8359292

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

March 28, 2023

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *15/642,096*
FILING DATE: *July 5, 2017*
PATENT NUMBER: *10,590,189*
ISSUE DATE: *March 17, 2020*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

M. Tarver

Miguel Tarver
Certifying Officer

ALXN2102
IPR2023-01070

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: July 5, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

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

Examiner: Not Yet Assigned

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FIRST PRELIMINARY AMENDMENT UNDER 37 C.F.R. § 1.115

Dear Sir:

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page 2 of this paper.

Remarks begin on page 3 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please insert the following paragraphs after the title:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 15/284,015, filed October 3, 2016, which is a continuation of U.S. Patent Application No. 15/260,888, filed September 9, 2016, which is a continuation of U.S. Patent Application No. 15/148,839, filed May 6, 2016, which is a continuation of U.S. Patent Application No. 13/426,973, filed March 22, 2012, which is a continuation of U.S. Patent Application No. 12/225,040, filed on May 13, 2009, which is a 35 U.S.C. 371 national stage filing of International Application No. PCT/US2007/006606, filed March 15, 2007. The contents of the aforementioned applications are hereby incorporated by reference in their entireties.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 5, 2017, is named AXJ_114BUSCN5_SL.txt and is 10,376 bytes in size.

Please amend the paragraph beginning on page 44 (lines 24-29) as follows:

SEQ ID NO: 4 – Eculizumab Light Chain

~~MDMRVPAQLLGLLLLWLRGARC~~DIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

Samsung Bioepis Exhibit No. 1002
Page 003

REMARKS

Sequence Listing and Amendment to the Specification

Applicant has amended the specification at page 1 to update the related applications and Sequence Listing sections.

It has come to Applicants' attention that the light chain recited in the specification and Sequence Listing as originally filed as SEQ ID NO:4 inadvertently contains the precursor peptide leader sequence, as shown below:

SEQ ID NO: 4 (Light Chain)
MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASE
NIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTIS
SLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Accordingly, Applicants submit herewith a Sequence Listing wherein SEQ ID NO:4 has been revised to delete the leader sequence (underlined above), which is ultimately cleaved from the active light chain. Thus, SEQ ID NO:4 corresponds to the mature portion of the complete light chain sequence of eculizumab. Applicants have also amended the specification to update the "Sequences" summary on page 44 (lines 24-29) of the specification.

Applicants respectfully note that the mature light chain sequence is an inherent portion of the precursor sequence (*i.e.*, original SEQ ID NO:4), and could have been readily identified at the relevant filing date using well established rules and art-recognized techniques (see, for example, Figure 6 on page 734 of Adderson *et al.*, *J. Clin. Invest.* 89:729-738 (1992) (enclosed herewith as Exhibit A), which shows the characteristic mature N-terminus (DIQ) of a light V kappa antibody light chain, as well as Kabat *et al.*, Sequences of Immunological Interest 5th Edition, U.S. Public Health Service, Bethesda MD). Therefore, the revised SEQ ID NO:4 does not constitute new matter. *No new matter has been added.*

Samsung Bioepis Exhibit No. 1002
Page 004

CONCLUSION

If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 217-4630.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN5.

Dated: July 5, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Attorney Docket Number:	AXJ-114BUSCN5

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1600**

Electronic Acknowledgement Receipt	
EFS ID:	29692492
Application Number:	15642096
International Application Number:	
Confirmation Number:	7606
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN5
Receipt Date:	05-JUL-2017
Filing Date:	
Time Stamp:	18:06:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1600
RAM confirmation Number	070617INTEFSW00005009120080
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Drawings-only black and white line drawings	AXJ_114BUSCN5_Figures.pdf	1867136 fdbbce82e3dfb1057404ddec7b994375cc5e9885	no	4
Warnings:					
Information:					
2	Oath or Declaration filed	AXJ_114BUSCN5_Decs.pdf	2597433 1a6b2a97a740557192de5966734c22fb51040f8a	no	4
Warnings:					
Information:					
3	Power of Attorney	AXJ_114BUSCN5_POA.pdf	3928366 197aa6651f9586a8037bb579b4c7928c8671de3f	no	2
Warnings:					
Information:					
4	CRF Statement Paper and CRF are the same	AXJ_114BUSCN5_SL_Statement.pdf	165281 b9590f5596d25ecdbd6d3e56c03bc3536964ad1d	no	2
Warnings:					
Information:					
5		AXJ_114BUSCN5_Specification.pdf	5134511 ce280632b0ddb4f4c8eb618c6a0eeff57d530b58	yes	52

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	45
Claims	46	51
Abstract	52	52

Warnings:					
Information:					
6	Sequence Listing (Text File)	AXJ_114BUSCN5_SL.txt	10376 d17b42605a51d3ff862e502b51c1d793297f1f32	no	-
Warnings:					
Information:					
7	Application Data Sheet	AXJ_114BUSCN5_ADS.pdf	115597 4a3a8ea5441d224992aad7c12fb6682d1cfc3080	no	9
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
8		AXJ_114BUSCN5_Prelim_Amdt.pdf	216690 0dbd27706be959958c0954398fe22a1ca2f7f863	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Preliminary Amendment		1	1	
	Specification		2	2	
	Applicant Arguments/Remarks Made in an Amendment		3	4	
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	35134 0dbd27706be959958c0954398fe22a1ca2f7f863	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	14070524		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

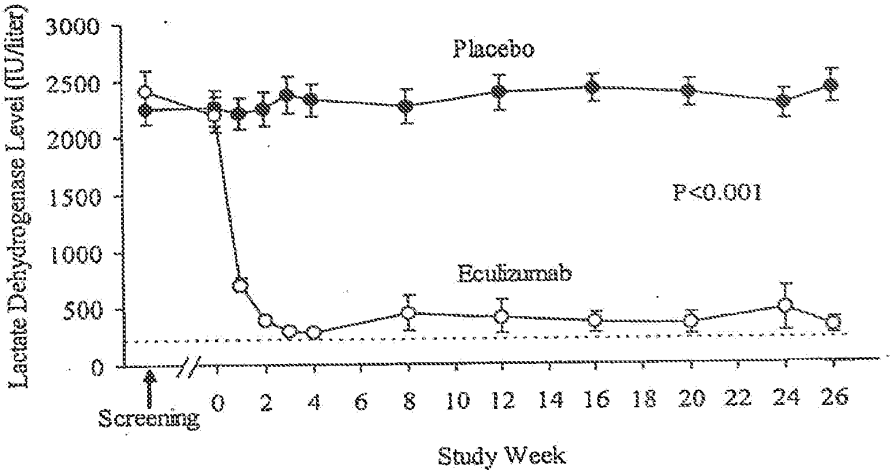
Lactate Dehydrogenase Level (IU/liter)
3000
2500
2000
1500
1000
500
0
Placebo
P<0.001
Eculizumab
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1A

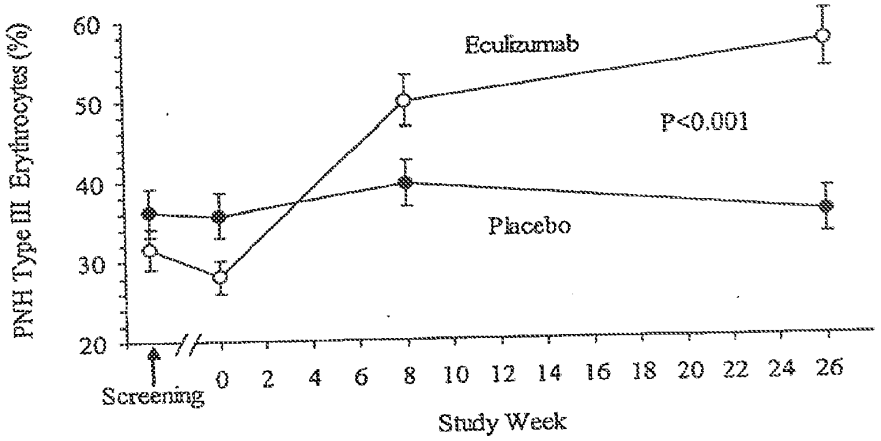
PNH Type III Erythrocytes (%)
60
50
40
30
20
Eculizumab
P<0.001
Placebo
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1B

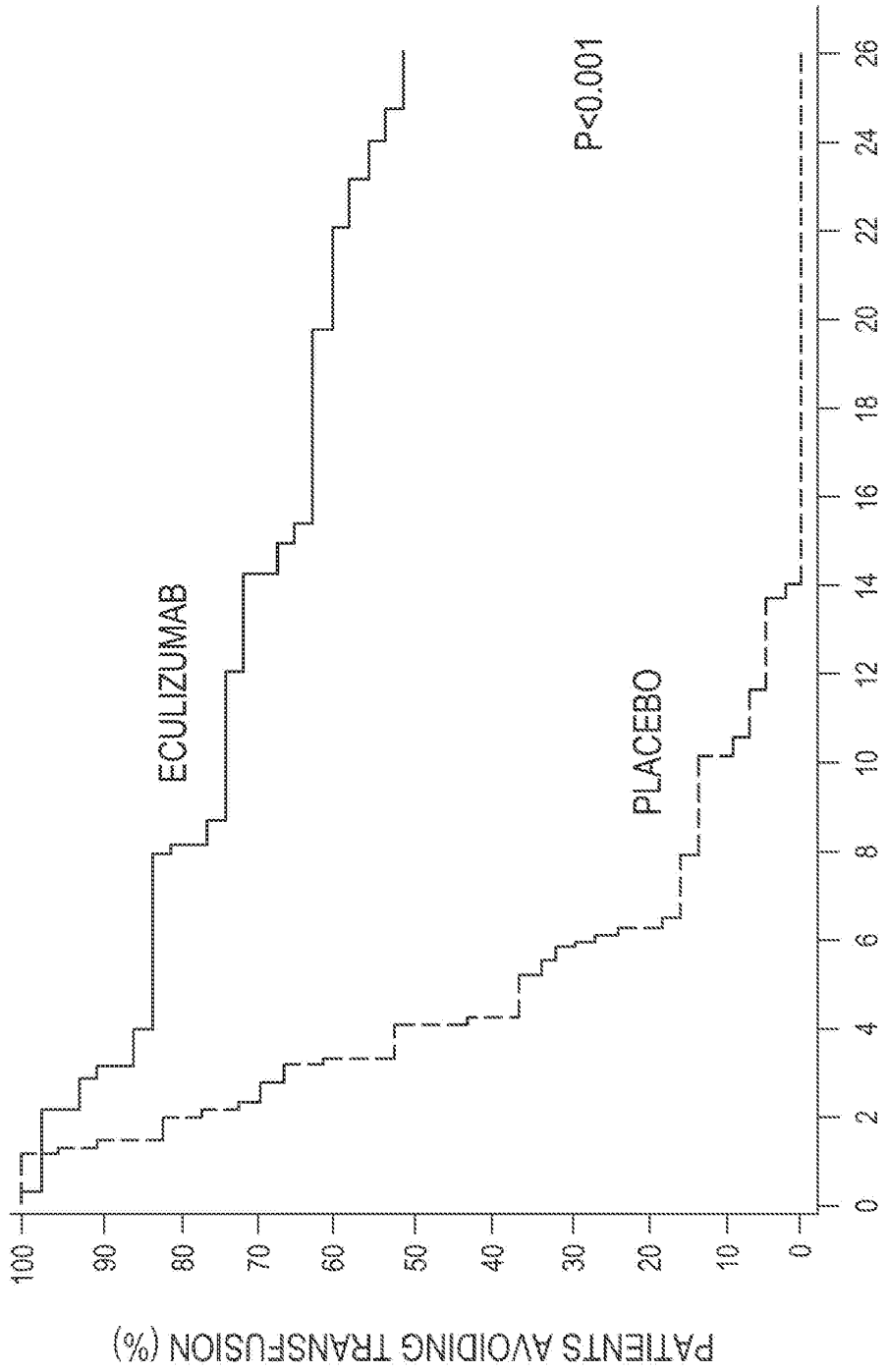
PATIENTS AVOIDING TRANSFUSION (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
STUDY WEEK
ECULIZUMAB
PLACEBO
P<0.001

FIGURE 2

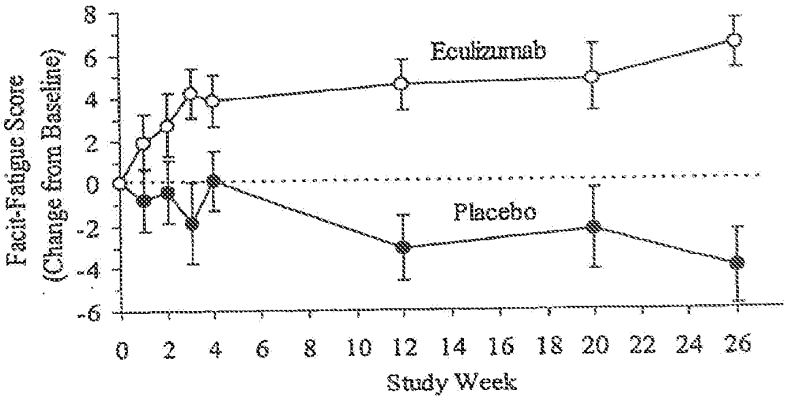
Facit-Fatigue Score
(Change from Baseline)
8
6
4
2
0
-2
-4
-6
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Eculizumab
Placebo

FIGURE 3

PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

As the below named inventor, I hereby declare that:

This declaration is directed to:
- [ ] The attached application, or
- [x] United States application or PCT international application number 15/148,839 filed on 05/06/2016

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Leonard Bell Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Doc code: Oath
Document Description: Oath or declaration filed

PTO/AIA/02 (07-13)
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SUBSTITUTE STATEMENT IN LIEU OF AN OATH OR DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (35 U.S.C. 115(d) AND 37 CFR 1.64)

Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

This statement is directed to:

[ ] The attached application,

OR

[X] United States application or PCT international application number 15/148,839 filed on 05/06/2016.

LEGAL NAME of inventor to whom this substitute statement applies:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Russell P. ROTHER

Residence (except for a deceased or legally incapacitated inventor):

Oklahoma City	OK	United States of America
City	State	Country

Mailing Address (except for a deceased or legally incapacitated inventor):

10325 Forest Meadow Drive

Oklahoma City	OK	73151	United States of America
City	State	Zip	Country

I believe the above-named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application.

