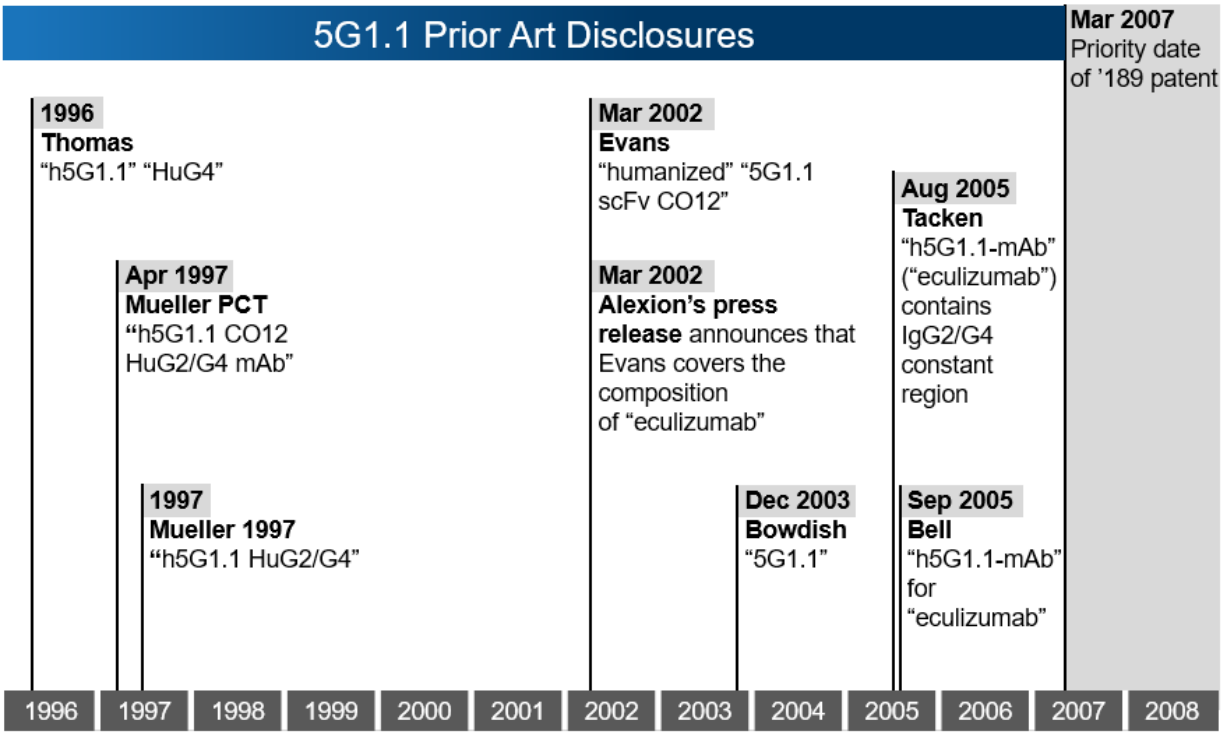
66. Additionally, a 2002 review of eculizumab also identified the terms 5G1.1 and h5G1.1 as "synonyms." (EX1023, Mariana Kaplan, *Eculizumab Alexion*, 3 Curr. Opin. Investig. Drugs 1017 (2002), 001.) In 2003, the World Health Organization ("WHO") also reported "eculizumab" as the Recommended INN for human-mouse monoclonal 5G1.1 antibody. (EX1018, 011.)

67. In 2003, Alexion disclosed that it used the 5G1.1 antibody as a framework to create antibodies for other targets, for example, a TPO mimetic peptide. (EX1004, U.S. Patent Application Publication No. 2003/0232972 A1 issued to Katherine S. Bowdish et al. (filed Dec. 2, 2002, published Dec. 18, 2003) ("Bowdish"), [0191].)

68. In 2005, another Alexion patent publication with lead inventor Bell equated the two terms: "h5G1.1-mAb" with "eculizumab." (EX1007, [0012].) Bell disclosed an anti-C5 antibody called "h5G1.1-mAb (eculizumab)," and further stated that h5G1.1-mAb is undergoing clinical trials under the "trade name

eculizumab." (EX1007, [0012], [0052].)

69. None of the references I discuss in the preceding paragraphs, namely Tacken, Mueller 1997, Mueller PCT, Kaplan, Rother 2005 PCT, Bowdish, or Bell, state that eculizumab has an IgG4 constant domain. Only the earlier Thomas reference describes a humanized 5G1.1 antibody as an IgG4 isotype, but this reference does not refer to that antibody as eculizumab, include the word eculizumab anywhere, or state that Alexion is developing the IgG4 isotype of 5G1.1 as a clinical candidate. The figure below shows the different publications that discussed the development of the 5G1.1 antibody before 2007.



70. Consistent with these publication and statements before 2007, I am informed that Alexion stated in another patent office proceeding that "it was well-known to one of ordinary skill in the art [as of 2002] that eculizumab has a G2/G4 Fc portion, *i.e.*, a mutated Fc portion" and that "h5G1.1 … [was] well-known to one of ordinary skill in the art as eculizumab[.]" (EX1029, 010-11.) Alexion based these statements on the teachings of Evans (EX1005) and Mueller 1997 (EX1006) that I discussed above and further in the Grounds below. (*See* EX1029, 010-11.)

V. THE '189 PATENT

A. Issued Claims

71. The '189 patent has eight issued claims:

> 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, and wherein the composition comprises a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution.
>
> 2. The method of claim 1, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

3. The method of claim 2, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

4. The method of claim 3, wherein the patient is treated with the antibody for at least 26 weeks.

5. 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, wherein the composition comprises a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution, and wherein the patient exhibits decreased lactate dehydrogenase levels.

6. The method of claim 5, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

7. The method of claim 6, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

8. The method of claim 7, wherein the patient is treated with the antibody for at least 26 weeks.

(EX1001, 39:16-32.) The eight claims recite methods of treating a patient with PNH

with a pharmaceutical composition comprising an anti-C5 antibody "consisting of" specifically-defined heavy and light chain protein sequences. There are two independent claims 1 and 5.

B. Overview of the Specification

72. The '189 patent describes the use of a pharmaceutical composition comprising anti-C5 antibody for the treatment of PNH. The '189 patent describes that the anti-C5 antibodies bind to complement C5 and inhibit its cleavage. Specifically, the '189 patent teaches that anti-C5 antibodies "are known," and such antibodies disclosed in U.S. Patent Number 6,355,245 (Evans) "include a preferred" antibody "now named eculizumab." (EX1001, 12:34-37.) The patent describes details of the Phase 3 "TRIUMPH" clinical trial in which eculizumab was evaluated in PNH patients. (*Id*., 19:63-28:45.)

73. The patent provides amino acid sequences for eculizumab's heavy chain in SEQ ID NO:2 and light chain in SEQ ID NO:4 at Columns 31-37 using the three letter amino acid codes, and at Columns 30-31 using the one letter amino acid codes. In one letter code, the corrected SEQ ID NO:2 is:

```
QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEW
MGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVY
YCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTS
```

```
ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLS
SVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPP
VAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL
PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNV
FSCSVMHEALHNHYTQKSLSLSLGK
```

In one letter code, SEQ ID NO:4 is:

```
DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLL
IYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNT
PLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP
REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
HKVYACEVTHQGLSSPVTKSFNRGEC
```

C. Prosecution History (EX1002)

74. On July 5, 2017, Alexion filed Application No. 15/642,096 that issued as the ’189 patent. Alexion initially sought claims 52-59 that issued as claims 1-8 in the ’189 patent. (EX1002, 924-25, 14836-37.) On April 29, 2019, Alexion submitted an Information Disclosure Statement that listed the three Amgen IPR Petitions challenging the claims of 9,732,149, 9,725,504, and 9,718,880 patents. (*Id*., 5390.)

75. On May 31, 2019, the Examiner rejected independent claim 52 as obvious over Hillmen in view of Evans, Wang and Bowdish. (EX1002, 11285-89.) The Examiner also rejected all claims 52-59 over Hillmen, Evans, Wang and

Bowdish as applied to claim 52, further in view of Bell. (*Id*., 11289-90.)

76. On December 11, 2019, Alexion responded to the Examiner's rejections. Alexion did not amend any claims. Alexion instead argued that (1) the literature prior to March 15, 2007 "repeatedly and consistently" describes "eculizumab" as having an IgG4 heavy chain constant region, (2) Evans "does not disclose any full-length humanized antibodies," (3) "a [POSA] would have had no reason to look to Bowdish *et al.*, and even looking to Bowdish, . . . would not have combined various portions of various sequences to arrive at the claimed sequence," (4) the rejection uses hindsight knowledge, and (5) "Wang does not disclose or teach the remaining claim limitations, and a [POSA] would not have reasonably expected the claimed composition to be successful in treating PNH." (EX1002, 14840-53.) In addition, Alexion provided evidence of secondary considerations of non-obviousness, including evidence of copying, long-felt needs, industry accolades and commercial success. (*Id*., 14855-63, 11393-96.)

77. Based on Alexion's arguments, the Examiner allowed the claims to issue on the belief that the cited combination would not result in the claimed antibody. With respect to Bowdish and Evans, the Examiner noted:

> Evan's [*sic*] scaffold 5G1.1 mouse antibody variable regions or the whole 5G1.1 mouse antibody with the sequences for

> Bowdish's TPO mimetic compound would still have revealed a mismatch in amino acids beyond those that Bowdish identified as the TPO mimetic peptide insert. Accordingly, it would appear that the scaffold taught by Evans is different from the scaffold used by Bowdish such that even if one of skill in the art were guided to Bowdish by reference to Evans, one of skill in the art would still not end up with the currently claimed antibody.

(EX1002, 14874-75.) With respect to evidence of secondary considerations, the Examiner stated:

> It is noted that at least some of the secondary considerations are evidence of non-obviousness, particularly that the invention as claimed satisfies a long felt need and that there is objective evidence of copying.

(*Id*., 14875.)

VI. APPLICATION OF THE PRIOR ART TO CHALLENGED CLAIMS

78. I have reviewed and analyzed the prior art references and materials listed in Part I.B above and discussed in more detail in Part VI.A below. In my opinion, all claims of the '189 patent are invalid based on the following prior art, organized into three "Grounds" as set forth below.

Ground	Claim(s)	Basis for Challenge
1	1-8	Obvious over Bell (EX1007), Bowdish (EX1004), Evans (EX1005), and Wang (EX1044) in view of Tacken (EX1008) and Mueller PCT (EX1009)
2	1-8	Obvious over Bell, Evans, Mueller PCT, and Wang in view of Tacken
3	1-8	Obvious over Bell and Wang

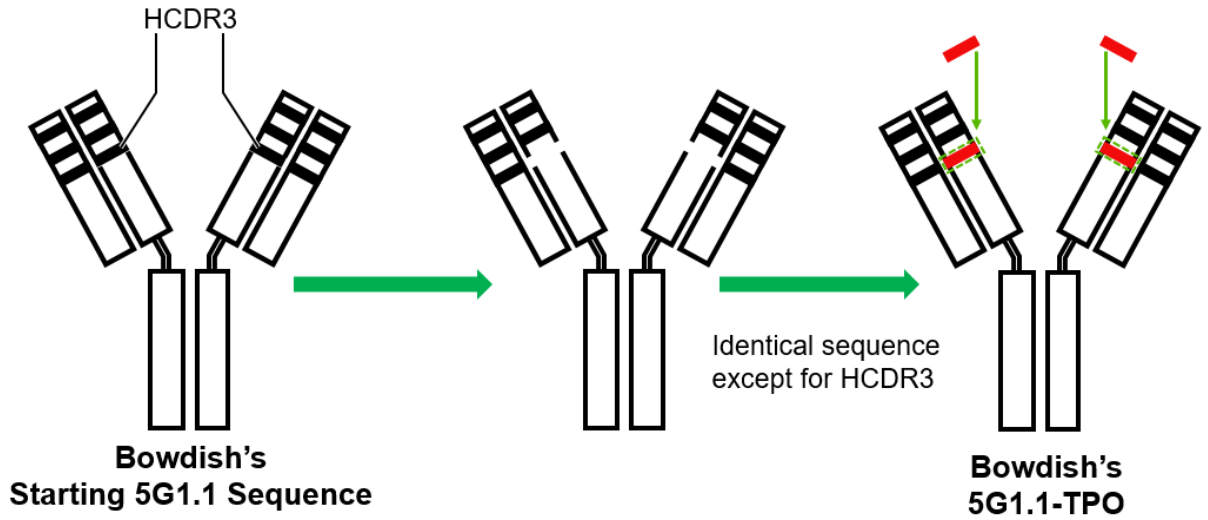
79. I understand that each of the references cited in the grounds above qualifies as prior art to the challenged claims because each reference was filed and/or published before the '189 patent critical date.

A. Brief Summary of Prior Art

1. Bowdish [EX1004]

80. **Bowdish** is a U.S. patent application that was published on December 18, 2003. Bowdish is titled "Rationally Designed Antibodies." Bowdish describes the generation of "[i]mmunoglobulins or fragments thereof [that] have a peptide of interest inserted into a complementarity determining region (CDR) of an antibody molecule." (EX1004, [0006].) The process uses a base antibody that "serves as a scaffold for presentation of the peptide." (*Id.*) As one example, Bowdish describes generating a TPO peptide in which the TPO mimetic peptide graft was "transplanted

into the heavy chain CDR3 of another antibody framework, 5G1.1." (*Id.*, [0191]-[0194], Figs. 13A-13B.) Bowdish thus began with the intact 5G1.1 antibody and used this as a starting point scaffold for constructing new antibodies. Bowdish incorporates by reference U.S. Patent Application No. 08/487,283, which issued as U.S. Pat. No. 6,355,245 ("Evans") for the process for creation of the 5G1.1 antibody. (EX1004, [0191].) Bowdish thus used the 5G1.1 antibody of Evans as a starting point for making a new heavy chain that includes a "TPO mimetic peptide" in place of the HCDR3 molecule, as shown in the figure below (*id.*, Figure 13A & [0191]):

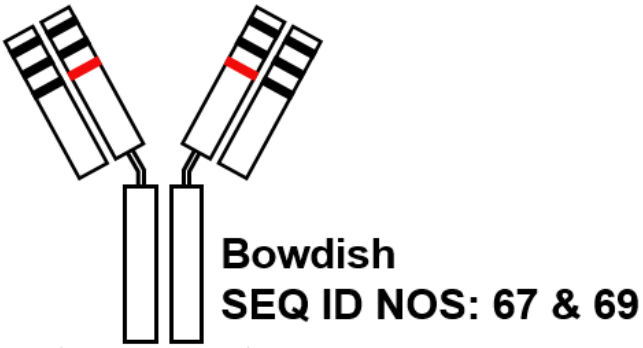


As explained in more detail below, Bowdish's modified antibody also made no changes to the light chain of 5G.1, thus the TPO-containing antibody described at the amino acid level in Bowdish contains the exact sequence of the light chain of

5G1.1.