The above-identified application was made or authorized to be made by me.

I hereby acknowledge that any willful false statement made in this statement is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Relationship to the inventor to whom this substitute statement applies:

[ ] Legal Representative (for deceased or legally incapacitated inventor only),

[X] Assignee,

[ ] Person to whom the inventor is under an obligation to assign,

[ ] Person who otherwise shows a sufficient proprietary interest in the matter (petition under 37 CFR 1.46 is required), or

[ ] Joint Inventor.

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SUBSTITUTE STATEMENT

Circumstances permitting execution of this substitute statement:

- [ ] Inventor is deceased,
- [ ] Inventor is under legal incapacity,
- [ ] Inventor cannot be found or reached after diligent effort, or
- [x] Inventor has refused to execute the oath or declaration under 37 CFR 1.63.

If there are joint inventors, please check the appropriate box below:

- [x] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) naming the entire inventive entity has been or is currently submitted.

OR

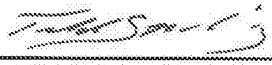
- [ ] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

Name: Todd Spalding	Date (Optional):

Signature: 

APPLICANT NAME AND TITLE OF PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

If the applicant is a juristic entity, list the applicant name and the title of the signer:

Applicant Name: Alexion Pharmaceuticals, Inc.

Title of Person Executing This Substitute Statement: Vice President, Head of Intellectual Property

The signer, whose title is supplied above, is authorized to act on behalf of the applicant.

Residence of the signer (unless provided in an application data sheet, PTO/AIA/14 or equivalent):

City	State	Country

Mailing Address of the signer (unless provided in an application data sheet, PTO/AIA/14 or equivalent)

100 College St.

City	State	Zip	Country
New Haven	CT	06510	US

Note: Use an additional PTO/AIA/02 form for each inventor who is deceased, legally incapacitated, cannot be found or reached after diligent effort, or has refused to execute the oath or declaration under 37 CFR 1.63.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number 15/284,015 filed on 10/03/2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

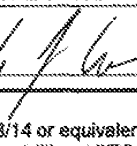
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Mark J. EVANS Date (Optional): 22 Jan 2017

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	Not Yet Assigned
Filing Date	Concurrently Herewith
First Named Inventor	Leonard BELL
Title	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	AXJ-114BUSCN5

SIGNATURE of Applicant or Patent Practitioner

Signature	/Jill Gorny Sloper, Esq./	Date (Optional)	July 5, 2017
Name	Jill Gorny Sloper, Esq.	Registration Number	60,760
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of 1 forms are submitted.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: July 5, 2017 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[X] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 133485

OR

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Firm or Individual Name	Jane E. Remillard, Esq. NELSON MULLINS RILEY & SCARBOROUGH LLP				
Address	One Post Office Square				
City	Boston	State	MA	Zip	02109-2127
Country	US				
Telephone	(800) 237-2000	Email	IPBoston.Docketing@nelsonmullins.com		

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Alexion Pharmaceuticals, Inc.

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

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SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	07/20/15
Name	Todd Spalding		
Title	Vice President, Head of Intellectual Property		

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Dated: July 5, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: Not Yet Assigned

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

Examiner: Not Yet Assigned

MS Sequence
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT PURSUANT TO 37 CFR 1.821

Dear Sir:

Submitted herewith in connection with the above-referenced patent application and in full compliance with 37 C.F.R. §§1.821-1.825 is a computer readable copy and paper copy of the Sequence Listing (filed together as a .txt file via the United States Patent Office's Electronic Filing System).

I hereby state that I have reviewed the paper copy of the Sequence Listing, as required by 37 CFR 1.821(c), and have reviewed the computer readable form of the Sequence Listing, as required by 37 CFR 1.821(e), and that the content of the paper and computer readable copies for the above-referenced patent application are the same as required by 37 CFR 1.821(f) (note that these documents are submitted as one electronic file). No new matter has been added to the Sequence Listing.

Dated: July 5, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disease that results from clonal expansion of hematopoietic stem cells with somatic mutations in the X-linked gene called PIG-A.[1,2] Mutations in PIG-A lead to an early block in the synthesis of glycosylphosphatidylinositol (GPI)-anchors, which are required to tether many proteins to the cell surface. Consequently, PNH blood cells have a partial (type II) or complete (type III) deficiency of GPI-anchored proteins.

Intravascular hemolysis is a prominent feature of PNH and a direct result of the absence of the GPI-anchored complement regulatory protein CD59.[3,4] Under normal circumstances, CD59 blocks the formation of the terminal complement complex (also called the membrane attack complex) on the cell surface, thereby preventing erythrocyte lysis and platelet activation.[5-8] Excessive or persistent intravascular hemolysis in PNH patients not only results in anemia (normal ranges of hemoglobin are 14-18 g/dL for men and 12-16 g/dL for women, and persons with lower levels are considered to be anemic), but also hemoglobinuria and clinical sequelae related to the release of the erythrocyte contents into the circulation: fatigue, thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9,10,21,22] Indeed, impaired quality of life in PNH is disproportionate to the degree of anemia. Many PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels. There have been no therapies that effectively reduce intravascular hemolysis and improve the associated clinical morbidities in PNH.

Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5.[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

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SUMMARY

The present pivotal, phase III study, Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH), evaluated the effect of eculizumab on the stabilization of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of 87 transfusion-dependent PNH patients. Measures of intravascular hemolysis and quality of life were also assessed. This is the first placebo controlled study of a PNH patient population to control hemolysis and to differentiate between the effects due to hemolysis and the effects due to anemia.

It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits

intravascular hemolysis. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method of prolonging the health-adjusted life expectancy of a patient comprising administering to said patient in need thereof a compound which inhibits formation of C5b-9. In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman. In certain embodiments, said patient suffers from paroxysmal nocturnal hemoglobinuria.

In certain aspects, the application provides a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria by administering a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system

include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

In certain embodiments, said quality of life is measured by a FACIT-Fatigue score. In certain embodiments, the FACIT-Fatigue score increases by at least 3 points. In certain embodiments, the FACIT-Fatigue score increases by $\geq$ 4 points.

In certain embodiments, said quality of life is measured by an EORTC QLQ-C30 score. In certain embodiments, said EORTC QLQ-C30 score improves by $\geq$ 10% of the pretreatment score. In certain embodiments, said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia. In certain embodiments, said aspect of quality of life is fatigue.

In certain embodiments, said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. In certain embodiments, said compound is a steroid that suppresses complement.

In certain embodiments, said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors. In certain embodiments, said compound is an antibody or an active antibody fragment. In certain embodiments, said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

In certain embodiments, said antibody or an active antibody fragment thereof binds C5. In certain embodiments, said antibody or active antibody fragment blocks C5 cleavage. In certain embodiments, said antibody or active antibody fragment inhibits the formation of C5b-9. In certain embodiments, said antibody is eculizumab. In certain embodiments, said antibody or active antibody fragment is administered for at least 6

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months. In certain embodiments, said patient has aplastic anemia or myelodysplastic syndrome.

In certain embodiments, said antibody that binds C5 or an active antibody fragment thereof is administered in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the single unit dosage form is lyophilized. In certain embodiments, the single unit dosage form is a sterile solution. In certain embodiments, the single unit dosage form is a preservative free formulation. In certain embodiments, the 300 mg single-use dosage form comprises 30 ml of a 10 mg/ml sterile, preservative free solution.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises an altered constant region, wherein said antibody or antigen-binding fragment exhibits decreased effector function relative to an anti-CDCP1 antibody with a native constant region. In certain embodiments, decreased effector function comprises one or more properties of the following group: a) decreased antibody-dependent cell-mediated cytotoxicity (ADCC), and b) decreased complement dependent cytotoxicity (CDC), compared to an anti-CDCP1 antibody with a native constant region. In certain embodiments, the altered constant region comprises a G2/G4 construct in place of the G1 domain.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 1 and the light chain variable region consists of SEQ ID NO: 3. In certain embodiments, the pharmaceutical composition comprises eculizumab. In certain embodiments, the pharmaceutical composition comprises pexelizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ ID NO: 4.

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In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

In certain embodiments, said health-adjusted life expectancy is measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one day. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least week. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one month. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one year.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the pharmaceutical composition comprises an antibody that binds C5 or an active antibody fragment thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-B show that eculizumab treatment decreases intravascular hemolysis and increases PNH type III erythrocytes. Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels. Figure 1B shows the mean proportion of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients.

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Figure 2 shows the effect of eculizumab treatment on transfusion requirements in PNH patients. This is a Kaplan-Meier plot of time to first transfusion for eculizumab- and placebo-treated patients from baseline through week 26. The P value is from the log rank analysis.

Figure 3 shows the effect of eculizumab on fatigue assessed by the FACIT-Fatigue Instrument. Quality of Life scores were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. Values for change from baseline to 26 weeks represent least-square means. A positive change indicates an improvement and a negative change indicates deterioration in the FACIT-Fatigue measures of quality of life.

DETAILED DESCRIPTION

I. Definitions

The term "derived from" means "obtained from" or "produced by" or "descending from".

The term "genetically altered antibodies" means antibodies wherein the amino acid sequence has been varied from that of a native antibody. Because of the relevance of recombinant DNA techniques to this application, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. The possible variations are many and range from the changing of just one or a few amino acids to the complete redesign of, for example, the variable or constant region. Changes in the constant region will, in general, be made in order to improve or alter characteristics, such as complement fixation, interaction with membranes and other effector functions. Changes in the variable region will be made in order to improve the antigen binding characteristics.

The term "an antigen-binding fragment of an antibody" refers to any portion of an antibody that retains the binding utility to the antigen. An exemplary antigen-binding fragment of an antibody is the heavy chain and/or light chain CDR, or the heavy and/or light chain variable region.

The term "homologous," in the context of two nucleic acids or polypeptides refers to two or more sequences or subsequences that have at least about 85%, at least 90%, at least 95%, or higher nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using the following sequence comparison

method and/or by visual inspection. In certain embodiments, the "homolog" exists over a region of the sequences that is about 50 residues in length, at least about 100 residues, at least about 150 residues, or over the full length of the two sequences to be compared.

Methods of determining percent identity are known in the art. "Percent (%) sequence identity" with respect to a specified subject sequence, or a specified portion thereof, may be defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul et al., J. Mol. Biol. 215:403-410 (1997); http://blast.wustl.edu/blast/README.htm- l) with search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A "% identity value" is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported.

II. Overview

The present disclosure relates to a method of treating paroxysmal nocturnal hemoglobinuria ("PNH"), more specifically to improving certain aspects of quality of life which are impaired in PNH patients, and other hemolytic diseases in mammals. Specifically, the methods of treating hemolytic diseases, which are described herein, involve using compounds which bind to or otherwise block the generation and/or activity of one or more complement components. The present methods have been found to provide surprising results. For instance, hemolysis rapidly ceases upon administration of the compound which binds to or otherwise blocks the generation and/or activity of one or more complement components, with hemoglobinuria being significantly reduced after treatment. Also, hemolytic patients can be rendered less dependent on transfusions or transfusion-independent for extended periods (twelve months or more), well beyond the 120 day life cycle of red blood cells. In addition, type III red blood cell count can be increased dramatically in the midst of other mechanisms of red blood cell lysis (non-complement mediated and/or earlier complement component mediated e.g., Cb3). Another example of a surprising result is that symptoms resolved, indicating that NO serum levels were increased

enough even in the presence of other mechanisms of red blood cell lysis. These and other results reported herein are unexpected and could not be predicted from prior treatments of hemolytic diseases.

III The Complement System

The complement system, useful complement inhibitors, and use of these inhibitors to treat PNH and other patients are more fully described in PCT Patent Application PCT/US2005/003225 filed February 3, 2005 and published as International Publication Number WO 2005/074607 A2 on August 18, 2005, the contents of which are incorporated herein by reference in their entirety.

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most

important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment

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(Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction.

IV Measures of Quality of Life

Various measurements exist to assess quality of life and the effect of medical interventions on quality of life for example the Mini-Mental State Examination (MMSE), the Short Test of Mental Status, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the FACIT questionnaires and subscales including fatigue and anemia, the Likert Scale, and Borg Scale (Tombaugh, et al., J. Am. Geriatr. Soc. 40:922, 1992; Cummings, JAMA. 269(18):2420, 1993; Crum, et al., JAMA. 269(18):2386, 1993; Folstein, et al., J. Psychiat. Res. 12:189,1975; Kokmen, et al., Mayo Clin. Proc. 62:281, 1987; Tang-Wai, et al., Arch. Neurol. 60:1777, 2003; Tamburini, Ann.

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Oncol. 12(Suppl. 3):S7, 2001; Webster et al., Health and Quality of Life Outcomes. 1:79, 2003, www.hqlo.com/content/I/I/79; Grant, et al., Chest. 116:1208, 1999; and www.qolid.org). Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. In certain embodiments, improvement in quality of life is measured by: a) full scales; b) stand-alone subscales; and c) symptom indices.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by a European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. In certain embodiments, the EORTC questionnaire is the QLQ-C30.

In certain embodiments, improvement in quality of life is measured by the health-adjusted life expectancy (HALE) index as described in Wilkins, R. and Adams, OB., Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein MC and Stason WB, N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

In certain embodiments, improvement in quality of life is measured by the following instruments: Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, and Years of healthy life. These measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods improve the quality of life of a patient for at least one day, at least one week, at least two weeks, at least three weeks, at least one

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month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years, or the duration of treatment.

In certain embodiments, the symptoms used to measure quality of life are scaled for intensity. In certain embodiments, the symptoms are scaled for frequency. In certain embodiments, the symptoms are scaled for intensity and frequency.

In certain aspects, the application provides a method for prolonging the health-adjusted life expectancy of a subject comprising administering to the subject a compound which inhibits complement or inhibits formation of C5b-9. The above measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality-adjusted life expectancy due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods prolong the health-adjusted life expectancy in a subject by at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years as measured by the health-adjusted life expectancy (HALE) index as described in Wilkins et al. Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein et al., N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

V Inhibitors of the Complement Cascade

In certain embodiments, any compound which binds to or otherwise blocks the generation and/or activity of one or more complement components can be used in the present methods. In certain embodiments, a complement inhibitor may be a small molecule (up to 6,000 Da in molecular weight), a nucleic acid or nucleic acid analog, a peptidomimetic, or a macromolecule that is not a nucleic acid, a serine protease inhibitor, or a protein. These agents include, but are not limited to, small organic molecules, RNA

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aptamers including ARC187 (which is commercially available from Archemix Corp., Cambridge, Mass.), L-RNA aptamers, Spiegelmers, antisense compounds, molecules which may be utilized in RNA interference (RNAi) such as double stranded RNA including small interfering RNA (siRNA), locked nucleic acid (LNA) inhibitors, peptide nucleic acid (PNA) inhibitors.