81. A POSA would have easily determined that the sequences shown in Figures 13A and 13B of Bowdish are humanized 5G1.1 with a hybrid IgG2/IgG4 heavy chain, which would match with what was expected for eculizumab. For example, a POSA evaluating the sequences of the constant region from the heavy and light chains of Bowdish's 5G1.1 antibody would immediately recognize that the heavy chain constant region is not purely of one type, IgG2 or IgG4, but rather clearly a hybrid of the two. Similarly, a POSA in 2007 would have immediately recognized that the 5G1.1 antibody was primarily human rather than from a non-human source such as mouse – just as a POSA seeking a humanized antibody would expect. The humanized nature of Bowdish's 5G1.1 antibody is also evident from the use of an "anti-human IgG" in a binding assay to detect 5G1.1. (EX1004, [0192] (describing detecting 5G1.1 in FACS analysis using an "anti-human IgG").)

82. The figure below shows the structure of the 5G1.1-TPO antibody that is disclosed in Bowdish's SEQ ID NOS:67 and 69, with red indicating the CDR3 region in the heavy chain where the TPO peptide was inserted:

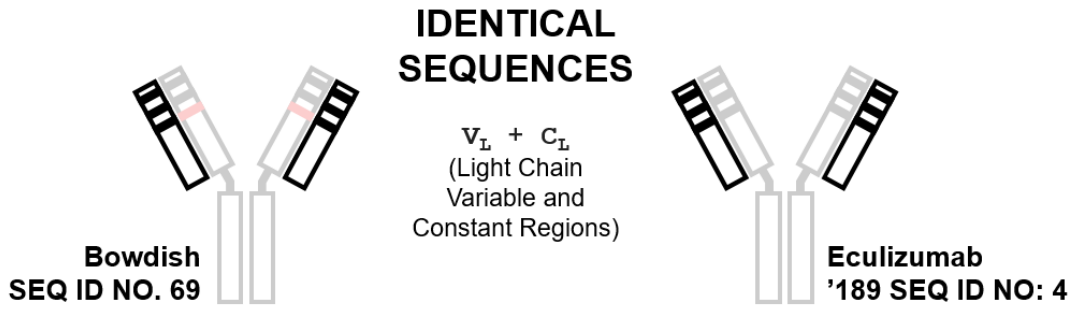


83. Figure 13B of Bowdish discloses SEQ ID NO:69, which corresponds to the light chain sequence of the eculizumab-based 5G1.1 antibody, and includes a leader sequence (identified as the portion of the sequence that is italicized) and the light chain variable and constant regions (V_L and C_L). A POSA would have understood that the leader sequence is cleaved off as a standard process of maturation of an antibody. (EX1053, Bruce Alberts et al., *Chapter 12: Intracellular Compartments and Protein Sorting*, Molecular Biology of the Cell (1994), 059; *see also* EX1002, 003-04.) The figure below shows an alignment for rest of the mature sequence from Bowdish's SEQ ID NO:69 with the '189 patent's SEQ ID NO:4. Bowdish's disclosed light chain sequence for 5G1.1 antibody is identical to the light chain sequence disclosed in SEQ ID NO:4 recited in claims 1 and 5 of the '189 patent.

```
Bowdish SEQ ID NO: 69   1  MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGV  80
'189 SEQ ID NO: 4       1  ----------------------DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGV  58
                                                                  CDR1                  CDR2

Bowdish SEQ ID NO: 69  81  PSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN  160
'189 SEQ ID NO: 4      59  PSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN  138
                                                  CDR3

Bowdish SEQ ID NO: 69 161  FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC  236
'189 SEQ ID NO: 4     139  FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC  214
```



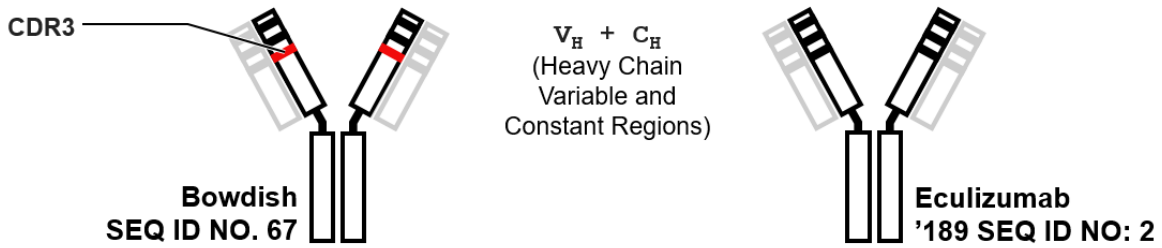
84. Figure 13A of Bowdish discloses SEQ ID NO:67, which corresponds to the heavy chain sequence of the eculizumab-based 5G1.1 antibody with the "native CDR3" substituted for the "TPO mimetic peptide." The sequence in SEQ ID NO:67 includes a leader sequence (identified as the portion of the sequence that is italicized), and the heavy chain variable and constant regions (V_H and C_H). The figure below shows an alignment for the mature sequence from Bowdish's SEQ ID NO:67 with the '189 patent's SEQ ID NO:2. Bowdish's disclosed heavy chain sequence is identical to the heavy chain sequence disclosed in SEQ ID NO:2 recited in claims 1 and 5 of the '189 patent, except for the CDR3 sequence that Bowdish substituted for the TPO mimetic peptide insert.

```
Bowdish SEQ ID NO: 67   1 MKWSWVILFLLSVTAGVHSQVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYT  80
'189 SEQ ID NO: 2       1 ------------------QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYT  61
                                                                          CDR1                 CDR2
Bowdish SEQ ID NO: 67  81 ENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAPVWGQGTLVTVSSASTKGPSVFPLAPC 160
'189 SEQ ID NO: 2      62 ENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSP--NWYF---DVWGQGTLVTVSSASTKGPSVFPLAPC 136
                          CDR2                                   CDR3
Bowdish SEQ ID NO: 67 161 SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKV 240
'189 SEQ ID NO: 2     137 SRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKV 216

Bowdish SEQ ID NO: 67 241 DKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ 320
'189 SEQ ID NO: 2     217 DKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQ 296

Bowdish SEQ ID NO: 67 321 FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS 400
'189 SEQ ID NO: 2     297 FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS 376

Bowdish SEQ ID NO: 67 401 DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 472
'189 SEQ ID NO: 2     377 DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448
```



85. Bowdish also discloses that its antibodies can be formulated and administered as "pharmaceutical compositions." (EX1004, [0151].) These pharmaceutical compositions "can be administered intravenously" using known methods and "must be sterile." (*Id*., [0148]-[0150].) Bowdish further states that "preservatives … can be incorporated according to accepted pharmaceutical practice," meaning that preservatives are optional in such pharmaceutical compositions. (*Id*., [0150].)

86. Additional details about Bowdish are provided in my discussion of application of Bowdish in Ground 1 below.

2. Evans [EX1005]

87. **Evans** is a U.S. patent that issued on March 12, 2002, based on U.S. Application number 08/487,283. Evans is titled "C5-Specific Antibodies for the Treatment of Inflammatory Diseases." Evans describes generating the murine 5G1.1 antibody and making humanized 5G1.1 scFvs and full-length antibodies containing the CDR regions from the murine 5G1.1 antibody. Evans also provides exemplary sequences of humanized scFvs and humanized light chain sequences. (EX1005, 37:35-39:30, 42:59-45:33.) Evans discloses the CDR regions used in the humanized 5G1.1 antibodies, which are underlined in the sequences provided in Figures 18 and 19 of Evans, and also identified by sequence numbers in Example 11. (*Id*., Figs. 18-19, Example 11 (42:56-45:4).)

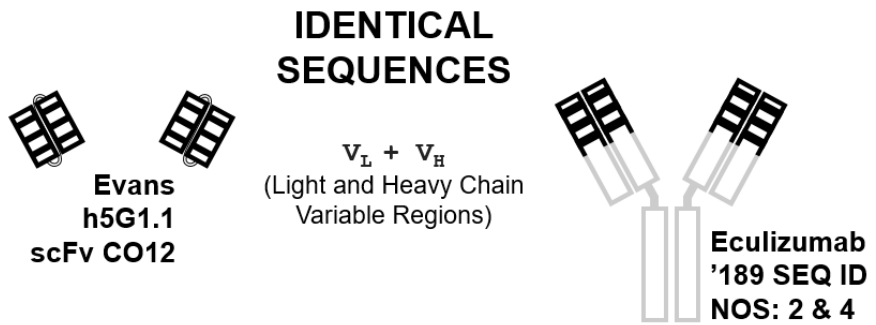
88. Example 11 of Evans provides eighteen constructs of "recombinant mAb-encoding DNAs" comprising recombinant mAbs with 5G1.1 CDRs. Nine of these constructs in Example 11 (2) and (11)-(18) disclose sequences for humanized 5G1.1 single-chain variable fragments (scFv), which correspond to V_H and V_L domains joined by a short peptide linker and starting with the "MA" leader sequence. (EX1005, 43:6-14, 43:61-45:4 (Example 11 (2) and (11)-(18)).) These nine constructs disclose CDR sequences within the variable regions of humanized 5G1.1. All nine humanized 5G1.1 scFv constructs have the same heavy chain CDR3

sequence, YFFGSSPNWYFDV, which matches the heavy chain CDR3 sequence of SEQ ID NO:2 of claims 1 and 5. (*See* Appendix A; EX1005, 9:65-10:20, 42:56-45:33, 143:22-144:14, Figs. 18-19, Claim 19.) Further, Example 11 at construct (12) provides a sequence for SEQ ID NO:20, denoted by "humanized' "5G1.1 scFv CO12," which includes all six CDR sequences and variable regions of SEQ ID NOS:2 and 4 of claims 1 and 5. (EX1005, Example 11 (12).)

89. In the figure below, I omitted the "MA" leader sequence of Evans' CO12 scFv (SEQ ID NO:20) that is cleaved upon maturation of the antibody, and then aligned the remaining Evans' SEQ ID NO:20 with the variable regions of the '189 patent's SEQ ID NOS:4 and 2. The alignment shows that amino acid sequence of the VL and VH domains of Evans' CO12 scFv (SEQ ID NO:20) with the same domains of the '189 patent's SEQ ID NOS:4 and 2 shows an identical match:

```
Evans h5G1.1     1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP  80
'189 SEQ ID NO: 4  1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP  80
                                          CDR1                    CDR2                                  VL
Evans h5G1.1    81 EDFATYYCQNVLNTPLTFGQGTKVEIKRT                    109
'189 SEQ ID NO: 4  81 EDFATYYCQNVLNTPLTFGQGTKVEIKRTGGGGSGGGGSGGGGS    124
                          CDR3

Evans h5G1.1     1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY  80
'189 SEQ ID NO: 2  125 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY  204
                                                CDR1                    CDR2                                  VH
Evans h5G1.1    81 MELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS  122
'189 SEQ ID NO: 2  205 MELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS  246
                                      CDR3
```



90. In addition, Evans discloses that anti-C5 antibodies can be administered "in a variety of unit dosage forms." (EX1005, 17:60-61.) Evans further states that typical doses for human patients are from 1 to 100 mg per kg and preferably 5 to 50 mg per kg of patient weight. (*Id.*, 18:7-11.) Evans also discloses that "[a]dministration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection," and that "[s]uch formulations must be sterile," and "may contain … preservatives[.]" (*Id.*, 18:29-43.)

91. Additional details about Evans are provided in my discussion of application of Evans in Grounds 1-2 below.

3. Bell [EX1007]

92. **Bell** is a U.S. patent application that was published on September 1, 2005. Bell teaches that a "particularly useful" treatment for PNH is the anti-C5 antibody known as "h5G1.1-mAb (eculizumab)." (EX1007, [0052], [0082].) Bell also discloses that "[t]he antibody h5G1.1" carried the "tradename eculizumab." (*Id.*, [0052].) Bell also teaches that "[m]ethods for the preparation of" h5G1.1 "are described in" Evans (EX1005) and Thomas (EX1010) and incorporates those disclosures "in their entirety." (EX1007, [0052].)

93. Bell provides clinical results from a Phase 2 pilot study in which eleven transfusion-dependent PNH patients were successfully treated with eculizumab. Bell discloses that the patients received "a weekly 600 mg intravenous infusion" of eculizumab "[o]ver the course of four weeks," meaning that eculizumab was administered intravenously at a dose of 600 mg every 7±1 days for four weeks. (EX1007, [0082].) Bell further discloses that after this initial phase, patients were given "900 mg of eculizumab 1 week later then 900 mg on a bi-weekly basis[,]" meaning eculizumab was administered intravenously at a 900 mg maintenance dose every 14±2 days. (*Id.*) Two of the patients also received the 900 mg maintenance dose every 12 days instead of 14 days. (*Id.*, [0088].) Bell further discloses that the trial treated PNH patients with eculizumab for up to two years. (*Id.*, [0082], [0091].)

94. Bell discloses that eculizumab effectively treated PNH. (EX1007, [0081]-[0097], Figs. 1a, 1b, 3, 6a, 6b, 7-10.) Bell also notes that eculizumab "protected PNH type III [red blood cells] from complement-mediated lysis, prolonging the cells survival." (*Id*., [0083].) Bell notes that "[t]his protection of the PNH-affected cells reduced the need for transfusions, paroxysms and overall hemolysis in all patients in the trial." (*Id*.) Eculizumab also successfully decreased levels of lactate dehydrogenase ("LDH") and aspartate transferase (indicators of hemolysis). (*Id.*, [0085]-[0086], Fig. 1.) In fact, Bell teaches that eculizumab resulted in an immediate (i.e., within one week of administration) and sustained decrease in the mean levels of LDH. (*Id*., [0085], Fig. 1b.) Bell also explains that paroxysm rates "reduced by 93%," serum hemolytic activity was "completely blocked," and the need for transfusions was reduced with eculizumab. (*Id*., [0087]-[0089], Figs. 3-6.) Bell also reports results from an extension study that showed that the reduction in transfusion need was durable, lasting over two years. (*Id.*, [0092].) Bell also discloses eculizumab pharmacodynamic data, improvement in overall patent quality of life, and a reduction in adverse symptoms associated with PNH. (*Id.*, [0093]-[0096], Figs. 8-10.)

95. Bell discloses that the inclusion criteria for its trial required that the PNH patients should have received four or more transfusions in the 12 months

preceding the trial. (EX1007, [0081].) Four patients in the trial had platelet counts "greater than 150,000 per microliter." (*Id*., [0089], Claim 14.)

96. In addition, Bell teaches that the anti-C5 antibody formulations "suitable for injection" "must be sterile" and "may contain … preservatives[.]" (EX1007, [0062].)

97. Additional details about Bell are provided in my discussion of application of Bell in Grounds 1-3, below.

4. Tacken [EX1008]

98. **Tacken** is a journal article that was published in Aug. 15, 2005. As shown in the author affiliation disclosures on the cover sheet of Tacken, Alexion employed several authors of the article. (EX1008, 010.) The first page of the Tacken article also discloses that Alexion's "potential product was studied" in the underlying work. (*Id*.) Tacken describes the generation of a humanized antihuman DC-SIGN antibody by CDR grafting of hypervariable domains into human framework regions. (*Id.*, 011.) The variable regions were then fused with a human hybrid IgG2/G4 heavy chain constant domain and a human kappa light chain constant domain. Tacken expressly cites reference 17—which is the Mueller 1997 article—for the hybrid IgG2/G4 constant domain. Tacken further discloses use of

an isotype control antibody, "h5G1.1-mAb (5G1.1, eculizamab [sic]; Alexion Pharmaceuticals)" that contains "the same IgG2/IgG4 constant region" and "is specific for the human terminal complement protein C5." (*Id*., 011.)

99. Additional details about Tacken are provided in my discussion of application of Tacken in Grounds 1-2, below.

5. Mueller PCT [EX1009]

100. **Mueller PCT** is an international patent application concerning the same work described in the Mueller 1997 article that was published by Alexion. Mueller PCT discloses the sequence of eculizumab's hybrid IgG2/IgG4 heavy chain constant region, and methods of how to make and use an antibody with this hybrid constant region.

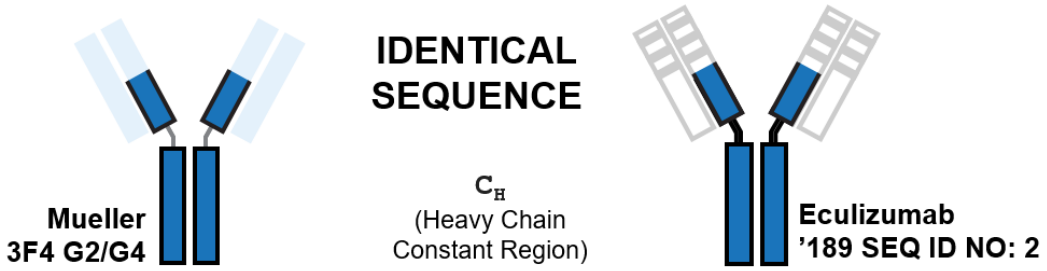
101. Mueller PCT teaches development of recombinant antibodies to reduce immune-mediated organ transplant rejection, including antibodies comprising a hybrid IgG2/IgG4 constant region. Mueller PCT provides sequences for two antibodies that target P-selectin protein VCAM (anti-VCAM antibodies), including the full-length 3F4 HuG2/G4 antibody, which contains a hybrid IgG2/G4 heavy chain constant region with "the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4" that eliminates interaction with Fc receptor. (EX1009,

8:23-26, 12:23-27.)

102. Mueller PCT discloses that antibodies with the "recombinant (chimeric and/or humanized)" antibody molecules with the IgG2/G4 constant region will be referred to as "HuG2/G4 mAb." (EX1009, 8:23-26.) Mueller PCT describes using "h5G1.1 CO12 HuG2/G4 mAb" as a control antibody that shares that same IgG2/G4 constant region as the other HuG2/G4 mAbs that it discloses. (*Id*., 12:34-37.)

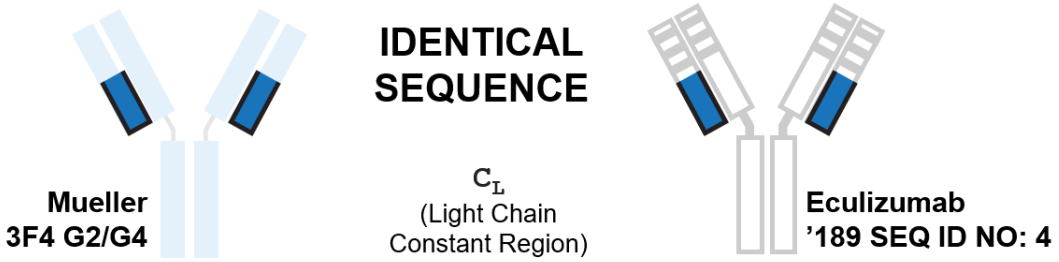
103. Mueller PCT provides the complete amino acid sequence of the hybrid IgG2/G4 constant region used in its anti-VCAM antibody, 3F4. As shown in the figure below, an alignment of the amino acid sequence of Mueller PCT's hybrid IgG2/G4 heavy chain constant region of the 3F4 (chimeric) human G2/G4 antibody with the heavy chain constant region of '189 patent's SEQ ID NO:2 shows that Mueller PCT discloses the same IgG2/G4 heavy chain constant region as described in SEQ ID NO:2 of claims 1 and 5 of the '189 patent:

Mueller 3F4 G2/G4 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
'189 SEQ ID NO: 2 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Mueller 3F4 G2/G4 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
'189 SEQ ID NO: 2 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Mueller 3F4 G2/G4 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
'189 SEQ ID NO: 2 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Mueller 3F4 G2/G4 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
'189 SEQ ID NO: 2 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Mueller 3F4 G2/G4 C_H	321	SLSLGK	326
'189 SEQ ID NO: 2 C_H	321	SLSLGK	326



104. Mueller PCT also discloses the amino acid sequence of the light chain of 3F4 antibody. As shown in the figure below, the constant region of the light chain in 3F4 is identical to the constant region of the light chain disclosed in SEQ ID NO:4 claimed in claims 1 and 5 of the '189 patent:

Mueller 3F4 C_L	1	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH	80
'189 SEQ ID NO: 4 C_L	1	VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH	80
Mueller 3F4 C_L	81	KVYACEVTHQGLSSPVTKSFNRGEC	105
'189 SEQ ID NO: 4 C_L	81	KVYACEVTHQGLSSPVTKSFNRGEC	105



105. Additional details about Mueller PCT are provided in my discussion of application of Mueller PCT in Grounds 1-2, below.

6. Wang [EX1044]

106. **Wang** is a U.S. patent application that was published on December 8, 2005. Wang relates to "methods and compositions" for antibody formulations, such as eculizumab, that inhibit "activation of the complement system." (EX1044, Abstract, [0004].) Wang also identifies these antibodies as useful for treating pulmonary diseases. (*Id.*, [0064], [0111].) Wang expressly references the Evans reference described above and identifies the anti-C5 antibody eculizumab as a preferred embodiment. (*Id.*, [0004], [0011], [0067].)

107. Wang further discloses that the formulations of anti-C5 antibody, such as eculizumab formulations, "may be stable in a formulation at a concentration

ranging from 1 mg/ml to 200 mg/ml." (EX1044, [0067].) Wang provides examples of formulations that have eculizumab concentrations ranging from 1 mg/ml to 30 mg/ml while maintaining the effectiveness and integrity of the antibody. (*Id*., Fig. 10, [0025], [0170]-[0173].)

108. Additional details about Wang are provided in my discussion of application of Wang in Grounds 1-3, below.

B. Ground 1: Claims 1-8 Are Obvious Over Bell, Bowdish, Evans, and Wang in view of Tacken and Mueller PCT

1. Claim 1

(a) Antibody Sequence (SEQ ID NOS:2 and 4) and Method of Treatment Limitations

109. As described above, Bell teaches that eculizumab, also referred to as "h5G1.1-mAb," is a "[p]articularly useful" treatment for PNH. (EX1007, [0052], [0082].) Bell also discloses that "[t]he antibody h5G1.1" carried the "tradename eculizumab." (*Id*., [0052].) Bell reports results from a clinical trial, stating that eculizumab successfully "protected PNH type III [red blood cells] from complement-mediated lysis, prolonging the cells survival." (*Id.*, [0083].) Bell teaches human clinical trial evidence, which shows that eculizumab is an effective treatment for PNH. (*Id.*, [0003], [0012], [0081]-[0097], Figs. 1a, 1b, 3, 6a, 6b, 7-

10.) Based on Bell's definitive clinical results, a POSA would have been motivated to obtain the structure of eculizumab.

110. Bell further discloses that "[m]ethods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in" Evans and Thomas references, the "disclosures of which are incorporated [into Bell] in their entirety[.]" (EX1007, [0052].) Since Bell expressly references (and even incorporates) Evans for preparing h5G1.1, and Evans discloses humanized 5G1.1 scFv sequences, a POSA would have easily understood that the scFv sequences of Evans correspond to the heavy and light chain variable region sequences for eculizumab. Further, as explained below, since Tacken expressly discloses that eculizumab has the IgG2/G4 constant domain, a POSA would have not concluded from Bell's citation of Thomas that the eculizumab disclosed in Bell would have the IgG4 isotype discussed in Thomas. (*See also* ¶128 below.)

111. Bowdish incorporates U.S. Application Ser. No. 08/487,283 (published in 2002 as the Evans '245 patent, EX1005) by reference for construction of the anti-C5 5G1.1 antibody, thereby disclosing both SEQ ID NOS:2 and 4 recited in claim 1 of the '189 patent. (*See* EX1004, [0191].)

112. Bowdish's SEQ ID NO:69 discloses the light chain sequence of its antibody 5G1.1. (EX1004, Fig. 13B.) The sequence comprises a leader sequence

(that is italicized) and the light chain variable and constant regions. The leader sequence is cleaved upon maturation of the antibody. As shown in the figure below, for the mature antibody sequence, Bowdish's SEQ ID NO:69 discloses the identical light chain sequence, including both variable and constant light chain regions, of SEQ ID NO:4 in claim 1 of the '189 patent.

```
Bowdish SEQ ID NO: 69   1  MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGV  80
'189 SEQ ID NO: 4       1  ----------------------DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGV  58
                                                                  CDR1                  CDR2

Bowdish SEQ ID NO: 69  81  PSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN  160
'189 SEQ ID NO: 4      59  PSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN  138
                                                  CDR3

Bowdish SEQ ID NO: 69 161  FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC  236
'189 SEQ ID NO: 4     139  FYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC  214
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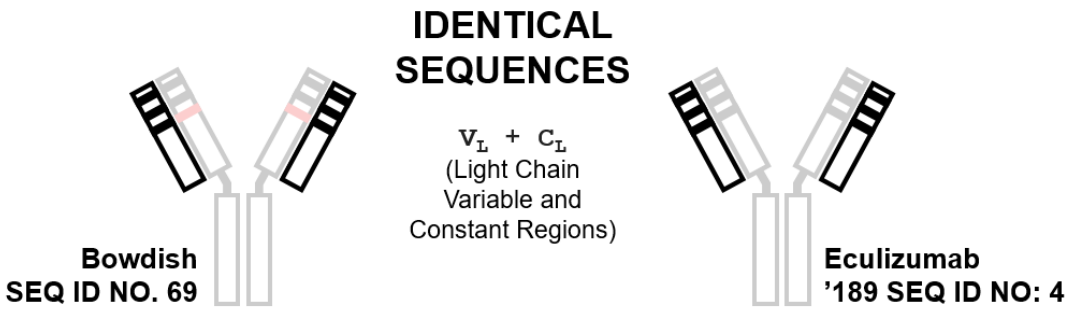
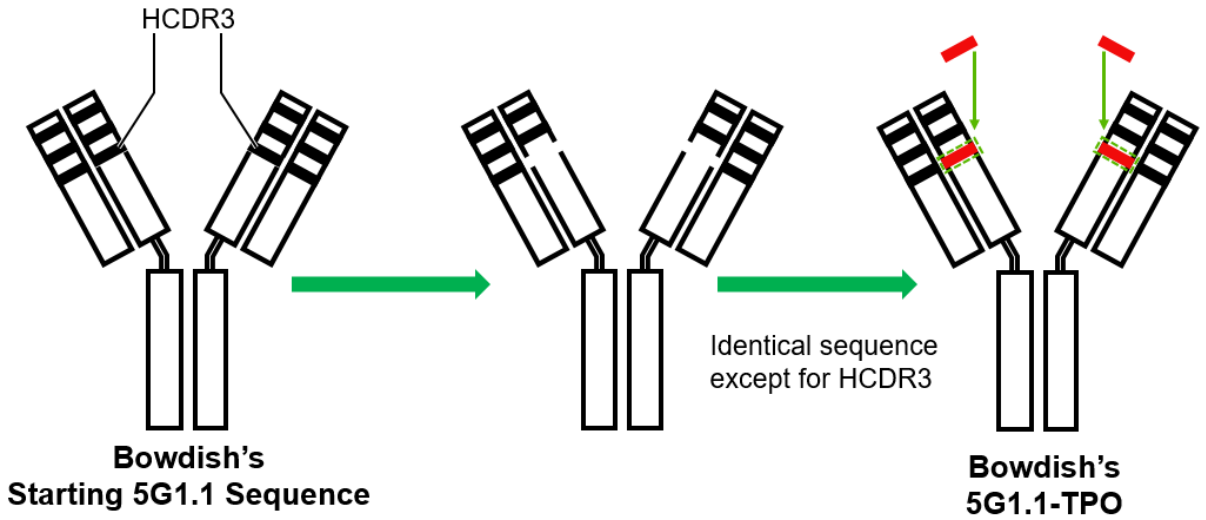


113. Bowdish's SEQ ID NO:67 discloses the heavy chain sequence of the antibody framework 5G1.1 that was used as a starting point to create a TPO mimetic peptide. Bowdish explains that the "native CDR3" of the antibody framework 5G1.1 was replaced with a "TPO mimetic peptide graft" and identifies the sequence of the inserted peptide as LPIEGPTLRQWLAARAPV. (EX1004, Fig. 13A, [0191].)

Bowdish also identifies that Evans discloses the "native CDR3," and incorporates Evans by reference. (*See id*., [0191].) Therefore, as depicted in the figure below, Bowdish identifies the heavy chain sequence of 5G1.1 that had the "native CDR3" before it was replaced with the HCDR3 of TPO peptide:



114. To put it a different way, the disclosures of Bowdish make clear that the original heavy chain sequence of the starting 5G1.1 antibody contained the "native CDR3" of h5G1.1 disclosed by Evans, YFFGSSPNWYFDV, before it was replaced with Bowdish's disclosed TPO mimetic peptide, LPIEGPTLRQWLAARAPV all as shown in SEQ ID NO:67. (EX1004, [0191]; EX1005, Fig. 19, Example 11(2), (11)-(18) (43:6-14; 43:61-45:4).) As shown in the figures below, this original heavy chain disclosed by the Bowdish and Evans integrated document has the identical sequence as SEQ ID NO:2 of claim 1.