In certain embodiments, a complement inhibitor may be a protein or protein fragment. Proteins are known which inhibit the complement cascade, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated neural injury, and C3a and C5a production. In certain embodiments, a complement inhibitor may be naturally occurring or soluble forms of complement inhibitory compounds such as CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

In certain embodiments, a complement inhibitor may be an antibody capable of inhibiting complement, such as an antibody that can block the formation of MAC. For example, an antibody complement inhibitor may include an antibody that binds C5. Such anti-C5 antibodies may directly interact with C5 and/or C5b, so as to inhibit the formation of and/or physiologic function of C5b.

Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

The concentration and/or physiologic activity of C5a and C5b in a body fluid can be measured by methods well known in the art. For C5a such methods include chemotaxis assays, RIAs, or ELISAs (see, for example, Ward and Zvaifler, J Clin Invest. 1971 Mar;50(3):606-16; Wurzner, et al., Complement Inflamm. 8:328-340, 1991). For C5b, hemolytic assays or assays for soluble C5b-9 as discussed herein can be used. Other assays

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known in the art can also be used. Using assays of these or other suitable types, candidate antibodies capable of inhibiting complement such as anti-C5 antibodies, now known or subsequently identified, can be screened in order to 1) identify compounds that are useful in the practice of the application and 2) determine the appropriate dosage levels of such compounds.

An antibody capable of inhibiting complement such as an antibody that binds C5 affecting C5b is preferably used at concentrations providing substantial reduction (i.e., reduction by at least about 25% as compared to that in the absence of the antibody that binds C5) in the C5b levels present in at least one blood-derived fluid of the patient following activation of complement within the fluid. Such concentrations can be conveniently determined by measuring the cell-lysing ability (e.g., hemolytic activity) of complement present in the fluid or the levels of soluble C5b-9 present in the fluid. Accordingly, a specific concentration for an antibody that affects C5b is one that results in a substantial reduction (i.e., a reduction by at least about 25%) in the cell-lysing ability of the complement present in at least one of the patient's blood-derived fluids. Reductions of the cell-lysing ability of complement present in the patient's body fluids can be measured by methods well known in the art such as, for example, by a conventional hemolytic assay such as the hemolysis assay described by Kabat and Mayer (eds), "Experimental Immunochemistry, 2d Edition", 135-240, Springfield, IL, CC Thomas (1961), pages 135-139, or a conventional variation of that assay such as the chicken erythrocyte hemolysis method described below.

Specific antibodies capable of inhibiting complement, such as an antibody that binds C5, are relatively specific and do not block the functions of early complement components. In particular, such specific agents will not substantially impair the opsonization functions associated with complement component C3b, which functions provide a means for clearance of foreign particles and substances from the body.

C3b is generated by the cleavage of C3, which is carried out by classical and/or alternative C3 convertases and results in the generation of both C3a and C3b. Therefore, in order not to impair the opsonization functions associated with C3b, specific antibodies capable of inhibiting complement such as an antibody that binds C5 do not substantially interfere with the cleavage of complement component C3 in a body fluid of the patient (e.g., serum) into C3a and C3b. Such interference with the cleavage of C3 can be detected by measuring body fluid levels of C3a and/or C3b, which are produced in equimolar ratios

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by the actions of the C3 convertases. Such measurements are informative because C3a and C3b levels will be reduced (compared to a matched sample without the antibody capable of inhibiting complement such as an antibody that binds C5) if cleavage is interfered with by an antibody capable of inhibiting complement such as an antibody that binds C5.

In practice, the quantitative measurement of such cleavage is generally more accurate when carried out by the measurement of body fluid C3a levels rather than of body fluid C3b levels, since C3a remains in the fluid phase whereas C3b is rapidly cleared. C3a levels in a body fluid can be measured by methods well known in the art such as, for example, by using a commercially available C3a EIA kit, e.g., that sold by Quidel Corporation, San Diego, Calif., according to the manufacturer's specifications. Particularly specific antibodies capable of inhibiting complement such as an antibody that binds C5 produce essentially no reduction in body fluid C3a levels following complement activation when tested in such assays.

Certain antibodies of the disclosure will prevent the cleavage of C5 to form C5a and C5b, thus preventing the generation of the anaphylatoxic activity associated with C5a and preventing the assembly of the membrane attack complex associated with C5b. As discussed above, in a particular embodiment, these anti-C5 antibodies will not impair the opsonization function associated with the action of C3b.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include a preferred whole antibody (now named eculizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)). Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, single-chain antibody, and Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., Nature 321:522-5 (1986)), chimerized, or deimmunized. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies.

In specific embodiments, a therapeutic agent of the disclosure comprises an antibody or antibody fragment. Antibodies and fragments thereof may be made by any conventional method, such as those methods described herein. Antibodies are found in multiple forms, e.g., IgA, IgG, IgM, etc. Additionally, antibodies can be engineered in numerous ways. They can be made as single-chain antibodies (including small modular immunopharmaceuticals or SMIPs™), Fab and $F(ab')_2$ fragments, etc. Antibodies can be humanized, chimerized, deimmunized, or fully human. Numerous publications set forth the many types of antibodies and the methods of engineering such antibodies. For example, see U.S. Patent Nos. 6,355,245; 6,180,370; 5,693,762; 6,407,213; 6,548,640; 5,565,332; 5,225,539; 6,103,889; and 5,260,203.

This invention provides fragments of anti-C5 antibodies, which may comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8:1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment of an antibody yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" refers to the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although likely at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a

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free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the scFv to form the desired structure for antigen binding. For a review of scFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

SMIPs are a class of single-chain peptide engineered to include a target binding region, effector domain (CH2 and CH3 domains). *See, e.g.*, U.S. Patent Application Publication No. 20050238646. The target binding region may be derived from the variable region or CDRs of an antibody, e.g., an antibody that binds C5 of the application. Alternatively, the target binding region is derived from a protein that binds C5.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

It is well known that the binding to a molecule (or a pathogen) of antibodies with an Fc region assists in the processing and clearance of the molecule (or pathogen). The Fc portions of antibodies are recognized by specialized receptors expressed by immune effector cells. The Fc portions of IgG1 and IgG3 antibodies are recognized by Fc receptors present on the surface of phagocytic cells such as macrophages and neutrophils, which can thereby bind and engulf the molecules or pathogens coated with antibodies of these isotypes (C. A. Janeway et al., Immunobiology 5th edition, page 147, Garland Publishing (New York, 2001)).

This disclosure also provides monoclonal anti-C5 antibodies. A monoclonal antibody can be obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal

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antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are often synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. Monoclonal antibodies may also be produced in transfected cells, such as CHO cells and NS0 cells. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and does not require production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler et al., Nature 256:495-497 (1975), or may be made by recombinant DNA methods (*see, e.g.*, U.S. Patent Nos. 4,816,567 and 6,331,415). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature 352:624-628 (1991) and Marks et al., J. Mol. Biol. 222:581-597 (1991), for example.

A description of the preparation of a mouse anti-human-C5 monoclonal antibody with specific binding characteristics is presented in U.S. Patent Application Publication No. 20050226870. Wurzner et al., Complement Inflamm. 8:328-340 (1991), describe the preparation of other mouse anti-human-C5 monoclonal antibodies referred to as N19-8 and N20-9.

Other antibodies specifically contemplated are "oligoclonal" antibodies. As used herein, the term "oligoclonal" antibodies" refers to a predetermined mixture of distinct monoclonal antibodies. *See, e.g.*, PCT publication WO 95/20401; U.S. Patent Nos. 5,789,208 and 6,335,163. In one embodiment, oligoclonal antibodies consisting of a predetermined mixture of antibodies against one or more epitopes are generated in a single cell. In other embodiments, oligoclonal antibodies comprise a plurality of heavy chains capable of pairing with a common light chain to generate antibodies with multiple specificities (*e.g.*, PCT publication WO 04/009618). Oligoclonal antibodies are particularly useful when it is desired to target multiple epitopes on a single target molecule (*e.g.*, C5). In view of the assays and epitopes disclosed herein, those skilled in the art can generate or select antibodies or mixtures of antibodies that are applicable for an intended purpose and desired need.

In certain embodiments that include a humanized and/or chimeric antibody, one or more of the CDRs are derived from an anti-human C5 antibody. In a specific embodiment, all of the CDRs are derived from an anti-human C5 antibody. In another specific embodiment, the CDRs from more than one anti-human C5 antibody are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first anti-human C5 antibody combined with CDR2 and CDR3 from the light chain of a second anti-human C5 antibody, and the CDRs from the heavy chain may be derived from a third anti-human C5 antibody. Further, the framework regions may be derived from one of the same anti-human C5 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. Human or humanized antibodies are specific for administration to human patients.

In certain embodiments, single chain antibodies, and chimeric, humanized or primatized (CDR-grafted) antibodies, as well as chimeric or CDR-grafted single chain antibodies, comprising portions derived from different species, are also encompassed by the present disclosure as antigen-binding fragments of an antibody. The various portions of these antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, nucleic acids encoding a chimeric or humanized chain can be expressed to produce a contiguous protein. See, e.g., U.S. Pat. Nos. 4,816,567 and 6,331,415; U.S. Pat. No. 4,816,397; European Patent No. 0,120,694; WO 86/01533; European Patent No. 0,194,276 B1; U.S. Pat. No. 5,225,539; and European Patent No. 0,239,400 B1. See also, Newman et al., BioTechnology 10:1455-1460 (1992), regarding primatized antibody. See, e.g., Ladner et al., U.S. Pat. No. 4,946,778; and Bird et al., Science 242:423-426 (1988), regarding single chain antibodies.

In addition, functional fragments of antibodies, including fragments of chimeric, humanized, primatized or single chain antibodies, can also be produced. Functional fragments of the subject antibodies retain at least one binding function and/or modulation function of the full-length antibody from which they are derived. Preferred functional fragments retain an antigen-binding function of a corresponding full-length antibody (such as for example, ability of antibody that binds C5 to bind C5).

General methods for the immunization of animals (in this case with C5 and/or C5b, etc.), isolation of antibody producing cells, fusion of such cells with immortal cells (e.g., myeloma cells) to generate hybridomas secreting monoclonal antibodies, screening of

hybridoma supernatants for reactivity of secreted monoclonal antibodies with a desired antigen (in this case the immunogen or a molecule containing the immunogen), the preparation of quantities of such antibodies in hybridoma supernatants or ascites fluids, and for the purification and storage of such monoclonal antibodies, can be found in numerous publications. These include: Coligan, et al., eds. Current Protocols In Immunology, John Wiley & Sons, New York, 1992; Harlow and Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Liddell and Cryer, A Practical Guide To Monoclonal Antibodies, John Wiley & Sons, Chichester, West Sussex, England, 1991; Montz et al., Cellular Immunol. 127:337-351 (1990); Wurzner et al., Complement Inflamm. 8:328-340 (1991); and Mollnes et al., Scand. J. Immunol. 28:307-312 (1988).

VI Methods of Treatment

Methods of the application may be used to treat paroxysmal nocturnal hemoglobinuria associated symptoms. Methods of the application may be used to treat anemia associated symptoms. Treatment of paroxysmal nocturnal hemoglobinuria and/or anemia may be administered by standard means. Treatments of the application may be used in combination with other treatments of the application or known treatments for paroxysmal nocturnal hemoglobinuria and/or anemia. Treatments of the application may be co-administered with other treatments that treat symptoms of paroxysmal nocturnal hemoglobinuria and/or anemia.

VII Pharmaceutical Formulations and Uses

Methods of administration of small molecules, proteins, and nucleic acids are well-known to those of skill in the art. Methods of administration of antibodies are well-known to those of skill in the art. To achieve the desired inhibition, the antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab fragments will also require differing dosages than the equivalent intact immunoglobulins, as they are of considerably smaller mass than intact immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood. The dose will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing

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physician. Dosage levels of the antibodies for human subjects are generally between about 1 mg per kg and about 100 mg per kg per patient per treatment, and preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment. In terms of plasma concentrations, the antibody concentrations are preferably in the range from about 25 μg/mL to about 500 μg/mL. However, greater amounts may be required for extreme cases and smaller amounts may be sufficient for milder cases.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the antibody is administered according to the following protocol:

600 mg via 25 to 45 minute IV infusion every 7 ± 2 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 ± 2 days later, then 900 mg every 14 ± 2 days thereafter. Antibody is administered via IV infusion over 25 to 45 minute.

Administration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection. Other routes of administration may be used if desired but an intravenous route will be the most preferable. Formulations suitable for injection are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985). Such formulations must be sterile and non-pyrogenic, and generally will include a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The formulations may contain pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like. In certain embodiments, complement inhibitors such as eculizumab may be administered via IV infusion and diluted to a final concentration of 5 mg/ml prior to administration.

Administration of the antibodies capable of inhibiting complement such as an antibody that binds C5 will generally be performed by a parenteral route, typically via injection such as intra-articular or intravascular injection (e.g., intravenous infusion) or intramuscular injection. Other routes of administration, e.g., oral (p.o.), may be used if

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desired and practicable for the particular antibody capable of inhibiting complement to be administered. Antibodies capable of inhibiting complement such as an antibody that binds C5 can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and in vivo half-life of the particular antibody capable of inhibiting complement being administered. Doses of antibodies capable of inhibiting complement such as an antibody that binds C5 will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

In certain embodiments, a typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints with the dosage levels adjusted as needed to achieve the desired clinical outcome. In certain embodiments, treatment is administered in multiple dosages over at least a week. In certain embodiments, treatment is administered in multiple dosages over at least a month. In certain embodiments, treatment is administered in multiple dosages over at least a year. In certain embodiments, treatment is administered in multiple dosages over the remainder of the patient's life.