```
Bowdish SEQ ID NO: 67   1  MKWSWVILFLLSVTAGVHSQVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYT  80
'189 SEQ ID NO: 2       1  ------------------QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYT  61
                                                                          CDR1                CDR2
                           Original Evans CDR3 in starting 5G1.1
Bowdish SEQ ID NO: 67  81  ENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTS  160
'189 SEQ ID NO: 2      62  ENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTS  141
                           CDR2                                  CDR3
Bowdish SEQ ID NO: 67  161  ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE  240
'189 SEQ ID NO: 2      142  ESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE  221

Bowdish SEQ ID NO: 67  241  RKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY  320
'189 SEQ ID NO: 2      222  RKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY  301

Bowdish SEQ ID NO: 67  321  RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE  400
'189 SEQ ID NO: 2      302  RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE  381

Bowdish SEQ ID NO: 67  401  WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK  467
'189 SEQ ID NO: 2      382  WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK  448
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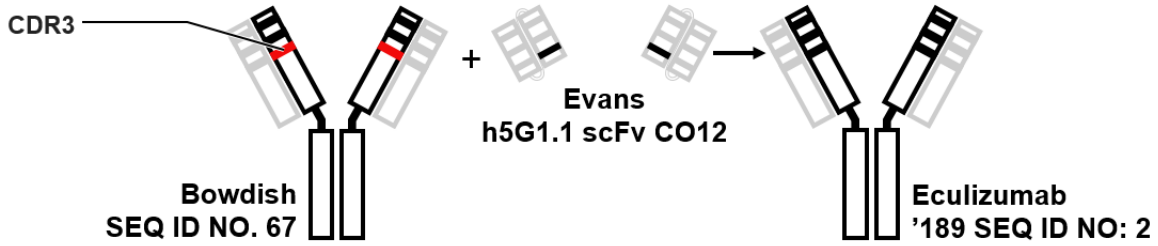


115. Bowdish thus teaches SEQ ID NOS:2 and 4 recited in claim 1. This is also consistent with the Board's prior statement in the previously-instituted IPR that "Bowdish discloses a substantial portion of the anti-C5 antibody 5G1.1 and points to Evans as evidencing the remaining amino acid sequence." (EX1024, 045.) Indeed, a POSA following Bowdish's incorporation of Evans would have easily identified the HCDR3 sequence from Evans that Bowdish refers to as "native CDR3." Evans expressly discloses that the 5G1.1 sequences, which include CDR sequences, encode antibodies that bind C5. (EX1005, Cover (Title), 7:60-64, 9:44-45, 143:22-144:14, Fig. 8, Claim 19; *see also* EX1022, 16:10-12.) Example 11 of

Evans teaches the construction of recombinant antibodies using the six CDRs of 5G1.1 antibody. (EX1005, 42:56-45:33.) Evans provides eighteen constructs of "recombinant mAb-encoding DNAs" numbered as (1)-(18). Nine of these constructs, disclosed under (2) and (11)-(18), provide "humanized" 5G1.1 single-chain variable domain structures ("scFvs"), which comprise the V_H and V_L domains of an antibody joined by a short peptide linker. (EX1005, 42:56-45:33 (Example 11 (2), (11)-(18)).) All humanized scFv constructs in Evans use the commonly-known peptide linker "GGGGSGGGGSGGGGS." (EX1047, 006.)

116. The humanized scFv constructs also have a "MA" leader sequence at amino acid residues 1-2. During '189 prosecution, Alexion argued that "the mature portion of the complete light chain sequence … could have been readily identified at the relevant filing date using well established rules and art-recognized techniques," and stated that *Adderson et al.* (1992) "shows the characteristic mature N-terminus (DIQ) of a light V kappa antibody light chain[.]" (EX1002, 004 (citing EX1054, Elisabeth E. Adderson et al*., Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to Haemophilus influenzae Type b Capsular Polysaccharide Are Dominated by a Limited Number of V_κ and V_λ Segments and VJ Combinations*, 89 J Clin. Invest. 729 (1992), 017, Fig 6).) Including as shown by Alexion's own statements, a POSA would recognize that a mature kappa light chain

sequence starts with "DIQ" at the N terminus, and thus the first two amino acids "MA" in Evans' nine humanized scFv constructs constitute a leader sequence.

117. A POSA looking at the amino acid sequence provided for these nine scFvs, for example construct 12 within Example 11, would be able simply by eye to immediately identify the parts of the construct which correspond to the V_H and V_L domains. For example, a POSA would immediately recognize the canonical starting sequence "DIQ" that begins the V_L domain at amino acids residue 3, and the starting sequence "QVQ" that begins the V_H domain at amino acid residue 127. A POSA would similarly immediately recognize the portion of the construct that is the leader sequence, and the repeating glycine-serine sequence that constitutes the linker separating the V_H and V_L domains. (EX1047, 006.)

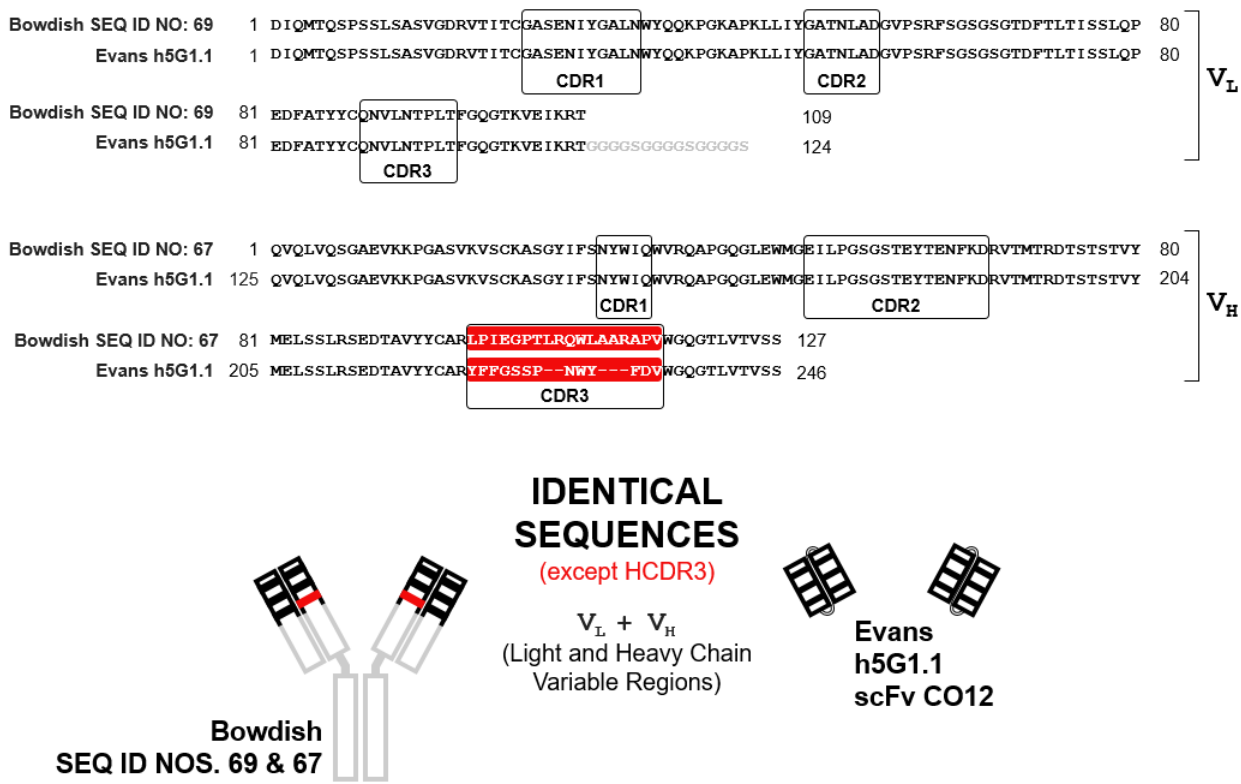
118. I compared Evans' nine humanized 5G1.1 scFv constructs in Appendix A, and note that every one of these constructs discloses the identical HCDR3 sequence, YFFGSSPNWYFDV. (EX1005, 9:65-10:20, 42:56-45:33, 143:22-144:14, Figs. 18-19, Claim 19.) It is not surprising that all constructs have this identical HCDR3 sequence because the CDR regions determine binding to C5 target, and also determine the uniqueness of a particular antibody such as 5G1.1. Bowdish also expressly teaches a "pharmaceutical composition" for its disclosed antibodies, as recited in claim 1. (EX1004, [0148]-[0150].)

119. Bowdish incorporates Evans by express reference for "[c]onstruction of 5G1.1," thereby specifying exactly what material from Evans is being incorporated. (EX1004, [0191].) With such express incorporation by reference, a POSA would recognize that Bowdish brings the entire disclosure of Evans within Bowdish itself. Accordingly, a POSA would treat Bowdish and Evans as an integrated single reference, and that integrated document discloses sufficient information to make the claimed sequences of SEQ ID NOS:2 and 4 that correspond to eculizumab.

120. A POSA looking for the amino acid sequences encoding eculizumab would have easily found Bowdish, and considered it to be analogous art to Bell and Evans for at least three reasons: (1) it provides express disclosures about the structure of the antibody "5G1.1," (2) it identifies "Alexion Pharmaceuticals" as the inventors' addressee that is the same as the assignee for Evans, and (3) it cites to the same Evans patent as does Bell for the structure of 5G1.1. Thus, a POSA would have been motivated to combine the teachings of Bowdish and Evans in view of Bell to arrive at the claimed sequence.

121. Bowdish refers to "5G1.1," but a POSA would have easily understood that it is referring to the humanized form of 5G1.1, also sometimes called h5G1.1, based on a routine alignment of the variable region sequences disclosed in Bowdish

with Evans. Bowdish discloses that its SEQ ID NO:69 discloses the light chain sequence, and SEQ ID NO:67 discloses the heavy chain sequence of "5G1.1" antibody framework, into which the HCDR3 was replaced for the TPO mimetic peptide graft. (*See* EX1004, Figs. 13A & 13B.) I have omitted the leader sequences of Evans' SEQ ID NO:20 and Bowdish's SEQ ID NOS:69 and 67 because the leader sequence is cleaved upon maturation of the antibody, and provided a comparison of the variable regions in Bowdish's SEQ ID NOS:69 and 67 with Evans' SEQ ID NO:20 (a scFv comprising sequences for VL and VH separated by a peptide linker). This comparison shows that the sequences are identical in all variable regions (*i.e.,* the framework region, HCDR1 and HCDR2), except for the HCDR3 sequence that Bowdish replaced:



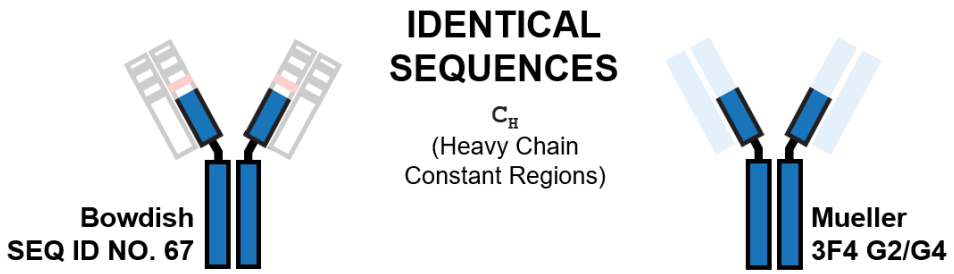
122. Evans refers to SEQ ID NO:20 as "humanized" 5G1.1 scFv. Since Bowdish's antibody framework regions are identical to Evans' humanized 5G1.1 framework regions, a POSA would have understood that Bowdish's sequences in SEQ ID NOS:67 and 69 are also humanized 5G1.1. Also, as I noted in my discussion of Bowdish in Part VI.A above, the humanized nature of Bowdish's 5G1.1 antibody is also evident from the use of an "anti-human IgG" in a binding assay to detect 5G1.1. (EX1004, [0192] (describing detecting 5G1.1 in FACS analysis using an "anti-human IgG.").)

123. A POSA would have also recognized that Bowdish contains the desired

constant regions for eculizumab based on Tacken's teachings. Tacken equates h5G1.1 with eculizumab, and calls it Alexion's "potential product." (EX1008, 010.) Tacken further teaches that eculizumab contains an IgG2/G4 constant domain that is the "same" as the human hybrid IgG2/G4 constant domain disclosed in its cited reference 17, which is the Mueller 1997 article. (EX1008, 011 (citing EX1006).)

124. The Mueller 1997 article discloses the CH1, hinge, and CH2 regions of the IgG2/G4 constant domain heavy chain. Mueller 1997's companion patent application, Mueller PCT, teaches the complete amino acid sequence for the hybrid IgG2/G4 constant domain heavy chain used in its "h5G1.1 HuG2/G4" and 3F4 antibodies. (*See* Part IV.E above.) A POSA would have been able to perform a routine alignment of the IgG2/G4 constant domain heavy chain from Mueller PCT and Bowdish, as provided below, and recognized that Bowdish indeed has the exact sequence required for eculizumab:

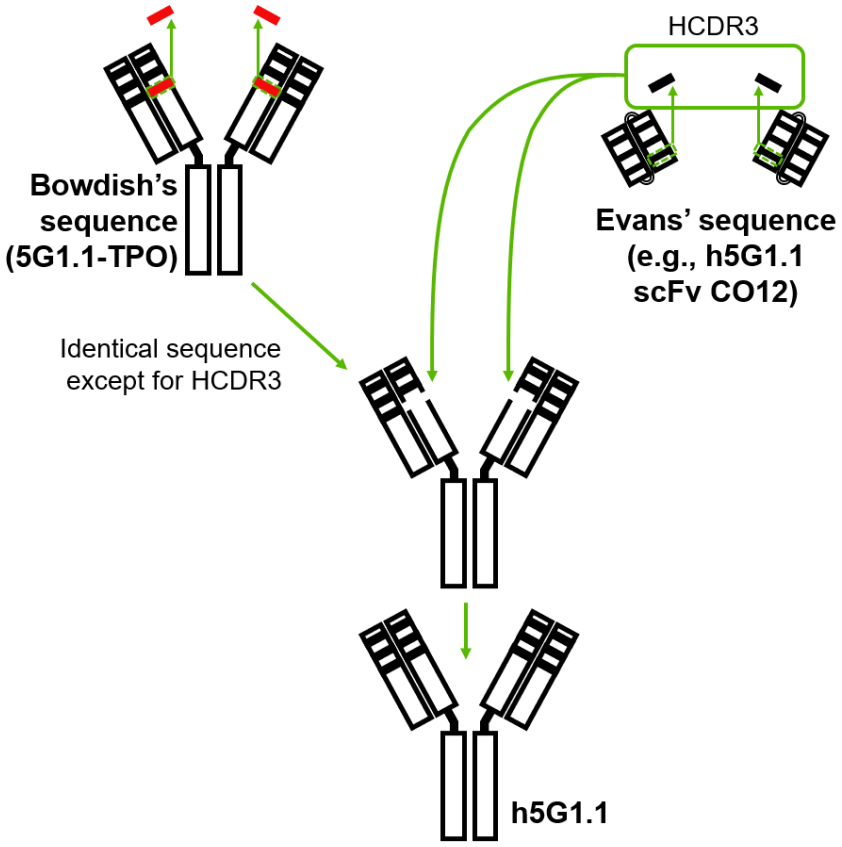
Bowdish SEQ ID NO: 67 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Mueller 3F4 G2/G4 C_H	1	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQT	80
Bowdish SEQ ID NO: 67 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Mueller 3F4 G2/G4 C_H	81	YTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG	160
Bowdish SEQ ID NO: 67 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Mueller 3F4 G2/G4 C_H	161	VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKN	240
Bowdish SEQ ID NO: 67 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Mueller 3F4 G2/G4 C_H	241	QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL	320
Bowdish SEQ ID NO: 67 C_H	321	SLSLGK	326
Mueller 3F4 G2/G4 C_H	321	SLSLGK	326



125. Thus, a POSA would have understood from the collective teachings of Bell and Tacken that eculizumab has the variable domains described in Evans and the constant domains described in Mueller PCT (which are also identical to those in Bowdish's starting 5G1.1 antibody).