The frequency of administration may also be adjusted according to various parameters. These include the clinical response, the plasma half-life of the therapeutic of the disclosure, and the levels of the antibody in a body fluid, such as, blood, plasma, serum, or synovial fluid. To guide adjustment of the frequency of administration, levels of the therapeutic of the disclosure in the body fluid may be monitored during the course of treatment.

In certain embodiments, the frequency of administration may be adjusted according to an assay measuring cell-lysing ability of complement present in one or more of the patient's body fluids. The cell-lysing ability can be measured as percent hemolysis in hemolytic assays of the types described herein. A 10% or 25% or 50% reduction in the cell-lysing ability of complement present in a body fluid after treatment with the antibody capable of inhibiting complement used in the practice of the application means that the percent hemolysis after treatment is 90, 75, or 50 percent, respectively, of the percent hemolysis before treatment.

For the treatment of hemolytic diseases such as PNH by systemic administration of an antibody capable of inhibiting complement such as an antibody that binds C5 (as opposed to local administration), administration of a large initial dose is specific, i.e., a

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single initial dose sufficient to yield a substantial reduction, and more preferably an at least about 50% reduction, in the hemolytic activity of the patient's serum. Such a large initial dose is preferably followed by regularly repeated administration of tapered doses as needed to maintain substantial reductions of serum hemolytic titer. In another embodiment, the initial dose is given by both local and systemic routes, followed by repeated systemic administration of tapered doses as described above.

Formulations particularly useful for antibody-based therapeutic agents are also described in U.S. Patent App. Publication Nos. 20030202972, 20040091490 and 20050158316. In certain embodiments, the liquid formulations of the application are substantially free of surfactant and/or inorganic salts. In another specific embodiment, the liquid formulations have a pH ranging from about 5.0 to about 7.0. In yet another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from about 1 mM to about 100 mM. In still another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from 1 mM to 100 mM. It is also contemplated that the liquid formulations may further comprise one or more excipients such as a saccharide, an amino acid (e.g., arginine, lysine, and methionine) and a polyol. Additional descriptions and methods of preparing and analyzing liquid formulations can be found, for example, in PCT publications WO 03/106644, WO 04/066957, and WO 04/091658.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the application.

In certain embodiments, formulations of the subject antibodies are pyrogen-free formulations which are substantially free of endotoxins and/or related pyrogenic substances. Endotoxins include toxins that are confined inside microorganisms and are released when the microorganisms are broken down or die. Pyrogenic substances also include fever-inducing, thermostable substances (glycoproteins) from the outer membrane of bacteria and other microorganisms. Both of these substances can cause fever, hypotension and shock if administered to humans. Due to the potential harmful effects, it is advantageous to remove even low amounts of endotoxins from intravenously administered pharmaceutical drug solutions. The Food & Drug Administration ("FDA") has set an upper limit of 5 endotoxin units (EU) per dose per kilogram body weight in a

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single one hour period for intravenous drug applications (The United States Pharmacopeial Convention, Pharmacopeial Forum 26 (1):223 (2000)). When therapeutic proteins are administered in amounts of several hundred or thousand milligrams per kilogram body weight, as can be the case with monoclonal antibodies, it is advantageous to remove even trace amounts of endotoxin.

Formulations of the subject antibodies include those suitable for oral, dietary, topical, parenteral (e.g., intravenous, intraarterial, intramuscular, subcutaneous injection), ophthalmologic (e.g., topical or intraocular), inhalation (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops), rectal, and/or intravaginal administration. Other suitable methods of administration can also include rechargeable or biodegradable devices and controlled release polymeric devices. Stents, in particular, may be coated with a controlled release polymer mixed with an agent of the application. The pharmaceutical compositions of this disclosure can also be administered as part of a combinatorial therapy with other agents (either in the same formulation or in a separate formulation).

The amount of the formulation which will be therapeutically effective can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. The dosage of the compositions to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. For example, the actual patient body weight may be used to calculate the dose of the formulations in milliliters (mL) to be administered. There may be no downward adjustment to "ideal" weight. In such a situation, an appropriate dose may be calculated by the following formula: Dose (mL) = [patient weight (kg) x dose level (mg/kg)/ drug concentration (mg/mL)]

To achieve the desired treatment results, anti-C5 antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require

different dosage levels. Antibodies prepared as Fab' fragments or single chain antibodies will also require differing dosages than the equivalent native immunoglobulins, as they are of considerably smaller mass than native immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood.

Other therapeutics of the disclosure can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and *in vivo* half-life of the particular therapeutic being administered.

Doses of therapeutics of the disclosure will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

The formulations of the application can be distributed as articles of manufacture comprising packaging material and a pharmaceutical agent which comprises the antibody capable of inhibiting complement and a pharmaceutically acceptable carrier as appropriate to the mode of administration. The packaging material may include a label which indicates that the formulation is for use in the treatment of hemolytic diseases such as PNH. Although antibodies are preferred, especially anti-C5 antibodies which have already been shown to be safe and effective at decreasing the accumulation of downstream complement components in persons, the use of other complement inhibitors is also contemplated by this disclosure. The pharmaceutical formulations and uses of the disclosure may be combined with any known complement inhibitors or hemolytic diseases treatments known in the art.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

EXEMPLIFICATION

METHODS

Patient Selection

The TRIUMPH trial consisted of a 2-week screening period, an observation period of up to 3 months duration, and a 26-week treatment period.

During the screening period, patients were evaluated with respect to inclusion and exclusion criteria. Men and women, 18 years or older, diagnosed as having PNH with a type III erythrocyte population of ≥10%, and who had received at least 4 transfusions in the previous 12 months were eligible. Concomitant administration of erythropoietin, immunosuppressants, corticosteroids, coumadin, low molecular weight heparin, iron supplements, and folic acid were not reasons for exclusion, provided the doses were steady prior to the first visit and throughout the duration of the study. Because of the increased frequency of neisserial infections in individuals genetically deficient in terminal complement proteins, all patients were vaccinated against *Neisseria meningitides*. Patients were to avoid conception. The protocol was approved by an Investigational Review Board at each clinical site and written informed consent was obtained from all patients enrolled.

Patients transfused with a mean pre-transfusion hemoglobin level >10.5 g/dL over the previous 12 months, and those who showed evidence of having a suppressed immune response, complement deficiency, or active bacterial infection, including any history of meningococcal disease, were excluded from the study. Patients were also not eligible if they had previously received a bone marrow transplant or if they had participated in another trial or received another investigational drug within 30 days of the first visit. An individualized transfusion algorithm was calculated for each patient based on their prior 12-month transfusion history; the written algorithm documented the number of packed red blood cell (PRBC) units transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during observation and treatment periods.

Each patient considered eligible entered an observation period of up to 13 weeks in order to confirm their PBRC transfusion dependence. At least one transfusion --termed the "qualifying" transfusion-- during the 13-week observation period at a hemoglobin value at or below 9 g/dL with symptoms, or at or below 7 g/dL with or without symptoms, in accordance with the transfusion algorithm indicated for each patient, was a requirement to

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proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set point" for that individual for the purpose of the primary efficacy variable. A platelet count ≥100,000/mL and a LDH level ≥1.5 times the upper limit of the normal range were also required either at screening or during the observation period for eligibility.

Study Design

Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Measures of Clinical Efficacy

There were two co-primary endpoints in the study: (1) stabilization of hemoglobin levels, defined as a hemoglobin value maintained above the individual hemoglobin set point in the absence of transfusions for the entire 26-week treatment period, and (2) reduction in units of PRBCs transfused during the 26-week treatment phase of the study. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia and reached their individualized, pre-determined "set point". Pre-specified secondary endpoints included transfusion avoidance, hemolysis as measured by LDH area under the curve from baseline to 26 weeks, and QoL changes as measured from baseline to 26 weeks using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.[13] Pre-specified exploratory analyses included assessment of the EORTC QLQ-C30 instrument,[14] the change in LDH from baseline through week 26, and thrombosis. Other pre-specified measurements included pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. Time to first transfusion during the 26-week treatment phase and the proportion of PNH type III blood cells were also assessed.

Safety Assessments

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Treatment-emergent adverse events, clinical laboratory tests (e.g., serum chemical analyses and complete blood counts), electrocardiogram data, and vital signs were assessed. Adverse events were defined using the MedDRA preferred terms and tabulated as incidence rates per treatment group.

Statistical Analysis

For co-primary endpoints, analyses were performed according to the intention to treat using the data from all patients who were randomized and received study drug; stabilization of hemoglobin levels was analyzed using the Fisher's exact test and total PRBC units transfused were analyzed with the Wilcoxon's rank sum test. For comparison of treatment effect on transfusion avoidance, the Fisher's exact test was used on the incidence and the log rank test was used for time to first transfusion. For LDH area under the curve the Wilcoxon's rank sum test was used.

Quality of life measure of fatigue was assessed using the scoring guidelines for the FACIT-Fatigue instrument.[15] Assessment of quality of life measures based on the EORTC QLQ-C30 instrument was conducted in accordance with the appropriate scoring guidelines.[16] The changes of FACIT-Fatigue and EORTC QLQ-C30 scores from baseline through 26 weeks were analyzed using a mixed model, with baseline as covariate, treatment and time as fixed effects, and patient as a random effect. Changes in LDH levels and PNH type III erythrocytes from baseline through 26 weeks were analyzed using the same mixed model. Two-sided tests were used for all analyses. The adverse events and long-term safety checklist were tabulated separately and compared between treatments using the Fisher's exact test. A p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

Characteristics of Patients

A total of 115 PNH patients were screened. Six patients did not meet the inclusion/exclusion criteria during the screening period. Twenty-one other patients did not receive a qualifying transfusion and were not randomized into the treatment phase. One patient who did not meet the inclusion criteria was inadvertently randomized, but did not receive study medication. Thus 87 hemolytic PNH patients (35 men and 52 women) were enrolled and randomized to receive either eculizumab (N=43) or placebo (N=44), exceeding the original target of 75 randomized patients.

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Patient characteristics were similar in the eculizumab- and placebo-treated cohorts: median age, 41 (range 20-85) and 35 (range 18-78) years; median duration of PNH, 4.2 (range 0.8 to 29.7) and 9.2 (range 0.4 to 38.3) years; patients with history of aplastic anemia, 4 and 11; history of myelodysplastic syndrome, 1 and 0; and history of thrombosis, 9 (16 events) and 8 (11 events). Stable usage of concomitant medications at baseline in the eculizumab- and placebo-treated groups included the following: erythropoietin, 3 patients and 0 patients; cyclosporine, 1 and 1; anticoagulants (coumarins or heparins) 21 and 11; and steroids (glucocorticoids or androgenic steroids), 12 and 12, respectively.

Of the 87 patients randomized, 85 completed the trial. Two patients who did not complete the trial had been randomized to the eculizumab arm: one patient discontinued due to the inconvenience of travel to the study site and the second patient became pregnant. Ten patients in the placebo-treatment group discontinued infusions, in all cases due to perceived lack of efficacy, but they remained in the study for monitoring purposes.

Pharmacokinetics/Pharmacodynamics

In 42 of the 43 eculizumab-treated patients the levels of drug during the maintenance period (900 mg every 2 weeks±2 days) were sufficient to completely block serum hemolytic activity (mean trough value at week 26 of 101.8 μg/mL). A single patient did not sustain therapeutic trough levels of eculizumab and demonstrated a breakthrough in complement blockade during the last few days of each dosing interval. These breakthroughs were clinically manageable and quickly resolved following the next dose.

Hemolytic Efficacy Variables

The impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an immediate (one week) and sustained decrease in mean levels of LDH (Figure 1A). The median LDH area under the curve during the 26-week study period was reduced 85.8% in eculizumab- relative to placebo-treated patients ($P<0.001$). The mean LDH level decreased from 2199.7±157.7 IU/L at baseline to 327.3±67.6 IU/L by 26 weeks in eculizumab-treated patients while levels in placebo-treated patients remained consistently elevated with values of 2259.0±158.5 IU/L at baseline and 2418.9±140.3 IU/L at 26 weeks ($P<0.001$, for eculizumab versus placebo). A second biochemical measure of hemolysis, serum aspartate aminotransferase (AST), also showed a statistically significant improvement following eculizumab- versus placebo-treatment (data not shown). Haptoglobin levels were statistically significantly increased in eculizumab- as compared to placebo-treated patients

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but mean levels of haptoglobin were still below normal levels in eculizumab-treated patients (data not shown).

Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels (±standard error) from baseline (study week 0) to week 26 for both eculizumab- and placebo-treated patient populations. Screening occurred up to 3 months prior to study week 0. The upper limit of the normal range (103-223 IU/L) for LDH is indicated by a dashed line. LDH was reduced to a mean level just above the upper limit of normal at week 26 for eculizumab-treated patients; 15 of 41 patients who completed the study demonstrated LDH levels within the normal range. All placebo-treated patients remained at least 5 times above the upper limit of normal at week 26. The P value is based on a mixed model analysis from baseline through week 26. Figure 1B shows the mean proportion (±standard error) of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients. The screening visit occurred up to 3 months prior to study week 0. The P value is based on a mixed model analysis from baseline through week 26.

A corollary to the reduction in intravascular hemolysis during eculizumab treatment was an observed increase in the PNH type III erythrocyte population (Figure 1B). The mean proportions of type III erythrocytes increased from 28.1±2.0% at baseline to 56.9±3.6% by week 26 for eculizumab-treated patients while proportions in the placebo group remained constant with mean values of 35.7±2.8% before treatment to 35.5±2.8% at 26 weeks ($P<0.001$, for eculizumab versus placebo). By contrast, the proportions of PNH type III granulocytes and monocytes did not change significantly between the treatment groups during the treatment period and were greater than 90% at week 26.

CLINICAL EFFICACY

Co-primary endpoints

The co-primary efficacy endpoints in the TRIUMPH trial were stabilization of hemoglobin levels and reduction in PRBC units transfused. At the end of the treatment period, 48.8% of eculizumab-treated patients had maintained levels of hemoglobin above the pre-specified set-point (median set-point value of 7.7 g/dL for both treatment groups) in the absence of transfusions, whereas stabilization of hemoglobin did not occur in any of the patients in the placebo group ($P<0.001$; Table 1). By week 26, the median of PRBC units transfused per patient was 0 in the eculizumab group and 10.0 in the placebo cohort

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(P<0.001), while the mean of PRBC units transfused was 3.0 and 11.0 in the eculizumab and placebo cohorts, respectively. In the 6-month period prior to the study, the median of PRBC units transfused per patient was 9.0 in the eculizumab cohort and 8.5 in placebo patients while the mean of PRBC units transfused was 9.6±0.6 and 9.7±0.7, respectively. Mean hemoglobin levels were similar between the treatment groups at baseline (10.0±1.8 g/dL in eculizumab-treated patients and 9.7±1.8 g/dL in placebo-treated patients) and did not substantially change by week 26 (10.1±2.5 g/dL and 8.9±2.2 g/dL in eculizumab and placebo cohorts, respectively).

The median time to first transfusion was not reached during the study period in eculizumab-treated patients (it was greater than 26 weeks) while the placebo group reached the median time to first transfusion in only 4 weeks (P<0.001; Figure 2). Transfusion avoidance was achieved in 51.2% and 0% of the eculizumab and placebo cohorts, respectively (P<0.001). By the end of the 26-week treatment period, the total PRBC units transfused were 131 in eculizumab-treated patients versus 482 in the placebo group (Table 1). By contrast, in the 6-month period prior to the study, total PRBC units transfused in the eculizumab- and placebo-cohorts were 413 and 417, respectively.

Table 1

Stabilization of Hemoglobin Levels and Reduction

in Transfusion Requirements during Eculizumab Treatment

	PRE-TREATMENT HISTORY*		TREATMENT PERIOD		
	Placebo	Eculizumab	Placebo	Eculizumab	P Value
†Stabilization of Hemoglobin Levels in the absence of transfusions (percent of patients)	NA	NA	0	48.8	<0.001‡
†Units Transfused per Patient					
Median	8.5	9.0	10	0	<0.001§
Mean±SE	9.7±0.7	9.6±0.6	11.0±0.83	3.0±0.67	
Total Units Transfused per Group	417	413	482	131	

*Twelve month historical transfusion data normalized to 6 months

†Co-primary endpoints

‡Base on 2-sided Fisher's exact test

§Based on Wilcoxon's rank sum test

NA, not applicable

Improvements in quality of life measures

Assessments of quality of life in PNH patients during eculizumab treatment were performed using two different instruments; FACIT-Fatigue and the EORTC QLQ-C30. Eculizumab-treated patients showed a mean increase (improvement) in the FACIT-Fatigue score of 6.4±1.2 points from baseline to 26-weeks while the mean score in placebo patients decreased by 4.0±1.7 points, a total difference between the treatment groups of 10.4 points (Figure 3). Mixed model analysis of covariance demonstrated a statistically significant difference between treatment groups (P<0.001).

For the EORTC instrument, improvements were observed with eculizumab-treatment in each subscale. Statistically significant improvements with eculizumab-compared with placebo-treated groups were observed in the following quality of life

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subscales (Table 2): global health status (P<0.001), physical functioning (P<0.001), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P<0.001), social functioning (P=0.003), fatigue (P<0.001), pain (P=0.002), dyspnea (P<0.001), appetite loss (P<0.001), and insomnia (P=0.014). The improvements with eculizumab treatment in the other scales, including nausea and vomiting, diarrhea, constipation, and financial difficulties, did not reach statistical significance.

Table 2

Effect of Eculizumab Treatment on

Quality of Life Assessed by the EORTC QLQ-C30 Instrument

	Mean Change from Baseline to Week 26*			
	Placebo	Eculizumab	Absolute Difference	P Value†
Global Health Status	-8.5	10.9	19.4	<0.001
Functional				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.6	=0.003
Cognitive	-6.1	7.9	14.0	=0.002
Physical	-3.5	9.4	13.0	<0.001
Emotional	-3.7	7.5	11.2	=0.008
Symptoms/Single Items				
Fatigue	10.0	-16.9	27.0	<0.001
Pain	5.3	-12.3	17.6	=0.002
Dyspnea	8.9	-7.9	16.9	<0.001
Appetite Loss	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	=0.014

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Financial Difficulties	0.0	-10.3	10.3	=0.186
Constipation	0.0	-6.3	6.3	=0.199
Nausea/vomiting	2.8	-0.4	3.2	=0.056
Diarrhea	5.7	4.8	0.9	=0.147

*A positive change indicates an improvement in global health status and functional scales and a negative change indicates an improvement in symptom and single item scales.

†Based on a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect and baseline as a covariate.

Relationship between FACIT-Fatigue quality of life and intravascular hemolysis

In order to determine if there was a treatment independent relationship between the FACIT-Fatigue quality of life instrument and intravascular hemolysis, an analysis was performed whereby the mean LDH level (through the 26 week study period) for each TRIUMPH patient was analyzed as a function of the patient's respective mean change in FACIT-Fatigue score from baseline (through the 26 week study period) (see Table 3). For this analysis, mean levels of LDH were divided into 4 groups that included: normal levels, 1-2 times the upper limit of normal (ULN), 2-10 times the upper limit of normal, and greater than 10 times the upper limit of normal. The analysis demonstrated that patients who maintained normal LDH levels throughout the study experienced significant improvements in fatigue when compared to patients who had incrementally higher levels of LDH throughout the study (p=0.0048). These data establish a clear link between increasing intravascular hemolysis as measured by LDH levels and decreased quality of life as measured by the FACIT-Fatigue quality of life instrument.

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Table 3

Relationship between FACIT-Fatigue and Intravascular Hemolysis

Treatment Group	LDH Category	Change of FACIT from Baseline		
		< 4	>= 4	P-Value
Combined	Normal	4 (30.77%)	9 (69.23%)	.0048
	1 - 2 X ULN	16 (61.54%)	10 (38.46%)	
	2 - 10 X ULN	18 (72.00%)	7 (28.00%)	
	> 10 X ULN	16 (80.00%)	4 (20.00%)	

Safety

There were no deaths in the study. Serious adverse events (SAEs) were reported for 13 patients, of which 4 occurred in the eculizumab-treated cohort and 9 were in the placebo-treated cohort (see Table 4). All patients recovered without sequelae.

The most common AEs reported for eculizumab-treated patients were headache, nasopharyngitis, back pain, and upper respiratory tract infection. Headache and back pain occurred more commonly in the eculizumab-treatment group compared with the placebo group. However, the increase in headaches was limited to the first 2 weeks of therapy and was mild to moderate. There were no statistically significant differences in incidents rates between treatment groups for any AEs reported.

One episode of thrombosis (Budd-Chiari) occurred in a placebo-treated patient. There were no thromboses in eculizumab-treated patients.

Only one patient showed a detectable level of anti-eculizumab antibodies in the eculizumab-treated cohort; this response was weak (did not titrate), occurred at only one time point and did not result in a disruption of complement blockade.

Table 4

Adverse Event Reporting

SERIOUS ADVERSE EVENTS*	Placebo Patients n (percent)	Eculizumab Patients n (percent)
Total	9 (20.5)	4 (9.3)
Eculizumab treatment emergent		
Exacerbation of PNH	3 (6.8)	1 (2.3)
Renal colic	0	1 (2.3)
Lumbar sacral disc prolapse	0	1 (2.3)
Alpha streptococcal bacteremia	0	1 (2.3)
Central line infection and UTI	1 (2.3)	0 (0)
Upper respiratory tract infection	1 (2.3)	0 (0)
Probable viral infection	1 (2.3)	0 (0)
Neutropenia	1 (2.3)	0 (0)
Cellulitis / folliculitis / neutropenia	1 (2.3)	0 (0)
Anemia and pyrexia	1 (2.3)	0 (0)
MOST FREQUENT ADVERSE EVENTS*†		
Headache§	12 (27.3)	19‡ (44.2)
Nasopharyngitis	8 (18.2)	10 (23.3)
Upper respiratory tract infection	10 (22.7)	6 (14)
Back pain	4 (9.1)	8 (18.6)
Nausea	5 (11.4)	7 (16.3)
Cough	4 (9.1)	5 (11.6)
Diarrhea	5 (11.4)	4 (9.3)
Arthralgia	5 (11.4)	3 (7.0)
Abdominal pain	5 (11.4)	2 (4.7)
Dizziness	5 (11.4)	2 (4.7)
Vomiting	5 (11.4)	2 (4.7)
Fatigue	1 (2.3)	5 (11.6)

Viral infection	5 (11.4)	1 (2.3)

*By preferred terms

†Occurring in 10% or more of patients

‡Sixteen of 19 patients experienced headache within 48 hours of infusion

§Following the first 2 weeks of dosing, 20.9% of eculizumab- and 22.7% of placebo-treated patients experienced headache

DISCUSSION

Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44% reduction in the rate of transfusion (data now shown).

Lactate dehydrogenase, a biochemical marker of hemolysis in PNH,[9] was immediately and consistently decreased in all eculizumab-treated patients, while patients in the placebo cohort continued to hemolyze with levels of LDH exceeding 5 times the upper limit of the normal range in all patients at the study end. Levels of LDH were reduced into the normal range in approximately one-third of eculizumab-treated patients, while the remainder stabilized at a level just above the upper limit of normal suggesting residual low level hemolysis in some patients. Levels of haptoglobin, a more sensitive marker of the presence of cell free hemoglobin in the circulation, were undetectable in most patients. Low level hemolysis in a subset of eculizumab-treated patients is possibly due to an inherent decrease in survival of these cells or C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.[17]

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Before eculizumab treatment, hemoglobin levels in study patients were artificially maintained by frequent transfusion. Therefore, stabilization of hemoglobin levels with a concomitant cessation of or reduction in transfusions represents a net increase in endogenous hemoglobin levels. Our data suggest that resolution of hemolysis with eculizumab results in a new steady state hemoglobin level determined by a balance between the extent of the underlying bone marrow dysfunction, the number of PNH erythrocytes that are preserved by eculizumab therapy and the new level (if any) of transfusion requirement.

Patients with PNH generally experience markedly impaired quality of life characterized by fatigue, anemia, thrombosis, and pulmonary hypertension as well as smooth muscle dystonia including abdominal pain, dysphagia, and erectile dysfunction.[9,10,18] These symptoms have been attributed to both excessive intravascular hemolysis and downstream scavenging of nitric oxide by cell free hemoglobin in plasma. The reduction of intravascular hemolysis in eculizumab-treated patients in the current study was associated with significant improvements in the fatigue component of quality of life relative to placebo-treated patients as assessed via the FACIT-Fatigue instrument. Further, eculizumab therapy was associated with a median increase of 6.4 points over baseline values established before treatment. It has previously been demonstrated that an increase of 3 or more points from baseline represents a clinically important difference in this quality of life instrument.[19] Patients who received eculizumab also experienced a significant improvement in most domains of the EORTC QLQ-30 relative to the placebo-treated cohort including global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and insomnia. Improvement in the fatigue component of the EORTC QLQ-30 provides support for the improvement demonstrated in the FACIT-Fatigue instrument during eculizumab therapy. Importantly, these improvements in quality of life in the eculizumab-treated patients occurred despite similar levels of erythrocyte hemoglobin in the two treatment groups, further supporting the contribution of hemolysis per se, as opposed to anemia, in mediating the poor quality of life in PNH patients. Clinical assessment of additional life quality-related symptoms of PNH, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[20]

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Eculizumab was safe and well-tolerated. There were no deaths in the study and only a single thrombotic event which occurred in a placebo patient in a site (the hepatic veins) which is typical of the thrombosis in PNH. The relative brief duration of this study was not sufficient to address the relevant issue of a possible protection from thrombosis by terminal complement inhibition with eculizumab.

Adverse events were generally mild with headache occurring at increased frequency in the eculizumab-treated patients; however, this increased frequency did not persist following the first two doses of therapy. There were 4 SAEs in the eculizumab treatment group and 9 SAEs in the placebo group. There was no evidence of increased infection risk in eculizumab-treated patients during the study period. One eculizumab-treated patient showed a low level of anti-eculizumab antibodies at one time point during the study which did not persist and did not result in a disruption of complement blockade. There were no AEs associated with eculizumab withdrawal in the 2 eculizumab-treated patients who did not complete the trial. Additional safety assessments, as well as efficacy measures, are being examined in an ongoing multi-center, open-label Phase III safety trial of eculizumab (SHEPHERD) in approximately 95 patients with PNH.

Results from the current randomized, double-blind, placebo-controlled, global study show that terminal complement inhibition with eculizumab appears to be a safe and effective therapy for patients with the rare disorder PNH. Treatment with eculizumab reduced intravascular hemolysis, and stabilized hemoglobin levels despite a reduction of transfusions, to the point where most PNH patients were rendered transfusion independent. Substantial and clinically meaningful improvements in fatigue and other key quality of life parameters were also demonstrated. All of the 85 patients who completed the study elected to receive eculizumab in an open-label extension study and all currently remain on drug. The results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency.

The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

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All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

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SEQUENCES

SEQ ID NO: 1 – Eculizumab V_H

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSA

SEQ ID NO: 2 – Eculizumab Heavy chain

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
RKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP
SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK

SEQ ID NO: 3 – Eculizumab V_L

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRT

SEQ ID NO: 4 – Eculizumab Light chain

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

SEQ ID NO: 5 – Eculizumab CDRH1

NYWIQ

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SEQ ID NO: 6 – Eculizumab CDRH2
EILPGSGSTEYTENFKD

SEQ ID NO: 7 – Eculizumab CDRH3
YFFGSSPNWYFDV

SEQ ID NO: 8 – Eculizumab CDRL1
GASENIYGALN

SEQ ID NO: 9 – Eculizumab CDRL2
GATNLAD

SEQ ID NO: 10 – Eculizumab CDRL3
QNVLNTPLT

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WHAT IS CLAIMED IS:

1. A method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

2. The method of claim 1 wherein said quality of life is measured by a FACIT-Fatigue score.

3. The method, of claim 2 wherein the FACIT-Fatigue score increases by at least 3 points.

4. The method of claim 2 wherein the FACIT-Fatigue score increases by .gtoreq.4 points.

5. The method of claim 1 wherein said quality of life is measured by an EORTC QLQ-C30 score.

6. The method of claim 5 wherein said EORTC QLQ-C30 score improves by .gtoreq.10% of the pretreatment score.

7. The method of claim 5 wherein said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia.

8. The method of claim 7 wherein said aspect of quality of life is fatigue.

9. The method of claim 1 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

10. The method of claim 1 wherein said compound is a steroid that suppresses complement.

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11. The method of claim 1 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

12. The method of claim 11 wherein said compound is an antibody or an active antibody fragment.

13. The method of claim 12 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) F(ab').sub.2S, i) Fvs, j) diabodies, and k) human antibodies.