126. In March 2007, a POSA looking to make eculizumab with the IgG2/G4 constant region (as disclosed in Tacken) could also have run Bowdish's 5G1.1 antibody through a protein sequence search and confirmed that Bowdish's 5G1.1 antibody has hybrid IgG2/G4 constant regions as opposed to constant regions that were purely from IgG2 or IgG4. Just as an example, a POSA would have

immediately recognized, even by eye, that the Bowdish 5G1.1 antibody has an IgG2 core hinge region (ERKCCVECPPCP), structurally quite unlike the core hinge region of IgG4 (ESKYGPPCPSCP). (EX1033, Esther M. Yoo et al., *Human IgG2 Can Form Covalent Dimers*, 170 J. Immunol. 3134 (2003) ("Yoo 2003"), 005, Table 1; *see also* EX1037, Jette Wypych et al., *Human IgG2 Antibodies Display Disulfide-mediated Structural Isoforms*, 283 J. Biol. Chem. 16194 (2008) ("Wypych"), 005, Table 1.) After having confirmed that Bowdish's antibody has the desired hybrid IgG2/G4 constant region, a POSA would have undertaken the easy and routine step of swapping Bowdish's CDR3 sequence for the thirteen amino acid HCDR3 sequence of Evans to arrive at the claimed sequence. The figure below shows a schematic illustrating the simple substitution by recombinant molecular biology techniques of the heavy chain CDR3 sequence in Bowdish's heavy chain for Evans' HCDR3 sequence:



127. Tacken is analogous art to Bell, Evans, and Bowdish. Tacken discusses humanized antibodies, including eculizumab, and provides detailed information regarding the structure of eculizumab. Tacken further identifies eculizumab as an anti-C5 antibody and Alexion's "potential product." (EX1008, 010-11.) A POSA seeking the sequence of eculizumab in 2007 would have relied on Tacken's teaching that eculizumab has an IgG2/IgG4 constant domain.

128. Based on Tacken's teachings, a POSA would not have considered that the IgG4 isotype disclosed in the Thomas reference (which is also cited by Bell) was

eculizumab. The Thomas reference—which was published in 1996 before publication of the Mueller 1997 article or Mueller PCT—discloses the full-length sequence of the 5G1.1 antibody with an IgG4 isoform, not the hybrid IgG2/G4 constant domain of eculizumab as taught by Tacken. (EX1010, 013.)

129. A POSA would have combined Bell, Bowdish, Evans, and Tacken with Mueller PCT, because Mueller PCT is also analogous art to Bell, Bowdish, Evans, and Tacken for several reasons: (1) like the other references, it discusses construction of recombinant antibodies, (2) it expressly recites h5G1.1, (3) it is assigned to applicant Alexion Pharmaceuticals, and (4) Alexion scientist Mark Evans is identified as an inventor on both Mueller PCT and Evans. (EX1009, Cover, 12:19-27; *see also* EX1005, Cover.)

130. Based on the teachings of prior art Bowdish, Evans, Bell, Tacken and Mueller PCT, a POSA would have a direct route to the claimed sequence of eculizumab, would have been motivated to obtain the sequence of eculizumab, and would have had an expectation of success in doing so. Several publications from before 2007, including Bell, showed that eculizumab had proven to be a successful treatment for PNH. (*See* EX1007; *see also* EX1011; EX1013; EX1012; EX1014; EX1015.) Based on Bell's teachings, a POSA would have been strongly motivated to obtain the sequence of eculizumab. Further, based on Tacken's teachings

regarding the structure of eculizumab and Mueller PCT's disclosure of IgG2/G4 constant region sequences, a POSA would have understood that the combined sequence of Bowdish and Evans indeed contained the correct sequence for eculizumab with the desired IgG2/G4 constant region.

131. A POSA also would have had a reasonable expectation of success in assembling SEQ ID NOS:2 and 4 because the prior art provided and confirmed the sequences for all required parts of the heavy and light chains of the sequences. Bowdish provided the entire light chain sequence as well as all parts of the heavy chain sequence, except for HCDR3, and Evans provided that missing HCDR3. A POSA would have easily made the anti-C5 antibody containing SEQ ID NOS:2 and 4 using routine and well-known molecular biology methods and the teachings of Bowdish and Evans. Indeed, Evans teaches combining its variable region sequences with "constant region domains by recombinant DNA or other methods known in the art" (EX1005, 45:24-33), and Bowdish also references "recombinant DNA techniques known to those skilled in the art" for replacing CDRs in an antibody and "known techniques" for synthesizing antibodies (EX1004, [0069]-[0070], [0131]). Further, Bell teaches that anti-C5 antibodies "are prepared … according to known methods." (EX1007, [0053].) A POSA would therefore have a reasonable expectation of success in assembling SEQ ID NOS:2 and 4 corresponding to

sequence of anti-C5 antibody, eculizumab.

(b) Dose Form and Formulation Limitations

132. Claim 1 further adds trivial and uninventive limitations that were expressly disclosed by Bell and Wang, as described below:

(i) "single-unit dosage form"

133. Claim 1 adds the trivial and conventional limitation that the pharmaceutical composition be administered in a "single-unit dosage form." Bell discloses that antibodies can be administered "in a variety of unit dosage forms." (EX1007, [0058].) Further, in context of intravenous infusion, sterility must be maintained and is considered compromised when a vial is opened. (EX1062, ¶25.) Given this risk of compromising sterility, a POSA would have that single-use dosage units are the most convenient and appropriate for use in intravenous infusions. (EX1055 (Avastin), 002; EX1056 (Campath), 002; EX1057 (Erbitux), 001; EX1058 (Herceptin), 001-02; EX1059 (Remicade), 001; EX1060 (Rituxan), 001.) I have also reviewed Dr. Ippoliti's declaration on these points, and understand that she reaches equivalent conclusions regarding the obviousness of these conventional claim limitations. (*See* EX1062, ¶¶25, 48-49.)

(ii) "comprising 300 mg of the antibody in 30 mL"

134. Bell reports a Phase 2 clinical trial in PNH patients that used eculizumab in a dosing regimen with an initial 600 mg dose phase given weekly for four weeks followed by a maintenance dose of 900 mg dose given bi-weekly. (EX1007, [0082].) Bell discloses that doses were delivered by intravenous infusion. (*Id.*) Bell also discloses that its antibodies can be administered "in a variety of unit dosage forms." (*Id.*, [0058].) Given Bell's express teachings to use 600 mg and 900 mg doses of eculizumab, a POSA would have been motivated to choose a 300 mg single-use dosage form in the interest of convenience and scalability, and to avoid unnecessary waste of costly antibody treatments. In view of these considerations, a POSA aware of Bell's teachings would have been motivated to use a 300 mg single-use dosage form above all other options for treating PNH.

135. The limitation of "300 mg of the antibody in 30 ml" solution further implies that the antibody is at a concentration of 10 mg/ml. Wang renders this limitation obvious. By 2007, antibody therapies were commonly supplied in liquid solution that could easily be drawn into a syringe and added to IV bags for infusion. (EX1062, ¶51.) Wang teaches that eculizumab could be successfully and stably formulated in an aqueous solution at concentrations in the range of 1 to 30 mg/ml, which includes the concentration of 10 mg/ml. (EX1044, Fig. 10, [0025], [0067],

[0170]-[0173].) A POSA would have also known that 10 mg/ml was within the well-known range of concentrations of several FDA-approved antibody pharmaceutical compositions. (EX1061, Ann L. Daugherty & Randall J. Mrsny, *Formulation and delivery issues for monoclonal antibody therapeutics*, 58 Advanced Drug Delivery Reviews 686 (2006), 014 (Table 1); EX1056 (Campath), 013 (10 mg/ml); EX1057 (Erbitux) (2 mg/ml), 001; EX1058 (Herceptin), 001-02 (21 mg/ml); EX1059 (Remicade), 001 (10 mg/ml); EX1060 (Rituxan), 001 (10 mg/ml).) Thus, based on simple arithmetic, it would have been obvious for a POSA to use 30 ml of 10 mg/ml solution to administer the desired single-use dose of 300 mg. I have also reviewed Dr. Ippoliti's declaration on these points, and understand that she reaches equivalent conclusions regarding the obviousness of these conventional claim limitations. (*See* EX1062, ¶¶50-52.)

(iii) "of a sterile, preservative-free solution"

136. All three references, Bell, Bowdish and Evans disclose that formulations of anti-C5 antibodies, such as eculizumab, "must be sterile." (EX1007, [0062]; EX1004, [0150]; EX1005, 18:29-43.)

137. Bell and Evans also disclose that the antibody formulations "**may** contain … preservatives[.]" (EX1007, [0062]; EX1005, 18:29-43 (emphasis

added).) And Bowdish expressly discloses that "preservatives … **can** be incorporated according to accepted pharmaceutical practice." (EX1004, [0150] (emphasis added).) Each of Bell, Evans and Bowdish teaches that use of preservative is optional in the formulation, thus disclosing "preservative free" formulation. This is in accord with pharmaceutical practice regarding antibody formulations in 2007. Indeed, widely-prescribed antibodies that were approved by the FDA before 2007 were provided in sterile, preservative free formulations. (EX1062, ¶54; EX1055 (Avastin), 002; EX1056 (Campath), 002, 013; EX1057 (Erbitux), 001; EX1058 (Herceptin), 001-02; EX1059 (Remicade), 001; EX1060 (Rituxan), 001.) I have also reviewed Dr. Ippoliti's declaration on these points, and understand that she reaches equivalent conclusions regarding the obviousness of these conventional claim limitations. (*See* EX1062, ¶¶53-54.)

(iv) Manner, Motivation, and Rationale for Combination

138. Given the express teachings of the prior art, a POSA would have been motivated to prepare the recited pharmaceutical composition. Each of Bell, Bowdish and Evans expressly disclose antibody formulations and compositions that match the limitations of claim 6. (*See* EX1004, [148]-[151]; EX1005, 17:60-18:43; EX1007, [0062], [0082].) A POSA would have also considered Wang for its express

disclosures about eculizumab formulations and compositions. (EX1044, [0004], [0011], [0067]; EX1062, ¶55.)

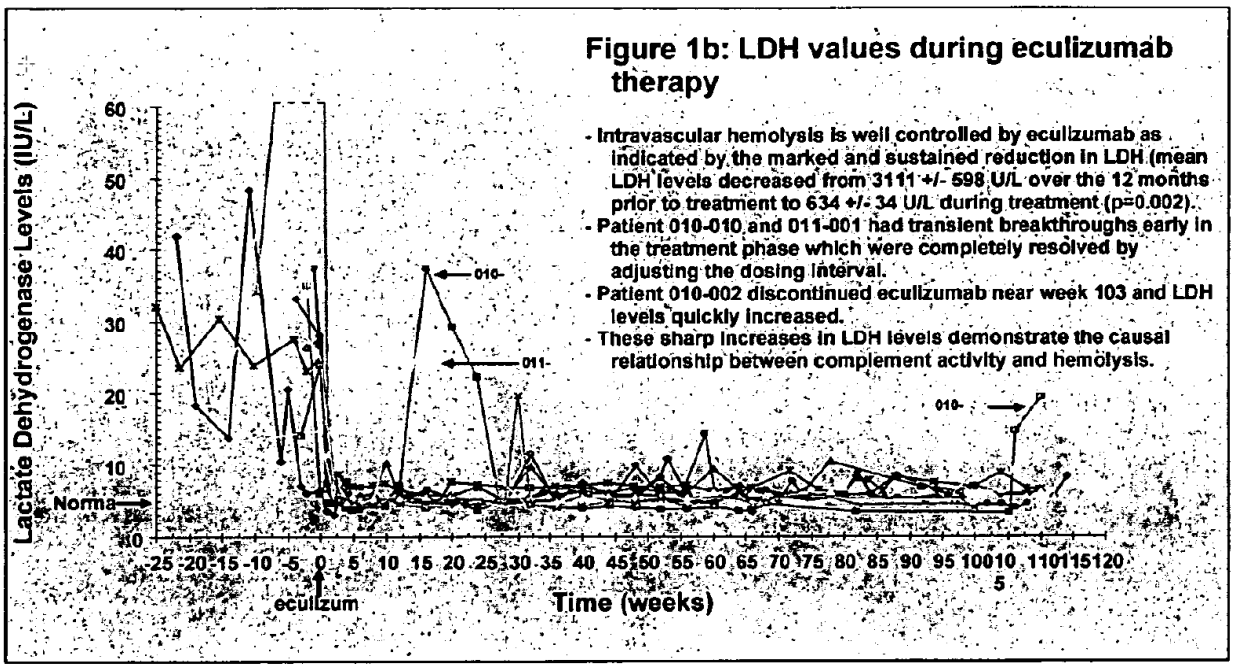
139. A POSA would have had a reasonable expectation of success in arriving at the recited characteristics of the pharmaceutical composition, because the prior art expressly discloses these characteristics in the context of anti-C5 antibody eculizumab. Further, Wang expressly teaches stable eculizumab formulations at concentrations as high as 30 mg/ml. (EX1044, Fig. 10, [0025], [0067], [0170]-[0173].) Thus, a POSA would have had a reasonable expectation of success that eculizumab prepared at a concentration of 10 mg/ml would be a stable, non-aggregated pharmaceutical composition suitable for therapeutic use. (EX1061, 009; EX1062, ¶56.)