14. The method of claim 12 wherein said antibody or active antibody fragment blocks C5 cleavage.

15. The method of claim 12 wherein said antibody or active antibody fragment inhibits the formation of C5b-9.

16. The method of claim 12 wherein said antibody is eculizumab.

17. The method of claim 12 wherein said antibody or active antibody fragment is administered for at least 6 months.

18. The method of claim 1 wherein said patient has aplastic anemia or myelodysplastic syndrome.

19. The method of claim 1 wherein said patient is anemic.

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20. The method of claim 19 wherein said patient remains anemic following treatment.

21. The method of claim 19 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

22. The method of claim 19 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

23. The method of claim 19 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

24. The method of claim 1 wherein said compound inhibits intravascular hemolysis.

25. The method of claim 1 wherein said method results in a greater than 30% reduction in LDH in said patient.

26. The method of claim 24 wherein said patient is anemic and said patient remains anemic after said administration.

27. A method of prolonging the health-adjusted life expectancy of a patient comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

28. The method of claim 27 wherein said patient is anemic.

29. The method of claim 28 wherein said patient remains anemic following treatment.

30. The method of claim 27 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

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31. The method of claim 27 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

32. The method of claim 27 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

33. The method of claim 27 wherein said patient suffers from paroxysmal nocturnal hemoglobinuria.

34. The method of claim 27 wherein said health-adjusted life expectancy is measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

35. The method of claim 34 wherein the health-adjusted life expectancy in a subject is prolonged by at least one day.

36. The method of claim 34 wherein the health-adjusted life expectancy in a subject is prolonged by at least week.

37. The method of claim 34 wherein the health-adjusted life expectancy in a subject is prolonged by at least one month.

38. The method of claim 34 wherein the health-adjusted life expectancy in a subject is prolonged by at least one year.

39. The method of claim 27 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

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40. The method of claim 27 wherein said compound is a steroid that suppresses complement.

41. The method of claim 27 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

42. The method of claim 41 wherein said compound is an antibody or an active antibody fragment.

43. The method of claim 42 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) F(ab').sub.2S, i) Fvs, j) diabodies, and k) human antibodies.

44. The method of claim 42 wherein said antibody or active antibody fragment blocks C5 cleavage.

45. The method of claim 42 wherein said antibody or active antibody fragment is administered for at least 6 months.

46. The method of claim 27 wherein said compound inhibits complement or inhibits the formation of C5b-9.

47. The method of claim 46 wherein said compound is an antibody or an active antibody fragment.

48. The method of claim 47 wherein said antibody is eculizumab.

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49. The method of claim 27 wherein said patient has aplastic anemia or myelodysplastic syndrome.

50. A method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis.

51. A method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic.

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TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Eculizumab, a humanized monoclonal antibody against C5 that inhibits terminal complement activation, showed activity in a preliminary 12-week open-label trial in a small cohort of patients with paroxysmal nocturnal hemoglobinuria (PNH). The present study examined whether chronic eculizumab therapy could reduce intravascular hemolysis, stabilize hemoglobin levels, reduce transfusion requirements, and improve quality of life in a double-blind, randomized, placebo-controlled, multi-center global Phase III trial. It has been found that eculizumab stabilized hemoglobin levels, decreased the need for transfusions, and improved quality of life in PNH patients via reduced intravascular hemolysis. Chronic eculizumab treatment appears to be a safe and effective therapy for PNH.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN5
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Leonard		BELL	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Woodbridge	State/Province	CT	Country of Residence	US

Mailing Address of Inventor:

Address 1	59 Tumblebrook Road		
Address 2			
City	Woodbridge	State/Province	CT
Postal Code	06525	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Russell	P.	ROTHER	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Oklahoma City	State/Province	OK	Country of Residence	US

Mailing Address of Inventor:

Address 1	10325 Forest Meadow Drive		
Address 2			
City	Oklahoma City	State/Province	OK
Postal Code	73151	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Mark	J.	EVANS	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN5
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

City	Radnor	State/Province	PA	Country of Residence	US

Mailing Address of Inventor:

Address 1	617 Twinbridge Drive		
Address 2			
City	Radnor	**State/Province**	PA
Postal Code	19087	**Country**	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	133485		
Email Address	ipboston.docketing@nelsonmullins.com	Add Email	Remove Email

Application Information:

Title of the Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT		
Attorney Docket Number	AXJ-114BUSCN5	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN5
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	133485		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15/284015	2016-10-03
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/284015	Continuation of	15/260888	2016-09-09
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/260888	Continuation of	15/148839	2016-05-06
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
15/148839	Continuation of	13/426973	2012-03-22
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
13/426973	Continuation of	12/225040	2009-05-13

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN5
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
12/225040	a 371 of international	PCT/US2007/006606	2007-03-15
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN5
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN5
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

(•) Assignee	( ) Legal Representative under 35 U.S.C. 117	( ) Joint Inventor
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. [x]

Organization Name	Alexion Pharmaceuticals, Inc.

Mailing Address Information For Applicant:

Address 1	100 College St.		
Address 2			
City	New Haven	**State/Province**	CT
Country	US	Postal Code	06510
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN5
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Jill Gorny Sloper, Esq./			Date (YYYY-MM-DD)	2017-07-05
First Name	Jill Gorny	Last Name	Sloper	Registration Number	60,760

Additional Signature may be generated within this form by selecting the Add button.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN5
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 15642096 Document Date: 07/05/2017

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

- Sequence Listing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via eDAN using the Supplemental Content tab, or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: August 26, 2013

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Sequence Listing was accepted.
See attached Validation Report.
If you need help call the Patent Electronic Business Center at (866)
217-9197 (toll free).
Reviewer: Saleem, Syed (ASRC)
Timestamp: [year=2017; month=7; day=14; hr=10; min=46; sec=4; ms=418; ]
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Validated By CRFValidator v 1.0.5

Application No: 15642096 Version No: 1.0

Input Set:

Output Set:

Started: 2017-07-05 18:07:19.682
Finished: 2017-07-05 18:07:20.096
Elapsed: 0 hr(s) 0 min(s) 0 sec(s) 414 ms
Total Warnings: 10
Total Errors: 1
No. of SeqIDs Defined: 10
Actual SeqID Count: 10

Error code		Error Description
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W	213	Artificial or Unknown found in <213> in SEQ ID (1)
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SEQUENCE LISTING

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<120> TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS
BY AN INHIBITOR OF COMPLEMENT

<130> AXJ-114BUSCN5

<140> US 15/642,096
<141> 2017-07-05

<150> 15/284,015
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<150> 15/260,888
<151> 2016-09-09

<150> 15/148,839
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<150> 13/426,973
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Ser Asn Tyr
20 25 30

Trp Ile Gln Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Glu Ile Leu Pro Gly Ser Gly Ser Thr Glu Tyr Thr Glu Asn Phe

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    50                  55                  60

Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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      polypeptide

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Ser Asn Tyr
            20                  25                  30

Trp Ile Gln Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Glu Ile Leu Pro Gly Ser Gly Ser Thr Glu Tyr Thr Glu Asn Phe
    50                  55                  60

Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
            100                 105                 110
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Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
    210                 215                 220

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
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Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
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            340                 345                 350

Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
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Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gly Ala Ser
        35                  40                  45

Glu Asn Ile Tyr Gly Ala Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
    50                  55                  60

Ala Pro Lys Leu Leu Ile Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val
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Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
                85                  90                  95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
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Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Thr Asn Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn Val Leu Asn Thr Pro Leu
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
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Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
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Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
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Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
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Phe Asn Arg Gly Glu Cys
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Gln Asn Val Leu Asn Thr Pro Leu Thr
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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5

CONFIRMATION NO. 7606

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

FORMALITIES LETTER

OC000000093088364

Date Mailed: 07/28/2017

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
  - The application papers (including any electronically submitted papers) are not in compliance with 37 CFR 1.52 because pages 36 contain text that is unreadable or of insufficient clarity.
    Application papers (including any electronically submitted papers) must be presented in a form having sufficient clarity and contrast between the background of the paper and the writing thereon to permit the Office to electronically reproduce the papers by use of digital imaging and optical character recognition. See 37 CFR 1.52(a)(1)(v).
- A substitute specification excluding claims in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125 is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). Since a preliminary amendment was present on the filing date of the application and such amendment is part of the original disclosure of the application, the substitute specification must include all of the desired changes made in the preliminary amendment. See 37 CFR 1.115 and 1.215.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ygizaw/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/642,096	07/05/2017	1662	4500	AXJ-114BUSCN5	51	4

CONFIRMATION NO. 7606

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

FILING RECEIPT

OC000000093088363

Date Mailed: 07/28/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;
Mark EVANS, Radnor, PA;

Applicant(s)

Alexion Pharmaceuticals, Inc., New Haven, CT;

Power of Attorney: The patent practitioners associated with Customer Number 133485

Domestic Priority data as claimed by applicant

This application is a CON of 15/284,015 10/03/2016 PAT 9732149
which is a CON of 15/260,888 09/09/2016 PAT 9725504
which is a CON of 15/148,839 05/06/2016 PAT 9718880
which is a CON of 13/426,973 03/22/2012 ABN
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 07/19/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/642,096**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

800

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Samsung Bioepis Exhibit No. 1002
Page 100

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/642,096

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	51 minus 20 =	* 31			OR	x 80 =	2480
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1				x 420 =	420
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	4500

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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Application	Document	Mailroom Date	Attorney Docket No.
15642096	NT.CR.APP.PA	07/28/2017	AXJ-114BUSCN5
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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: August 22, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/642,096

Confirmation No.: 7606

Filed: July 5, 2017

Art Unit: 1662

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

Examiner: Not Yet Assigned

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT (IDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08. It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The present application is a continuation of U.S. Application No. 15/284,015, filed October 3, 2016 (Atty. Docket No. AXJ-114BUSCN4). For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO Form SB/08, listing all references cited during the prosecution of the parent applications. In accordance with 37 C.F.R. §1.98(d), copies of the references previously cited by or submitted to the Office in the parent applications are not enclosed, but will be provided upon request.

Additionally, in accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant submits herewith copies of foreign patents and non-patent literature references, but has not included copies of U.S. patents and U.S. patent applications.

Applicant calls to the attention of the Examiner the following Applications and Office Actions cited therein:

Applications				
Examiner's Initials	*Serial No.*	*Filing Date*	*First Named Inventor*	*Docket No.*
	15/284,015	10-03-2016	Leonard Bell	AXJ-114BUSCN4
	15/260,888	09-09-2016	Leonard Bell	AXJ-114BUSCN3
	15/148,839	05-06-2016	Leonard Bell	AXJ-114BUSCN2
	13/426,973	03-22-2012	Leonard Bell	AXJ-114BUSCN
	12/225,040	05-13-2009	Leonard Bell	AXJ-114BUS
	12/621,792	11-19-2009	Leonard Bell	AXJ-114DV
	10/771,552	02-03-2004	Leonard Bell	AXJ-114RCE
	11/050,543	02-03-2005	Leonard Bell	AXJ-114CPRCE
	11/595,118	11-08-2006	Leonard Bell	AXJ-114CP2
	12/902,617	10-12-2010	Leonard Bell	AXJ-114CPCN
	13/335,518	12-22-2011	Leonard Bell	AXJ-114CPCN2RCE

Office Actions (copies enclosed)			
Examiner's Initials	Serial No.	Date Mailed from USPTO	Examiner
	15/284,015	07-03-2017	J. Rogers
	15/284,015	04-11-2017	J. Rogers
	15/284,015	11-01-2017	J. Rogers
	15/260,888	06-28-2017	J. Rogers
	15/260,888	04-11-2017	J. Rogers
	15/260,888	12-22-2016	J. Rogers
	15/260,888	10-27-2016	J. Rogers
	15/148,839	06-07-2017	J. Rogers
	15/148,839	04-04-2017	J. Rogers
	15/148,839	08-16-2016	J. Rogers
	13/426,973	01-27-2014	J. Rogers
	13/426,973	05-31-2013	J. Rogers
	13/426,973	08-20-2012	J. Rogers
	12/225,040	09-22-2011	J. Rogers
	12/225,040	06-01-2011	J. Rogers

	12/225,040	04-11-2011	J. Rogers
	12/621,792	09-30-2010	P. Gambel
	10/771,552	12-22-2008	F. Vandervegt
	10/771,552	03-21-2008	F. Vandervegt
	10/771,552	08-10-2007	F. Vandervegt
	10/771,552	02-26-2007	F. Vandervegt
	10/771,552	09-26-2006	F. Vandervegt
	11/050,543	07-09-2010	P. Gambel
	11/050,543	04-02-2008	F. Vandervegt
	11/050,543	10-10-2007	F. Vandervegt
	11/050,543	06-11-2007	F. Vandervegt
	11/595,118	01-21-2011	P. Gambel
	11/595,118	10-05-2010	P. Gambel
	11/595,118	07-07-2010	P. Gambel
	11/595,118	04-03-2009	F. Vandervegt
	12/902,617	06-23-2011	P. Gambel
	12/902,617	04-04-2011	P. Gambel
	13/335,518	08-22-2016	P. Gambel
	13/335,518	09-12-2014	P. Gambel
	13/335,518	02-06-2014	P. Gambel
	13/335,518	11-07-2013	P. Gambel

The Examiner is requested to review the file histories of these applications, including cited references, Office Actions, Responses, etc., and is asked to contact Applicant's Attorney if the Examiner would like the Applicant to supply copies of any or all of the information included in any of these applications. For any of these applications, if Applicant's Attorney is not contacted by the Examiner with such a request, then it will be concluded that the Examiner has reviewed or will review the file content of these applications.

Applicant respectfully requests that the Examiner initial the blank columns next to the cited Applications and Office Actions, to indicate that the information has been considered by the Examiner. Alternatively, Applicant requests that the Examiner insert the phrase, "All references considered except where lined through," on each page of the Information Disclosure Statement, along with the Examiner's initials.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited documents are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any documents herein be construed *per se* as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited documents.

This Information Disclosure Statement is filed within three months of the U.S. filing date (37 C.F.R. § 1.97(b)(1)).

Dated: August 22, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (03-15)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

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	Attorney Docket Number	AXJ-114BUSCN5

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	43	Notice of Opposition filed in EP 2359834 B1 on behalf of Amgen, Inc., dated August 4, 2017, 22 pages.	
	44	Notice of Opposition filed in EP 2359834 B1 on behalf of Hoffmann Eitle, dated August 9, 2017, 26 pages.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	AXJ-114BUSCN5

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Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-08-22
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-08-22
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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	9	9725504		2017-08-08	Bell et al.	
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	2	2 359 834	EP	B1	2016-11-09	Alexion Pharmaceuticals, Inc		☐

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	4	2004/029207	WO	A2	2004-04-08	Xencor Inc		☐
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

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	38	Clinical Trials Identifier: NCT0098280, "Eculizumab to Treat Paroxysmal Nocturnal Hemoglobinuria" 6/23/2005, pp. 1-4	
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	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

	46	ESPICOM Pharmaceutical and Medical Device News, "Eculizumab found to be well tolerated and efficacious during 52 weeks of treatment in PNH," (Jan 2, 2007), 2 pages.	
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If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2017-08-22
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	30118800
Application Number:	15642096
International Application Number:	
Confirmation Number:	7606
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Anita Costa
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN5
Receipt Date:	22-AUG-2017
Filing Date:	05-JUL-2017
Time Stamp:	13:08:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Other Reference-Patent/App/Search documents	10771552.pdf	1114546 a23606e7e66aa910baf63f4c3ca2b56f1bbfa40b	no	26

Warnings:

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2	Other Reference-Patent/App/Search documents	11050543.pdf	1247825 7837b49a9ad0a9a9a71bee8509656534a32ee811	no	27
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5	Other Reference-Patent/App/Search documents	12902617.pdf	987288 aa047c1a1d8fb0e467ec6a7c86d7b88052ab52f5	no	19
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6	Other Reference-Patent/App/Search documents	13335518.pdf	2969578 913a0073fd37b27b941c80f367cf6331a494f7e2	no	54
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7	Other Reference-Patent/App/Search documents	13426973.pdf	1458729 1f755fdca4620693b3c9b9e617ff0be92212cb83	no	27
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10	Other Reference-Patent/App/Search documents	15284015.pdf	1288087 16cc0152db81100b0cc591448c65f2a0c53bac4a	no	24
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11	Foreign Reference	WO2007106585A1.pdf	3304975 32f399a08cd92792f6be39607f0cf038f4b5b755	no	63
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 12/22/2008

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EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
12/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *109-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080623*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application, filed on February 3, 2004, does not claim priority to any earlier application.

Claims 1-108 and 121-171 have been canceled.

Claims 109-120 are currently pending and are the subject of examination in the present Office Action.

In view of Applicant's remarks filed June 23, 2008 the following ground of rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 109-120 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Alexion press release dated January 6, 2003 (CG on form PTO-1449 filed 5/10/2007, of record) in view of Collard et al (Arterioscler Thromb Vasc Biol. [1999]19(11):2623-2629; U on form PTO-892, newly cited).

It was previously stated: "The Alexion press release teaches the use of the anti-C5 antibody compound eculizumab (h5G1.1-scFv) for the treatment of subjects with the hemolytic disease paroxysmal nocturnal hemoglobinuria (see entire document). It is noted that h5G1.1-scFv is the same compound recited in claim 111. The Alexion press release is silent about the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria. However, because the compound used to treat paroxysmal nocturnal hemoglobinuria in the Alexion press release and the instantly claimed compound to treat NO deficiency in paroxysmal nocturnal hemoglobinuria are the same, the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria would be an inherent property of the anti-C5 antibody compound eculizumab (h5G1.1-scFv). The prior art teaching anticipates the claimed invention.

The Alexion press release does not specifically link the hemolytic disease with NO deficiency or the effect of h5G1.1-scFv on NO levels.

Collard teaches the treatment of hypoxic HUVECs with h5G1.1-scFv (see entire document). Collard teaches that terminal complement component C5b-9 deposition results in a functional loss of NO-dependent relaxation (page 2625 in particular), increases VCAM-1 expression and decreases cGMP levels (page 2623 and page 2625 in particular). Collard teaches that decreased cGMP levels may compromise vascular blood flow because of decreased endothelium-dependent relaxation and increased adhesion of

neutrophils to the endothelium (page 2623 in particular). Collard teaches that h5G1.1-scFv treatment of the HUVECS attenuates C5b-9 deposition and preserves acetylcholine induced increases in cGMP after hypoxia/reoxygenation (page 2625 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use the h5G1.1-scFv antibody taught by the Alexion press release for the treatment of NO deficiency in a subject. One would have been motivated to treat NO deficiency with h5G1.1-scFv with a reasonable expectation of success by the showing of Alexion that h5G1.1-scFv treatment of PNH relieved hemolysis and the teachings of Collard that C5b-9 deposition during reoxygenation after a hypoxic event inhibited NO-mediated cGMP expression, which adversely affects vascular blood flow and attracts damaging neutrophils to the endothelial surface. Collard teaches that treatment with h5G1.1-scFv inhibits this C5b-9 deposition and attenuates cGMP loss.

Claims 112-114 are included because, while the references are silent about the proportion of type III red blood cells, silence about a particular property does not necessarily constitute absence of that property. Also, claims 115-117 are included because, while the references are silent about the platelet counts in a subject, silence about a particular property does not necessarily constitute absence of that property. Furthermore claims 118-120 are included because, while the references are silent about the reticulocyte counts in a subject, silence about a particular property does not necessarily constitute absence of that property. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989)."

Applicant's arguments filed June 23, 2008 have been fully considered but they are not persuasive. Applicant argues that the instantly claimed invention cannot be considered obvious over the teachings of the Alexion press release in view of Collard et al because the "Alexion press release was specific to treating PNH patients" and "does not disclose that all patient populations could be treated for NO deficiency with compounds which bind to one or more complement components." Applicant further argues that the artisan would not expect that anti-C5 antibodies would relieve a functional loss of NO-dependent relaxation under all circumstances based on the teaching of Collard et al." Applicant argues therefore that because the scope of the prior art teaching is not as broad as the scope of what is recited in the instant claims, the instantly claimed invention cannot be obvious over the cited references. Applicant's arguments are without merit. In the instant case, the claims are drawn to the genus of conditions involving NO deficiency, while the teachings of the combined references are drawn to a species of NO deficiency in PNH. The prior art does not need to teach the entire genus of the claimed invention. A teaching of a species encompassed by that genus is sufficient to render the genus obvious.

Conclusion

2. No claim is allowed.

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
March 17, 2008

/Eileen B. O'Hara/
Supervisory Patent Examiner
Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 03/21/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
03/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *109-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080110*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application, filed on February 3, 2004, does not claim priority to any earlier application.

Claims 1-108 and 121-171 have been canceled.

Claims 109-120 are currently pending and are the subject of examination in the present Office Action.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 10, 2008 has been entered.

In view of Applicant's amendment filed January 10, 2008 no outstanding ground of rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 109-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexion press release dated January 6, 2003 (CG on form PTO-1449 filed 5/10/2007, of record) in view of Collard et al (Arterioscler Thromb Vasc Biol. [1999]19(11):2623-2629; U on form PTO-892, newly cited).

The Alexion press release teaches the use of the anti-C5 antibody compound eculizumab (h5G1.1-scFv) for the treatment of subjects with the hemolytic disease paroxysmal nocturnal hemoglobinuria (see entire document). It is noted that h5G1.1-scFv is the same compound recited in claim 111. The Alexion press release is silent about the treatment of NO deficiency in paroxysmal

nocturnal hemoglobinuria. However, because the compound used to treat paroxysmal nocturnal hemoglobinuria in the Alexion press release and the instantly claimed compound to treat NO deficiency in paroxysmal nocturnal hemoglobinuria are the same, the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria would be an inherent property of the anti-C5 antibody compound eculizumab (h5G1.1-scFv). The prior art teaching anticipates the claimed invention.

The Alexion press release does not specifically link the hemolytic disease with NO deficiency or the effect of h5G1.1-scFv on NO levels.

Collard teaches the treatment of hypoxic HUVECs with h5G1.1-scFv (see entire document). Collard teaches that terminal complement component C5b-9 deposition results in a functional loss of NO-dependent relaxation (page 2625 in particular), increases VCAM-1 expression and decreases cGMP levels (page 2623 and page 2625 in particular). Collard teaches that decreased cGMP levels may compromise vascular blood flow because of decreased endothelium-dependent relaxation and increased adhesion of neutrophils to the endothelium (page 2623 in particular). Collard teaches that h5G1.1-scFv treatment of the HUVECS attenuates C5b-9 deposition and preserves acetylcholine induced increases in cGMP after hypoxia/reoxygenation (page 2625 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use the h5G1.1-scFv antibody taught by the Alexion press release for the treatment of NO deficiency in a subject. One would have been motivated to treat NO deficiency with h5G1.1-scFv with a reasonable expectation of success by the showing of Alexion that h5G1.1-scFv treatment of PNH relieved hemolysis and the teachings of Collard that C5b-9 deposition during reoxygenation after a hypoxic event inhibited NO-mediated cGMP expression, which adversely affects vascular blood flow and attracts damaging neutrophils to the endothelial surface. Collard teaches that treatment with h5G1.1-scFv inhibits this C5b-9 deposition and attenuates cGMP loss.

Claims 112-114 are included because, while the references are silent about the proportion of type III red blood cells, silence about a particular property does not necessarily constitute absence of that property. Also, claims 115-117 are included because, while the references are silent about the platelet counts in a subject, silence about a particular property does not necessarily constitute absence of that property. Furthermore claims 118-120 are included because, while the references are silent about the reticulocyte counts in a subject, silence about a particular property does not necessarily constitute absence of that property. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of

ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

3. No claim is allowed.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

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F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
March 17, 2008

/David A Saunders/
Primary Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 08/10/2007

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
08/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-171* is/are pending in the application.

4a) Of the above claim(s) *1-108 and 121-171* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

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4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application, filed on February 3, 2004, does not claim priority to any earlier application.

Claims 1-171 are currently pending.

Election/Restrictions

1. Applicant's election without traverse of Group VI, claims 109-120, in the reply filed on November 24, 2006 is acknowledged.

Claims 1-108 and 121-171 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 245, 2006.

Accordingly, claims 109-120 are the subject of examination in the present Office Action.

2. This application contains claims drawn to an invention nonelected without traverse in the reply filed on November 24, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

In view of Applicant's amendment filed May 10, 2007 no outstanding grounds of rejection are maintained.

The following new ground of rejection has been necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 109-120 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexion press release dated January 6, 2003 (CG on form PTO-1449 filed 5/10/2007).

The Alexion press release teaches the use of the anti-C5 antibody compound eculizumab (h5G1.1-scFv) for the treatment of subjects with paroxysmal nocturnal hemoglobinuria (see entire

document). It is noted that h5G1.1-scFv is the same compound recited in claim 111. The Alexion press release is silent about the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria. However, because the compound used to treat paroxysmal nocturnal hemoglobinuria in the Alexion press release and the instantly claimed compound to treat NO deficiency in paroxysmal nocturnal hemoglobinuria are the same, the treatment of NO deficiency in paroxysmal nocturnal hemoglobinuria would be an inherent property of the anti-C5 antibody compound eculizumab (h5G1.1-scFv). The prior art teaching anticipates the claimed invention.

Claims 112-114 are included because, while the references are silent about the proportion of type III red blood cells, silence about a particular property does not necessarily constitute absence of that property. Also, claims 115-117 are included because, while the references are silent about the platelet counts in a subject, silence about a particular property does not necessarily constitute absence of that property. Furthermore claims 118-120 are included because, while the references are silent about the reticulocyte counts in a subject, silence about a particular property does not necessarily constitute absence of that property. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

4. No claim is allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action

is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
August 6, 2007

DAVID A. SAUNDERS
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 02/26/2007

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ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

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- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-171* is/are pending in the application.

4a) Of the above claim(s) *1-108 and 121-171* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050523, 20060824, 20061124*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The instant application, filed on February 3, 2004, does not claim priority to any earlier application.

Claims 1-171 are currently pending.

Election/Restrictions

1. Applicant's election without traverse of Group VI, claims 109-120, in the reply filed on November 24, 2006 is acknowledged.

2. Claims 1-108 and 121-171 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 245, 2006.

Accordingly, claims 109-120 are the subject of examination in the present Office Action..

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 109-120 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vakeva et al (Circulation [1998] 97:2259-2267; U on form PTO-892) in view of Reiter et al (Nature Medicine [2002] 8(12):1383-1389; V on form PTO-892) and Fitch et al (Circulation [1999] 100:2499-2506; CA cited on form PTO-1449 filed 08/24/2006), as evidenced by Claque et al (Biomed. Instrum. Technol. [1995] 29(5):419-424, Abstract only; W on form PTO-892).

The claims are drawn to the treatment of nitric oxide deficiency in a subject having a hemolytic disease. Vakeva teaches that subjects who undergo prolonged periods of myocardial ischemia experience tissue injury and cell death (Abstract and page 2259, column 1 in particular). Vakeva relates the damage to activated terminal complement components (Abstract in particular). Vakeva teaches that treatment with an anti-C5 antibody inhibits apoptosis and necrosis and blocks greater than 80% of serum hemolytic activity (Abstract, Figure 8, section bridging pages 2265-2266 and paragraph bridging 2264-2265 in particular).

Reiter teaches that cell-free hemoglobin in sickle cell disease limits the availability of nitric oxide (NO)(Abstract in particular). Reiter teaches that free hemoglobin in the serum binds to NO 1,000 more rapidly than hemoglobin sequestered in erythrocytes. Reiter teaches that NO can only reach levels needed for activating guanylyl cyclase in smooth muscle to cause vasodilation only when hemoglobin is sequestered in erythrocytes (page 1383, column 1 in particular). Reiter further teaches that this condition in sickle cell is similar to that seen in clinical diseases such as hemolysis during cardiopulmonary bypass procedures (page 1387, column 2 in particular).