2. Claim 5

140. I have compared claims 1 and 5 below. Both are identical, except for the additional limitation of claim 5, shown in underlining, that requires that the PNH patient "exhibits decreased lactate dehydrogenase levels."

Claim 1	**Claim 5**
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, and wherein the composition comprises a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution.	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, wherein the composition comprises a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution, **and wherein the patient exhibits decreased lactate dehydrogenase levels**.

141. The additional limitation of claim 5 is expressly disclosed by Bell. As described above in Part VI.A, Bell measured the effect of eculizumab on LDH for all eleven patients because LDH levels are used as an "objective indicator of hemolysis" underlying PNH disease. (EX1007, [0085].) Bell teaches that eculizumab successfully decreased levels of LDH. (*Id.*) Specifically, Bell discloses that "LDH levels were decreased by greater than 80% as compared to pre-treatment levels." (*Id.*) This decrease was immediate and "marked and sustained."



(EX1007, Figs. 1a-1b.) A POSA reviewing Bell's data would have recognized that LDH levels in patients treated with eculizumab decreased immediately and markedly to near-normal levels, and continued to remain low for the remaining duration of eculizumab treatment.

142. Hillmen 2004 and Hillmen 2003 references—both of which also report the same eleven patient Phase 2 study reported in Bell—confirm Bell's data and disclosures in Figures 1b. Hillmen 2004 confirms that eculizumab resulted in immediate and sustained decrease in LDH levels that "began after a single dose of eculizumab in all patients." (EX1011, 006.) Figure 2 in Hillmen 2004 calls LDH "a [b]iochemical [i]ndicator of [h]emolysis," and shows the decrease in LDH levels

before and during 12 weeks of eculizumab treatment. (*Id*., 005, Fig. 2.)

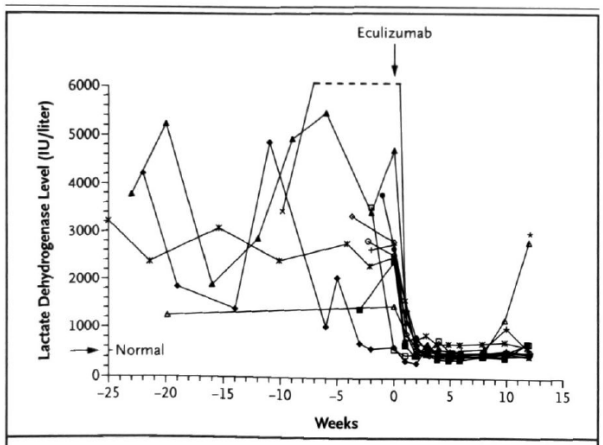


Figure 2. Analysis of Lactate Dehydrogenase Levels, a Biochemical Indicator of Hemolysis, in 11 Patients with Paroxysmal Nocturnal Hemoglobinuria up to 25 Weeks before and during 12 Weeks of Eculizumab Treatment.
The first dose of eculizumab is indicated by an arrow, as is the upper limit of the normal range of lactate dehydrogenase at the Leeds Teaching Hospital. The data point identified at week 12 by the asterisk represents a reading that was obtained from a duplicate serum sample since the original sample was lost. The dashed line represents off-scale points from one patient with a peak value of 12,100 IU per liter.

Similarly, Hillmen 2003 states that "dramatic improvement in the biochemical parameters of hemolysis occurring in all patients within a week of starting therapy persists. Mean LDH decreased from 3111 +/- 598 U/L … to 670 +/- 69 U/L over 6 months following treatment[.]" (EX1017, 002.) Bell confirmed that LDH levels are a biochemical parameter of hemolysis in PNH disease. (EX1007, [0064].)

3. Claims 2 and 6

143. Dependent claims 2 and 6 recite the additional limitation that the PNH patient "has received at least four transfusions in the twelve months prior to administration of the antibody." Bell expressly teaches this limitation as it discloses

that "[p]atients were defined as transfusion dependent with a history of four or more transfusions within twelve months." (EX1007, [0081].)

4. Claims 3 and 7

144. Dependent claims 3 and 7 recite the additional limitation that the PNH patient "has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody." Bell expressly teaches this limitation. Bell discloses that at least four of the eleven patients in its study were "non-thrombocytopenic," and had platelet counts greater than 150,000 per microliter prior to the study. (EX1007, [0089], Claim 14.) Bell further discloses that these patients became "transfusion-independent" in connection with the treatment. (*Id*., [0089].)

5. Claims 4 and 8

145. Dependent claims 4 and 8 recite the additional trivial limitation that the PNH patient be treated "for at least 26 weeks." Bell expressly teaches this limitation because it discloses that all eleven patients "participated in an extension study conducted to a total of 64 weeks." (EX1007, [0082].) Further, ten of the eleven patients "participated in an extension study conducted to a total of two years. (*Id*.) Thus, Bell expressly discloses treating PNH patients "for at least 26 weeks."

C. Ground 2: Claims 1-8 Are Obvious Over Bell, Evans, Mueller PCT, and Wang in view of Tacken

1. Claims 1 and 5

146. Bell and Tacken direct a POSA to the work of Evans and Mueller PCT to obtain the sequence of eculizumab that is recited in claims 1 and 5. As described above, Bell discloses an anti-C5 antibody called eculizumab. A POSA would have been strongly motivated by Bell's teachings to obtain the sequence of eculizumab as a pharmaceutical composition. Bell incorporates Evans and Thomas directly for information regarding the sequence of eculizumab. As noted above, given Tacken's express disclosure to use IgG2/G4 antibody for eculizumab, Bell's reference to Thomas would not have misled a POSA into using an IgG4 antibody for eculizumab. (*See* ¶128 above.)

147. Example 11 of Evans teaches the "Construction and Expression of Recombinant mAbs." (EX1005, 42:56-45:4.) It describes methods of constructing recombinant DNA antibodies using the critical CDR regions for the variable heavy and light chains of mouse antibody 5G1.1 that bind C5 protein. Example 11 provides eighteen "recombinant mAb-encoding DNAs" constructs, of which nine are humanized single-chain variable domain structures ("scFv"). The scFv structure corresponds to the VL and VH regions of an antibody that are joined by a short

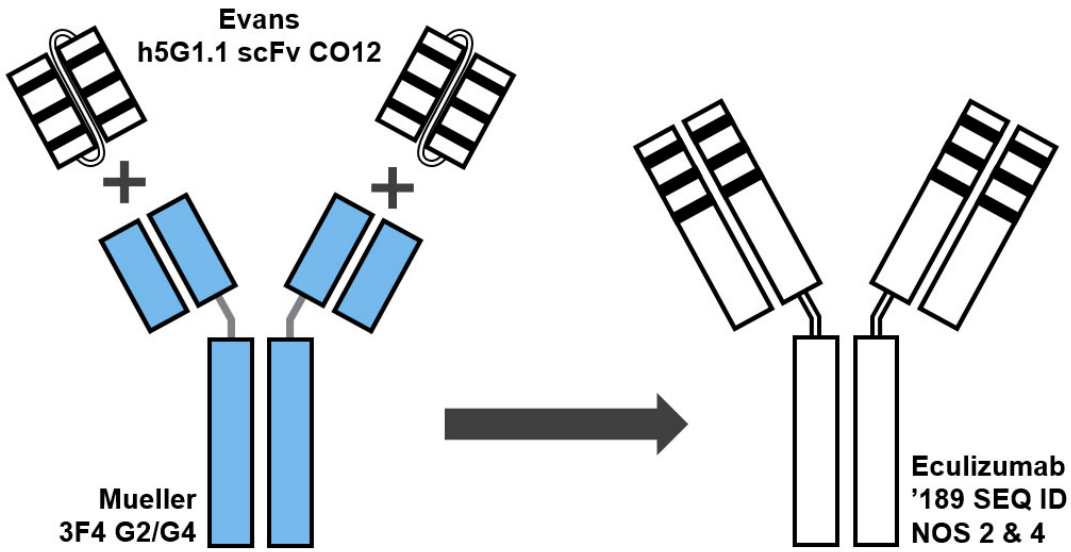
peptide linker. Evans also states that "one each of the various L1, L2, and L3 CDRs" and "one each of the various H1, H2, and H3 CDRs" disclosed in Example 11 can be assembled into "matched pairs of the variable regions (e.g. a VL and a VH region)" and that variable region "may be combined with constant region domains by recombinant DNA or other methods known in the art to form full length antibodies of the invention." (EX1005, 45:5-33.)

148. A POSA reading Evans would have understood that it teaches sequences for the six critical CDR regions for the variable heavy and light chains of mouse antibody 5G1.1 that bind C5 protein, as well as the variable framework regions for humanized 5G1.1. (EX1005, 1:1-3, 9:65-10:20, 42:56-45:23, 143:22-144:14, Figs. 18-19, Claim 19.) A POSA would have further been motivated to build full-length antibodies using each of the nine humanized scFv sequences labeled "humanized" "5G1.1" because Evans teaches that each of these constructs is useful for the assembly of C5-binding antibodies and fragments thereof.

149. Although Evans does not identify eculizumab by name, or specifically state which of the constructs corresponds perfectly to eculizumab, it states that the nine disclosed constructs include the VL and VH domains with the six CDRs that bind C5. Since Bell directs a POSA to Evans for preparing h5G1.1 (which Bell also calls eculizumab), a POSA would have been motivated to try any and all of the nine

sequences to arrive at the sequence for eculizumab. I have been informed that applying the legal standards for obviousness, the fact that Evans discloses other variable domains in addition to the variable domains that correspond to those in SEQ ID NOS:2 and 4 does not make claims 1 and 5 of the '189 patent any less obvious, because the prior art can render obvious more than one invention (or in this case, more than one C5-binding antibody sequence).

150. Even though it would have been simple and routine for a POSA to try Evans' nine sequences, Mueller PCT provides some additional guidance to a POSA specifically to prioritize the construct disclosed in Example 11 (12) that is identified as "humanized" "5G1.1 scFv CO12." Mueller PCT also uses the same identifier, and the only 5G1.1 with the hybrid IgG2/G4 discussed in Mueller PCT is referred to as "h5G1.1 **CO12** HuG2/G4." (EX1009, 014 (emphasis added).) Mueller PCT does not refer by name to any of the other constructs provided in Evans' Example 11. Therefore, a POSA would have been motivated to assemble a full-length antibody with Mueller PCT's IgG2/G4 region and constant light chain region, along with Evans' variable regions that use the same identifier, CO12. The schematic below shows how the disclosed sequences in Evans and Mueller PCT form the complete structure of the antibody recited in claims 1 and 5, consisting of SEQ ID NOS:2 and 4:



151. The resulting antibody, as shown in the comparisons below, shows a perfect match between the antibody comprising sequences from Mueller PCT and Evans and the claimed SEQ ID NOS:2 and 4.

```
Evans + Mueller    1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY  80
'189 SEQ ID NO: 2  1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY  80
                                              ← Evans | Mueller →
Evans + Mueller   81 MELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT 160
'189 SEQ ID NO: 2 81 MELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVT 160

Evans + Mueller  161 VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
'189 SEQ ID NO: 2 161 VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Evans + Mueller  241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY 320
'189 SEQ ID NO: 2 241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEY 320

Evans + Mueller  321 KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD 400
'189 SEQ ID NO: 2 321 KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD 400

Evans + Mueller  401 SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448
'189 SEQ ID NO: 2 401 SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448
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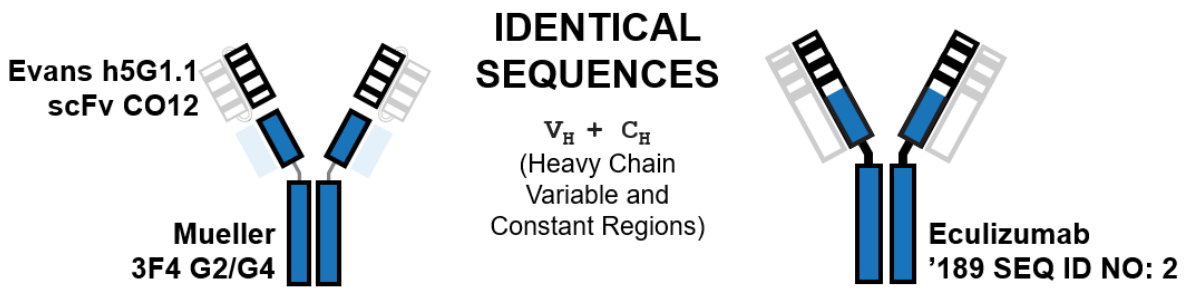


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Evans + Mueller    1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP  80
'189 SEQ ID NO: 4  1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP  80
                                              ← Evans | Mueller →
Evans + Mueller   81 EDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ 160
'189 SEQ ID NO: 4 81 EDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ 160

Evans + Mueller  161 ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
'189 SEQ ID NO: 4 161 ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
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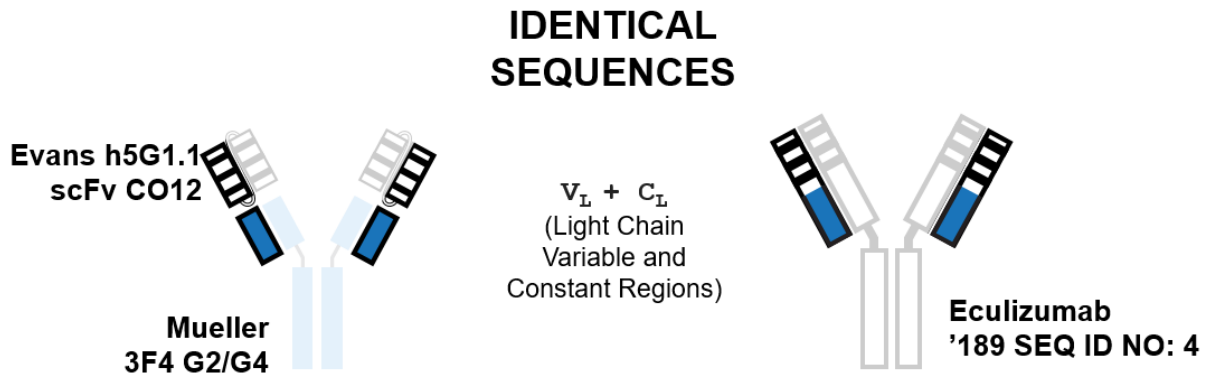


152. As noted above, Tacken also teaches that eculizumab has an IgG2/IgG4 constant region, and cites the Mueller 1997 reference for the hybrid IgG2/IgG4 constant region. Based on Tacken's teachings, a POSA would have been strongly motivated to create the eculizumab antibody using the IgG2/G4 constant region discussed in Mueller 1997 and expressly taught in its companion patent application Mueller PCT, in combination with the variable regions taught in Evans. Evans also provides instructions on how to combine its 5G1.1 variable regions with known constant regions to form a full-length antibody, and expressly discloses that it is "[p]articularly preferred" to use "a mixture of constant domains from IgGs of various subtypes[.]" (EX1005, 45:29-33.) This provides still further motivation to a POSA to use the hybrid IgG2/G4 constant domain that is disclosed in Tacken and Mueller PCT.

153. A POSA would have also been aware of Mueller 1997's teachings to use the hybrid IgG2/G4 constant domain instead of the IgG4 constant domain for eculizumab. Mueller 1997 discloses that "the HuG2/G4 antibody design" instead of the IgG4 isotype "should prove useful in humanization of other antibodies intended for human use where elimination of FcR binding and C activation may be desirable." (EX1006, 016.) Other prior art associated with Alexion, such as Rother WO2005/007809, also teach that the hybrid IgG2/G4 constant regions can reduce

inflammation and activation of the complement system. (EX1021.) A POSA would have immediately understood these benefits of using the IgG2/G4 constant region for creating an antibody intended for therapeutic use that involves blocking part of the complement system. Accordingly, a POSA would have easily arrived at an antibody with the IgG2/G4 constant region sequence that matches the constant region of SEQ ID NO:2 of claims 1 and 5. Further, a POSA would have combined that constant region that provides these benefits with the humanized 5G1.1 variable regions of Evans to arrive at the sequence of the antibody claimed in claims 1 and 5 of the '189 patent.

154. A POSA would also have an expectation of success in assembling the sequence of eculizumab based on teachings of Evans, Mueller PCT, Bell and Tacken. Tacken provides confirmation that the IgG2/G4 constant region had been used to create eculizumab, and Bell and several other publications confirmed that eculizumab had been used successfully to treat PNH. Therefore, a POSA would expect complete success in assembling SEQ ID NOS:2 and 4 using the sequences of Mueller PCT and Evans.

155. Further, as described above, Bell expressly teaches the additional limitation of claim 5 that the PNH patient "exhibits decreased lactate dehydrogenase levels." (*See* ¶¶140-142 above.)

2. Claims 2-4 and 6-8

156. As described in Ground 1 above, Bell discloses the various uninventive clinical limitations of claims 2-4 and 6-8. (*See* ¶¶143-145 above.) The same disclosures also render claims 2-4 and 6-8 obvious in the context of the Ground 2 combination of Bell, Evans, Mueller PCT, and Wang in view of Tacken. My opinions regarding prior art disclosures, motivation to combine and reasonable expectation of success for each challenged dependent claim are also equally applicable here. (*See id.*)

D. Ground 3: Claims 1-8 Are Obvious Over Bell and Wang

157. As noted above, Bell discloses results from a Phase 2 pilot study in which eleven transfusion-dependent PNH patients were successfully treated with eculizumab. (EX1007, [0081]-[0090].) Several other references, such as Hillmen 2004 and Hill 2005, also report results from the same clinical trial. (EX1011; EX1013.) Bell and Hill 2005 further report results from a long-term extension study. (*See supra* IV.C. (¶58).)

1. Claims 1 and 5

158. I am informed that Alexion has stated in Patent Office proceedings that the anti-C5 antibody used in the PNH clinical trial discussed in Bell was eculizumab.

Specifically, referring to the Phase 2 pilot study ("C02-001") and the extensions of that study ("E02-001" and "X03-001"), Alexion 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." (*See* EX1002, 13879-86, ¶¶5-6; *see also* 1066, 013.) I am further informed that, in the Amgen IPR2019-00739, Alexion also stated that "it is known today that SOLIRIS® as used in these studies had the claimed sequence of SEQ ID NOs: 2 and 4[.]" (EX1025, 041.)

159. Bell also expressly discloses that eculizumab is known as h5G1.1 antibody. As I explained in connection with Grounds 1 and 2 above, before 2007 a POSA would have known and been able to easily obtain the amino acid sequence of eculizumab, which is SEQ ID NOS:2 and 4 as recited in challenged claims 1 and 5. For example, Bowdish and Evans, and Evans and Mueller PCT, provide two separate direct routes to the sequence of eculizumab. Therefore, Bell inherently anticipates claims 1 and 5 of the '189 patent. This is further confirmed because Alexion has represented that the "eculizumab" antibody disclosed in Bell necessarily had the same sequences as SEQ ID NOS:2 and 4 of claims 1 and 5, and because the prior art fully enabled a POSA to prepare eculizumab no later than Tacken's publication date in 2005.

160. I understand that Alexion may argue that Bell does not necessarily

disclose the sequence of eculizumab, but instead that a POSA would have been uncertain whether the word "eculizumab" referred to any one particular antibody. In my opinion this argument is without merit. To the extent Alexion asserts the existence of some ambiguity regarding the known sequence of eculizumab because of Thomas 1996's reference to a version of 5G1.1 in an IgG4 form, the prior art does not support this assertion. As described above, none of the prior art references teach that "eculizumab" has the IgG4 isotype, indeed Thomas does not refer to "eculizumab" at all. (*See supra* ¶128.) Tacken instead is the only reference that discloses any information regarding the constant domain structure of "eculizumab," and it unambiguously teaches that eculizumab has the hybrid IgG2/G4 constant domain. Therefore, Tacken confirms that the "eculizumab" used in Bell's PNH clinical trials necessarily contains SEQ ID NOS:2 and 4 of claims 1 and 5.

161. As noted above, Bell and Wang also expressly disclose the other limitations of claim 1, reciting a method of treating a PNH patient, and the dose form and formulation limitations. (*See* ¶¶92-96, 106-107, 109, 132-139 above.) Further, Bell expressly teaches the additional limitation of claim 5 that the PNH patient "exhibits decreased lactate dehydrogenase levels." (*See* ¶¶92-96, 140-142 above.)

162. I have been informed that inherent anticipation can be supported when the prior art shows that a POSA can make the claimed subject matter based on the

description of the invention in the reference and his own knowledge of the particular art. In the case of eculizumab, the prior art already provided disclosures that enabled a POSA to create the "eculizumab" discussed in Bell. Specifically, the prior art described in Grounds 1 and 2 above would have provided multiple enabling routes to a POSA to make the exact eculizumab antibody that is recited in claims 1 and 5 as SEQ ID NOS:2 and 4. As a result, it does not matter for the purposes of inherent anticipation that Bell itself does not include any express teaching of how to make eculizumab. Because of the existing knowledge of a POSA (who is deemed to be aware of the prior art) by March 15, 2007 regarding the structure of eculizumab, Bell's use of the word "eculizumab" inherently anticipates the subject matter recited in claims 1 and 5 of the '189 patent.

2. Claims 2-4 and 6-8

163. As described in Ground 1 above, Bell expressly discloses the various uninventive clinical limitations of claims 2-4 and 6-8. (*See* ¶¶143-145 above.) Bell and Wang render claims 2-4 and 6-8 obvious because (1) Bell inherently anticipates the antibody sequences in claims 1 and 5, (2) Bell and Wang expressly disclose the remaining limitations of claims 1 and 5, and (3) Bell expressly discloses the added limitations of dependent claims 2-4 and 6-8.

VII. NO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

164. As explained in Part III.C, I understand that "secondary considerations" may be used as indicia of nonobviousness, provided that any such consideration has a nexus to the invention as claimed. I also understand that any secondary considerations evidence that is not both claimed and novel cannot have a nexus to the claimed invention.

165. Alexion cannot argue secondary considerations of nonobviousness based on commercial success of its drug Soliris (i.e., eculizumab) because the use of eculizumab as a treatment for PNH was already in the prior art, and thus cannot be novel to the claims. As described above, prior art publications such as Bell, Hillmen 2004 and Hill 2005 disclosed successful treatment of PNH with eculizumab well before the priority date of 2007. (Part IV.C.) Indeed, the use of eculizumab as a PNH therapy cannot be disputed as prior art to the '189 patent. Moreover, Alexion also stated in 2002 that the prior art Evans patent is associated with the claimed invention of eculizumab. (EX1020; EX1023.) Given that the prior art disclosed the eculizumab sequence and its use in PNH therapy before 2007, evidence of commercial success cannot be derived from the fact that Soliris was commercially approved in 2007.

166. Alexion similarly cannot argue that the sequence of eculizumab solved

a long-felt and art-recognized need, because prior art publications, such as Bell, Hillmen 2004, and Hill 2005—which were all published at least 2-3 years before 2007—already disclosed use of eculizumab as a successful treatment for PNH. Therefore, as of March 2007, no long-felt need existed for a treatment for PNH such as Soliris (i.e., eculizumab). I understand that Soliris was not FDA-approved as a treatment for PNH until March 2007, but this does not mean that a long-felt need existed as of that time for secondary considerations purposes. This is because secondary considerations evidence must be novel with respect to the patent claim at issue, and the use of eculizumab as a treatment for PNH was indisputably not novel by March 2007.

167. Alexion also cannot argue nonobviousness based on industry praise because any evidence of industry recognition following the launch of Soliris as a successful treatment for PNH has no nexus with anything novel in the challenged claims. As described above, by 2007 there was nothing novel about the use of eculizumab for treating PNH. Further, there is no nexus between any prizes awarded for use of Soliris and the claimed invention because nothing suggests that any prize was awarded due to the sequences claimed in claim 1, as opposed to what was already known about eculizumab in the prior art.

168. Lastly, the fact that other companies are developing biosimilars of

Soliris should not be used as evidence of "copying." I have been informed that according to statutes and regulations, biosimilars are required to be "highly similar to the reference product," i.e., Soliris in this case. Since this similarity is required by law, I understand that development of biosimilars should not be entitled to weight in an obviousness analysis.

169. It is my opinion that there is no evidence for secondary considerations of nonobviousness that would weigh against the strong case of obviousness set forth in Grounds 1-3 above. I reserve the right to rebut any evidence of secondary considerations that Alexion may assert in this proceeding.

VIII. EXAMINER'S EVALUATION OF ART AND ARGUMENTS DURING PROSECUTION OF THE '189 PATENT

170. I reviewed the Examiner's Office Action (EX1002, 11374-87); Alexion's Response and Remarks (*id*., 14835-66); and Examiner's Notice of Allowance (*id*., 14873-75) submitted during prosecution of the '189 patent. In my opinion, the Examiner erred in at least the following four respects: (1) overlooking the disclosures of Tacken and Mueller PCT, (2) misevaluating Bowdish and Evans, (3) misevaluating secondary considerations evidence, and (4) misevaluating Wang.

171. As described above, Tacken and Mueller PCT teach important information regarding the sequence of eculizumab – Tacken expressly teaches that

eculizumab contains the IgG2/G4 constant domain, and Mueller PCT discloses the sequence of that constant domain. But the Examiner did not cite either Tacken or Mueller PCT in the Office Action or Reasons for Allowance. Therefore, the Examiner overlooked Tacken's and Mueller PCT's critical disclosures regarding the claim limitations, particularly regarding the constant region of SEQ ID NO:2.

172. I also reviewed Alexion's statements made during prosecution about the pre-priority date literature regarding the sequence of eculizumab. In its Response, Alexion stated:

> [T]he literature as of March 15, 2007 … ***consistently*** identified "eculizumab" as the antibody described in the "Thomas" publication, … which has a naturally-occurring "IgG4" heavy chain constant region. Accordingly, a person of ordinary skill in the art as of March 15, 2007 would have had ***no doubt*** that "eculizumab" was Thomas's IgG4-isotype humanized antibody, because the pertinent literature ***consistently and unambiguously*** said so[.]

(EX1002, 14840 (emphasis added).) Alexion also listed several references that—according to Alexion—refer to "eculizumab" as the IgG4 antibody disclosed in Thomas. Alexion, however, provided an inaccurate account of the literature as of March 15, 2007. (*Id.*, 14840-42.) First, Thomas does not refer to the word "eculizumab" anywhere, indeed it is simply not true that the "pertinent literature"

"said" that eculizumab was Thomas' IgG4-isotype antibody. Second, Alexion listed Kaplan 2002 among these references, but failed to account for the fact that Kaplan 2002 expressly refers to Evans for the composition of eculizumab. Third, and most critically, Alexion failed to provide its own 2005 publication, the Tacken article, that teaches that "eculizumab" contains an IgG2/G4 constant domain. Based on this disclosure, a POSA would have no doubt that eculizumab has the IgG2/G4 constant region, not Thomas' IgG4 constant region. But because of Alexion's incorrect statements about the literature as of March 15, 2007, the Examiner overlooked critical disclosures of Tacken and Mueller PCT that directly pertain to the claimed limitations.

173. Alexion argued during prosecution that a POSA would not have used Bowdish's antibody as a result of the mismatches revealed from an alignment of Evans' 5G1.1 *mouse* antibody variable regions with Bowdish's sequence. Persuaded by Alexion's comparison, the Examiner allowed the claims to issue, noting:

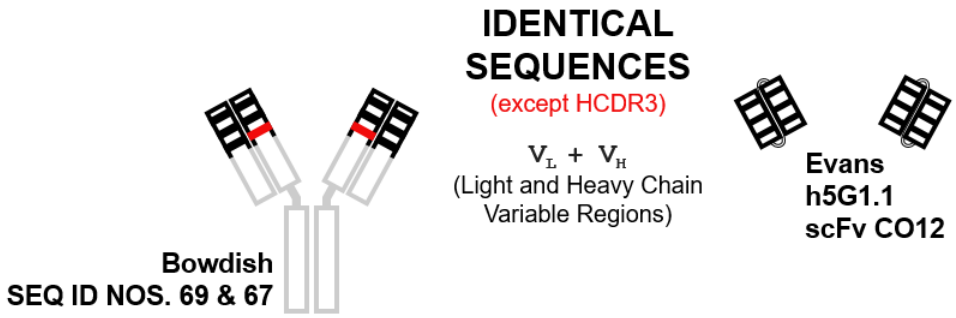
> Evan's [*sic*] scaffold 5G1.1 mouse antibody variable regions or the whole 5G1.1 mouse antibody with the sequences for Bowdish's TPO mimetic compound would still have revealed a mismatch in amino acids beyond those that Bowdish identified as the TPO mimetic peptide insert.

(EX1002, 14874-75.)

174. Alexion's alignment, however, is not the correct apples to apples comparison that a POSA would have made. A POSA would have aligned Evans' *humanized* sequence with Bowdish's sequences (while omitting their leader sequences that are cleaved upon maturation of the antibody), as shown below, and that would have shown the Examiner that the starting variable region sequence used by Bowdish matches the Evans sequence and that there is no mismatch beyond the expected HCDR3 region of the TPO mimetic peptide insert that Bowdish swapped in:

```
Bowdish SEQ ID NO: 69   1  DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP  80
Evans h5G1.1            1  DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQP  80
                                                 CDR1                  CDR2                                  VL
Bowdish SEQ ID NO: 69  81  EDFATYYCQNVLNTPLTFGQGTKVEIKRT                                                  109
Evans h5G1.1           81  EDFATYYCQNVLNTPLTFGQGTKVEIKRTGGGGSGGGGSGGGGS                                   124
                                 CDR3

Bowdish SEQ ID NO: 67   1  QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY  80
Evans h5G1.1          125  QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVY  204
                                                 CDR1                  CDR2                                  VH
Bowdish SEQ ID NO: 67  81  MELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAPVWGQGTLVTVSS  127
Evans h5G1.1          205  MELSSLRSEDTAVYYCARYFFGSSP--NWY---FDVWGQGTLVTVSS  246
                                                 CDR3
```



Given this proper comparison of Bowdish's and Evans' humanized variable region

sequences, a POSA looking to make *humanized* 5G1.1 would have sufficient rationale to reverse Bowdish's step of swapping out Evans' HCDR3 region for Bowdish's HCDR3 region to arrive at the sequence of eculizumab.

175. Further, the Examiner was apparently misled by Alexion's argument that Bowdish's "[c]onstruction of 5G1.1" would have directed a POSA only to Evans' mouse antibody in Examples 7-10. (EX1002, 14847.) Evans' Example 11 expressly teaches humanized 5G1.1 scFv **constructs** and is entitled "**Construction** and Expression of Recombinant mAbs." (EX1005, 42:56-45:33 (emphasis added).) Example 11 also discloses that "[r]ecombinant DNA **constructions** encoding the recombinant mAbs comprising the 5G1.1 CDRs are prepared by conventional recombinant DNA methods[.]" (*Id*., 42:59-62 (emphasis added).) Evans also teaches "CDR sequences that are useful in the **construction** of the humanized antibodies of the invention[.]" (*Id*., 8:50-54 (emphasis added).) But Alexion only focused the Examiner on Example 7, entitled "Preparation of anti-C5 Monoclonal Antibodies," which discloses preparing (not constructing) the parent 5G1.1 mouse antibody from mouse hybridomas. (*Id*., 37:34-39:30.) Contrary to Alexion's representations, a POSA considering Bowdish's "construction of 5G1.1" for assembly of a full-length antibody by recombinant means would have referred to Evans' Example 11 that teaches construction of the humanized 5G1.1 scFv

constructs, not Example 7 that teaches preparation of mouse antibodies.

176. Alexion also mischaracterized Evans' disclosures in arguing that even if a POSA were to consider Evans "for its disclosure of heavy chain CDR3 sequences, Evans *et al*. allows for **multiple options**, and nothing in Bowdish *et al*. or Evans *et al*. indicates which, if any, were used in the 'scaffold' antibody used to produce Bowdish *et al*.'s TPO-mimetic peptide[.]" (EX1002, 14852 (bold emphasis added) (citation omitted).) But this is plainly incorrect – a POSA would have no issues in identifying the HCDR3 sequence to use in Bowdish's antibody because, as described above and in Appendix A, all nine humanized scFv sequences of Evans only disclose one unique HCDR3 sequence (YFFGSSPNWYFDV), not "multiple options."

177. I reviewed Alexion's secondary considerations evidence submitted during prosecution, and the Examiner's Reasons for Allowance in which the Examiner noted that "some of the secondary considerations are evidence of nonobviousness, particularly the invention as claimed satisfies a long felt need and that there is objective evidence of copying." (EX1002, 14875.) However, based on the reasons described above in Part VII, it is my opinion that Alexion's arguments for the secondary considerations of long-felt need and copying are insufficient evidence of non-obviousness. Specifically, no long-felt need existed because the

use of the drug Soliris (i.e., eculizumab) as a treatment for PNH was already in the prior art. (*See* ¶166 above.) And development of biosimilars as evidence of copying should not be afforded weight in the analysis. (*See* ¶168 above.) Therefore, it is my opinion that the Examiner erred in considering this evidence as indicia of non-obviousness.

178. The Examiner also erred in not appreciating the significance of Wang, which teaches the claimed limitations regarding dose formulations. I note that the Examiner cited Wang in a rejection, but did not discuss any of its teachings in the Notice of Allowance. This is not surprising in view of Alexion's inaccurate statements regarding Wang's teachings. Specifically, in its Response, Alexion argued:

> Wang does not specifically teach eculizumab formulations of between 1 and 30 mg/ml, but rather discloses 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. Regarding stability that a person skilled in the art would understand is needed for a pharmaceutical composition, Wang only contains 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.

(EX1002, 14852-53 (emphasis added) (citations omitted).)

179. Alexion's statement that Wang's disclosures are about "unrelated" or "undefined" "anti-C5 antibodies" is inaccurate because it directly contradicts Wang's express disclosures that "eculizumab" is a "preferred embodiment" for its anti-C5 antibodies, and its teachings regarding the 1-30 mg/ml concentration in the context of "eculizumab" formulations. (EX1044, [0004], [0170]-[0173].) Wang even expressly refers to "eculizumab" as an "embodiment" for antibodies that are "stable" in a formulation of 1-200 mg/ml. (*Id*., [0067].) Thus, it is my opinion that given Alexion's mischaracterizations regarding Wang's disclosures, the Examiner erred and failed to appreciate its teachings.

IX. CONCLUSION

180. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in this proceeding. If required, I will appear for cross-examination at the appropriate time.

181. I hereby declare that all statements made herein of my own knowledge are true and that all statements are 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 18 U.S.C. § 1001.

Respectfully submitted,

Jeffrey V. Ravetch, M.D., Ph.D.

EXHIBIT A

CURRICULUM VITAE

Name: Jeffrey V. Ravetch

Date and Place of Birth: May 3, 1951; New York, New York

Citizenship: United States

Residence: 500 Park Ave, New York, NY 10022

Education:

June 1973 - **B.S.**, Yale University, New Haven, CT
June 1978 - **Ph.D.,** Laboratory of Genetics (N. Zinder and P. Model), The Rockefeller University, New York, NY
June 1979 - **M.D.,** Cornell University Medical College, New York, NY

Postdoctoral Training:

1979 - 1982 Laboratory of Molecular Genetics (P. Leder), NICHD, NIH, Bethesda, MD

Positions and Appointments:

1997- **Theresa and Eugene M. Lang Chair,** The Rockefeller University
1996- **Professor**, The Rockefeller University
1993 - 1996 **Adjunct Professor**, Department of Microbiology and Immunology, Jefferson Medical College and Jefferson Cancer Institute
1990 - 1996 **Attending**, Division of Hematologic Oncology, Department of Medicine, Memorial Hospital for Cancer and Allied Diseases
1990 - 1996 **Member,** Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Professor, Cornell University Medical College
1986 - 1990 **Associate Attending,** Division of Medical Oncology, Hematology-Lymphoma Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center
1986 - 1990 **Associate Member,** Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Associate Professor, Cornell University Medical College
1984 - 1987 **Guest Investigator,** Laboratory of Cellular Physiology and Immunology, The Rockefeller University
1982 - 1986 **Assistant Member,** Division of Molecular Biology, Memorial Sloan-Kettering Cancer Center
Assistant Professor, Cornell University Medical College
1979 - 1982 **Research Associate,** Laboratory of Molecular Genetics, NICHD, National Institutes of Health
1973 - 1979 **Biomedical Fellow,** The Rockefeller University
1972 - 1973 **Teaching Assistant,** Dept. of Chemistry, Yale University

Honors and Awards:

NSF Summer Research Fellowships, 1971, 1972
Cum laude, Yale College, 1973
Charles E. Culpeper Fellow, 1983-1985
Pew Scholar, 1985-1989
Burroughs-Wellcome Award in Molecular Parasitology, 1986
Irma T. Hirschl/Monique Weill-Caulier Trust Career Scientist Award, 1986
Boyer Research Award, Memorial Sloan-Kettering Cancer Center, 1988
Kunkel Lecturer, Rockefeller University, 1996
NIH MERIT Award, 1997
Ecker Lecturer, Case Western Reserve University, 2000
Lee J. Howley, Jr. Award, 2004
AAI-Huang Foundation Meritorious Career Award, 2005
Member, National Academy of Sciences, 2006
William B. Coley Award, Cancer Research Institute, 2007
Member, Institute of Medicine, 2007
Fellow, American Academy of Arts and Sciences, 2008
Fellow, American Association for the Advancement of Science, 2008
R.E. Dyer Lecture, NIH, 2010
Grabar Lecture, French Society of Immunology, 2010
Gairdner International Award, 2012
Sanofi-Institut Pasteur Award, 2012
Heidelberger-Kabat Lecture, Columbia University, 2013
Fahey/Rose Founders Lecture, Clinical Immunology Society, 2013
Honorary doctorate Friedrich-Alexander-University Erlangen-Nurenberg, 2013
Josephson Lecture, Downstate Medical College, 2014
Wolf Prize in Medicine, 2015
Distinguished Lecturer, Academia Sinica, 2015
Benacerraf Lecture, Harvard Medical School, 2016
Ross Prize in Molecular Medicine, 2017
Robert Koch Award, 2018
William Paul Memorial Award, 2021

Patents:

5,116,965-Methods of obtaining histidine-rich protein genes of plasmodia
5,723,593-Diagnostic assay for Charcot Marie Tooth disease type 1B
5,728,377-Methods and compositions Incorporating IP-10
5,824,487-Method for screening for targets for anti-inflammatory or anti-allergic agents.
5,876,927-Nucleic acid diagnostic assay for Charcot-Marie-Tooth Disease type IB
5,877,396-Mice mutant for Fc Receptors and method of treating autoimmune disease.
6,676,927-Animal model and methods for its use in the selection of cytotoxic antibodies
7,038,031-DNA encoding FcγR receptor protein on NK cells.
7,416,726-Enhancement of antibody-mediated immune responses
7,846,744-Methods of identifying anti-inflammatory compounds
8,470,318-Polypeptides with enhanced anti-inflammatory properties
8,470,321-Antibodies specific for the protofibril form of beta-amyloid protein

8,618,251-Fc mutants
8,815,237-Aglycosylated immunoglobulin mutant
9,134,310 Methods of identifying anti-inflammatory compounds
9,340,607-Antibodies specific for the protofibril form of beta-amyloid protein
9,481,724-hDC-SIGN binding peptides
9,587,025 Non-sialylated anti-inflammatory polypeptides
9,657,101 Fc mutants
9,845,358 Anti-inflammatory polypeptides
10,167,332 Polypeptides with enhanced anti-inflammatory and decreased cytotoxic properties
10,300,127 Immune complex
10,479,838 Antibodies to CD40 with enhanced agonist activity

Other Activities:

National

Ad hoc member, Immunobiology Study Section, 1986-1990
Ad hoc member, Tropical Medicine and Parasitology Study Section, 1988-1990
Member, Allergy and Immunology Study Section, 1990-1994
Member, Blood Diseases Advisory Panel of The New York Community Trust, 1990-1996
Founder and Organizer (with D. Wirth and L. van der Ploeg), Annual Woods Hole Molecular Parasitology Meeting, 1990-1992
NIH Task Force on Immunology and Aging, 1994
Institute of Medicine, Nat'l Academy of Sciences, Committee on Malaria Vaccines, 1995
AAI, American Association of Immunologists, Public Affairs Committee, 2003-2005

Editorial

Advisory Editor, The Journal of Experimental Medicine
Transmitting Editor, International Immunology

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Appendix A

Appendix A

Humanized 5G1.1 scFv sequences disclosed in EVANS, Example 11 with the three-letter code converted to one-letter code and HCDR3 sequence identified in bold and underlined

1. Example 11, Part (2) discloses SEQ ID NO:8 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQRKPGKAPKLLI     50
51   YGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF     100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA     150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDT     200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS       248
                             225         237
```

(EX1005, 43:6-14; cols. 83-87; Certificate of Correction, 107-10)

2. Example 11, Part (11) discloses SEQ ID NO:17 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLI     50
51   YGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF     100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA     150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYAQKFQGRVTMTRDT     200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS       248
                             225         237
```

(EX1005, 43:62-44:3; cols. 109-113; Certificate of Correction, pages 130-33)

3. Example 11, Part (12) discloses SEQ ID NO:20 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLI     50
51   YGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF     100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA     150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDT     200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS       248
                             225         237
```

(EX1005, 44:4-13; cols. 121-123; Certificate of Correction, 136-38)

4. Example 11, Part (13) discloses SEQ ID NO:21 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCRASENIYGALNWYQQKPGKAPKLLI     50
51   YGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF    100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA    150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYAQKFQGRVTMTRDT    200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS      248
                             225         237
```

(EX1005, 44:14-23; cols. 123-127; Certificate of Correction, 138-41)

5. Example 11, Part (14) discloses SEQ ID NO:22 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLI     50
51   YGATSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF    100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA    150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYAQKFQGRVTMTRDT    200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS      248
                             225         237
```

(EX1005, 44:24-32; cols. 127-129; Certificate of Correction, 141-43)

6. Example 11, Part (15) discloses SEQ ID NO:23 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCRASENIYGALNWYQQKPGKAPKLLI     50
51   YGATSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF    100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA    150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYAQKFQGRVTMTRDT    200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS      248
                             225         237
```

(EX1005, 44:33-41; cols. 129-133; Certificate of Correction, 143-46)

7. Example 11, Part (16) discloses SEQ ID NO:24 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCRASENIYGALNWYQQKPGKAPKLLI     50
51   YGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF    100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA    150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDT    200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS      248
                             225         237
```

(EX1005, 44:42-51; cols. 133-135; Certificate of Correction, 146-48)

8. Example 11, Part (17) discloses SEQ ID NO:25 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLI     50
51   YGATSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF    100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA    150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDT    200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS      248
                            225          237
```

(EX1005, 44:52-61; cols. 135-139; Certificate of Correction, 149-51)

9. Example 11, Part (18) discloses SEQ ID NO:26 has HCDR3 at residues 225-237:

```
1    MADIQMTQSPSSLSASVGDRVTITCRASENIYGALNWYQQKPGKAPKLLI     50
51   YGATSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF    100
101  GQGTKVEIKRTGGGGSGGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKA    150
151  SGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDT    200
201  STSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSS      248
                            225          237
```

(EX1005, 44:62-45:4; cols. 139-141; Certificate of Correction, 151-54)