Fitch teaches that coronary bypass surgery (CBP) elicits a systemic inflammatory response (page 2499, column 1 in particular). Fitch teaches a method of administering of a humanized single chain monoclonal antibody directed to human complement component C5 (h5G1.1-scFv) to subjects undergoing CBP. The h5G1.1-scFv antibody is a complement inhibitor that binds to complement component C5 and prevents the cleavage of C5 into C5a and C5b (Fitch page 2500, column 1 in particular). Fitch teaches that h5G1.1-scFv treatment inhibited pathological complement activation, had a pronounced anti-inflammatory effect, and was associated with a significant reduction in myocardial injury and blood loss (page 2504, column 2 in particular). Blood loss in bypass procedures is known to be associated with hemolysis, as evidenced by Claque (Abstract in particular). Based upon the teachings of Fitch in light of the teachings of Reiter, the artisan would recognize that this may be due to the reduced capacity for vasodilation due to the lack of NO caused by free hemoglobin resulting from hemolysis.

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to treat subjects experience hemolytic disease as a result of coronary bypass surgery for nitric oxide deficiency using the anti-C5 antibody h5G1.1-scFv. One would have been motivated to combine the teachings with a reasonable expectation of success by the teachings of Vakeva that treatment of ischemia with anti-C5 antibody greatly reduced hemolysis, the teachings of Reiter that free hemoglobin resulting from hemolysis during cardiopulmonary bypass procedures greatly reduces NO levels in serum

and the teachings of Fitch that treatment of bypass patients with h5G1.1-scFv antibody reduced cell injury and blood loss.

Claims 112-114 are included because, while the references are silent about the proportion of type III red blood cells, silence about a particular property does not necessarily constitute absence of that property. Also, claims 115-117 are included because, while the references are silent about the platelet counts in a subject, silence about a particular property does not necessarily constitute absence of that property. Furthermore claims 118-120 are included because, while the references are silent about the reticulocyte counts in a subject, silence about a particular property does not necessarily constitute absence of that property. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Conclusion

4. No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
February 20, 2007

DAVID A. SAUNDERS
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,552	02/03/2004	Leonard Bell	ALXN-PO1-114	6183

28120 7590 09/26/2006

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/771,552	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-171* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-171* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-171 are currently pending.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-47, 97-108, and 121-171, drawn to a method of treating a subject with hemolytic disease or hemoglobinuria with an anti-C5 antibody, classified in class 424, subclass 145.1.

II. Claims 48-59, drawn to a method of treating a subject with dysphagia with an anti-C5 antibody, classified in class 424, subclass 145.1.

III. Claims 60-71, drawn to a method of treating a subject with erectile dysfunction with an anti-C5 antibody, classified in class 424, subclass 145.1.

IV. Claims 72-84, drawn to a method of reducing thrombosis in a subject with an anti-C5 antibody, classified in class 424, subclass 145.1.

V. Claims 85-96, drawn to a method of increasing the proportion of type III blood cells in a subject with an anti-C5 antibody, classified in class 424, subclass 145.1.

VI. Claims 109-120, drawn to a method of treating a nitric oxide deficiency in a subject with an anti-C5 antibody, classified in class 424, subclass 145.1.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I-VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions use the same reagent for the treatment, but each of the conditions in Groups I-VIhas a different etiology and affects a different part of the body. The anti-C5 antibody is administered therefore to achieve different therapeutic goals in each invention.

3. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art in view of their different classification. Further, a prior art search requires a literature search. It is an undue burden for the Examiner to search more than one invention and restriction for examination purposes as indicated is proper.

4. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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F. Pierre VanderVegt, Ph.D.
Patent Examiner
September 19, 2006

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/050,543	02/03/2005	Leonard Bell	ALXN-P02-114	2128

28120 7590 07/09/2010

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
07/09/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/050,543	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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Status

1)☒ Responsive to communication(s) filed on *06/26/2008, 10/02/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-135* is/are pending in the application.

4a) Of the above claim(s) *1-45,48,51-75,78,81-98,101,106 and 109-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,47,49,50,76,77,79,80,99, 100,102-105,107,108 and 131-135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

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Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

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3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/30/2008, 01/20/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Art Unit 1644.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/02/2008 has been entered.

Applicant's amendment, filed 06/26/2008, has been entered
Claims 47, 79, 102 and 107 have been amended.

Claims 1-135 are pending.

Claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107, 108 and 131-135 are under consideration in the instant application as they read on the elected invention.

Claims 1-45, 48, 51-75, 78, 81-98, 101, 106 and 109-130 have been withdrawn from consideration as they read on non-elected inventions/species.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.
For example, see page 40 of the specification.

Appropriate corrections are required

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 49 and 99 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed:

The specification as originally filed does not provide support for the invention as now claimed:
(A) "within 38% of the upper limit of normal" as recited in claim 99 and
(B) "PNH type III granulocytes" recited in claim 49.

As noted previously, claim 99 has been amended to recite "38%" in place of the original "20%" limitation. The specification as originally filed discloses only reduction of LDH levels to within 20% of the upper limit of normal at page 23, lines 6-9. Applicant has asserted that the recitation of 38% in the claim is supported by the specification as originally filed in the data of Figure 1A. The Figure in question depicts data from treated patients showing ranges of LDH levels pre- and post-treatment. The Figure "38%" is a post-treatment value obtained from within one of these ranges. The data in the Figure does not specifically lead to a teaching of 38% and there is no teaching in the specification to indicate that this is a preferred value from within the range. Picking a specific value from within a disclosed range creates a new, previously undisclosed, sub-genus and this constitutes new matter.
With respect to the recitation of "38%", applicant's arguments, filed 06/26/2008, submits the following.

> Although the embodiment referred to by the Examiner on page 23, lines 6-9 does not state "38%" this number is specifically taught by the data in Figure 1A. Specifically, Figure 1A shows the upper limit of normal (uln) is 480 U/L, and the treated patients showed an average LDH level of 622.4 + 41.1 at 64 weeks. Thus, the maximum LDH level of treated patients was 38.2% above the uln. Therefore, the upper range of the LDH levels of treated patients is reduced to within 38% of the uln. One of ordinary skill in the art could have derived this number unambiguously from Figure 1A and 38% defines the range rather than being within the range as the Examiner suggests. Accordingly, no new matter has been introduced.

In contrast to applicant's assertions, applicant is relying upon a specific example determined to be 38.2%, while the claims are now drawn to range as well as a specific point that differs from the specific example relied upon by applicant (e.g., "38%" versus "38.2%").

Further, it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Upon a review of the prosecution, it is noted that claim 49 had been amended to change PNH type III granulocyte clones" to PNH type III granulocytes" (see applicant's amendment, filed 01/10/2008).

Applicant relied upon the following paragraph from page 24 of the specification.

Methods of reducing one or more symptoms associated with PNH or other hemolytic diseases are also within the scope of the present disclosure. Such symptoms include, for example, abdominal pain, fatigue, dyspnea and insomnia. Symptoms can be the direct result of lysis of red blood cells (e.g., hemoglobinuria, anemia, fatigue, low red blood cell count, etc.) or the symptoms can result from low nitric oxide (NO) levels in the patient's bloodstream (e.g., abdominal pain, erectile dysfunction, dysphagia, thrombosis, etc.). It has recently been reported that almost all patients with greater than 40% PNH type III granulocyte clone have thrombosis, abdominal pain, erectile dysfunction and dysphagia, indicating a high hemolytic rate (see Moyo et al., British J. Haematol. 126:133-138 (2004)).

Rather than claiming "PNH type III granulocytes" generically, the original claims and the instant specification as-filed limits the cells to "PHN type III granulocyte clones".
By deleting "clones", it appears that applicant has altered the cell populations recited in the claims and described in the specification.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.
See MPEP 714.02 and 2163.06

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title,if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(f) or (g) prior art under 35 U.S.C. § 103(a).

9. Claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107, 108 and 131-135 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449; #CD) (see entire document).

Since the public availability of this document is not clear and given that certain claims are subject to a rejection under 35 USC 112, first paragraph, written description / new matter; this rejection is being applied under 35 U.S.C. § 102(a)(b).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with an anti-C5 antibody and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH and PNH type III cells (see entire document).

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 49-50, 79-80, 99, 10—104, 107-108, 135),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again

patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same PNH patients are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

10. Claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107, 108 and 131-135 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449; #CD) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449; #CE)in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (892; of record) with respect to normal LDH levels.

Hillmen et al. (2003) teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), which is characterized by intravascular hemolysis and venous thrombosis with an anti-C5 antibody and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH and PNH type III cells (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

Hillmen (2002) does not teach treating a subject with EPO.

The mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors) and erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia).

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

11. Given copending applications encompassing similar subject matter and the restriction set forth herein, applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/

Primary Examiner
Technology Center 1600
Art Unit 1644
July 6, 2010

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/050,543	02/03/2005	Leonard Bell	ALXN-P02-114	2128

28120 7590 04/02/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
04/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/050,543	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-135* is/are pending in the application.

4a) Of the above claim(s) *1-45,48,51-75,78,81-98,101,106 and 109-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,47,49,50,76,77,79,80,99,100,102-105,107,108 and 131-135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20071009, 20080110*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation-in-part of U.S. Application Serial Number 10/771,552.

New claims 131-135 have been added.

Claims 1-135 are currently pending.

Election/Restrictions

1. **Claims 1-45, 51-75, 81-98 and 109-130 stand withdrawn** from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 16, 2007.

2. **Claims 48, 78, 101 and 106 stand withdrawn** from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 16, 2007.

3. Accordingly, **claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107, 108 and 131-135 are the subject of examination** in the present Office Action.

4. In view of Applicant's amendment filed January 10, 2008, only the following grounds of rejection are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 99 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 99 has been amended to recite 38% in place of the original 20% limitation. The specification as originally filed discloses only reduction of LDH levels to within 20% of the upper limit of normal at page 23, lines 6-9. Accordingly, the recitation of 38% constitutes new matter and must be removed.

Applicant's arguments filed January 10, 2008 have been fully considered but they are not persuasive. Applicant asserts that the recitation of 38% in the claim is supported by the specification as originally filed in the data of Figure 1A. The figure in question depicts data from treated patients showing ranges of LDH levels pre- and post-treatment. The figure "38%" is a post-treatment value obtained from within one of these ranges. The data in the figure does not specifically lead to a teaching of 38% and there is no teaching in the specification to indicate that this is a preferred value from within the range. Picking a specific value from within a disclosed range creates a new, previously undisclosed, sub-genus and this constitutes new matter. Accordingly, the ground of rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 49, 79, 102 and 107 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49, 79, 102 and 107 remain ambiguous and unclear in the recitation of "greater than 40% of said subject's granulocytes are paroxysmal nocturnal hemoglubinuria (PNH) type III granulocytes. It is unclear whether this percentage of granulocytes being type III granulocytes is before or after treatment with the complement inhibitor. Clarification is required.

7. The following represents a new ground of rejection that has been necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 46, 47, 50, 76, 77, 80, 100, 103-105 and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen (44th ASH Annual Meeting Abstract, Blood, vol. 100 [2002]; CE on form PTO-1449 filed November 24, 2006, of record), as evidenced by Garba et al. (Singapore Med. J. [2005] 46(11):632-634; U on form PTO-892, of record) in view of Stebler et al. (Exp. Hematol. [1990] 18:1204-1208; V on form PTO-892, newly cited).

Hillmen teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59. Hillmen teaches treating transfusion-dependent PNH patients with ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter. The mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Hillmen does not teach treating a subject with EPO.

It is noted that the specification teaches the treatment with EPO as a combination therapy with the complement inhibitor. The specification discloses that the purpose of the EPO is to stimulate hematopoiesis and does not disclose that EPO modifies the activity of the complement inhibitor in any way. Accordingly, there is no disclosure that there any unobvious effects of the EPO on the inhibitor or vice versa.

Stebler teaches the use of high doses of recombinant human EPO to treat the anemia in patients with PNH (see entire document).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to treat a patient with PNH with ECULIZUMAB to inhibit hemolysis as taught by Hillmen and to simultaneously treat that patient with EPO to stimulate hematopoiesis and alleviate anemia as taught by Stebler. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the

patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone.

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
March 27, 2008

/David A Saunders/
Primary Examiner, Art Unit 1644

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/050,543	02/03/2005	Leonard Bell	ALXN-P02-114	2128

28120 7590 10/10/2007
ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/050,543	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-130* is/are pending in the application.

4a) Of the above claim(s) *1-45,48,51-75,78,81-98,101,106 and 109-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46,47,49,50,76,77,79,80,99,100,102-105,107 and 108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050511, 20060824, 20061124*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation-in-part of U.S. Application Serial Number 10/771,552.

Claims 1-130 are currently pending.

Election/Restrictions

1. Applicant's election with traverse of Group V, claims 46-50, in the reply filed on July 16, 2007 is acknowledged. The traversal is on the ground(s) that claims 76-80 and 99-108 should have also been included in this group because they are drawn to the same method. Upon further review of the claims in light of Applicant's remarks, the Examiner concurs and will rejoin the aforementioned claims with the invention of Group V.

Claims 1-45, 51-75, 81-98 and 109-130 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 16, 2007.

2. Applicant's election of the species "antibody" in the reply filed on July 16, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 48, 78, 101 and 106 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 16, 2007.

3. Accordingly, **claims 46, 47, 49, 50, 76, 77, 79, 80, 99, 100, 102-105, 107 and 108 are the subject of examination** in the present Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 99 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claim 99 has been amended to recite 38% in place of the original 20% limitation. The specification as originally filed discloses only reduction of LDH levels to within 20% of the upper limit of normal at page 23, lines 6-9. accordingly, the recitation of 38% constitutes new matter and must be removed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 49, 79, 102 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49, 79, 102 and 107 are ambiguous and unclear in the recitation of the abbreviation "PNH." The first recitation of an abbreviation in a line of claims should be in addition to a recitation of the full term, as the same abbreviation can be used to identify other cells or conditions. This ground of rejection can be overcome by amending the claim to recite --paroxysmal nocturnal hemoglubinuria (PNH)-- in place of the recitation of "PNH."

Claims 49, 79, 102 and 107 are ambiguous and unclear in the recitation of "subject has a greater than 40% PNH type III granulocytes clone. It is not clear what is exactly is supposed to be greater than 40% in the subject. Type III cells? Granulocytes? The ratio of granulocytes to type III cells? What is a "40% PNH type III granulocyte clone?" Clarification is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 46, 47, 50, 76, 77, 80, 100, 103-105 and 108 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, vol. 100 [2002]; CE on form PTO-1449 filed November 24, 2006), as evidenced by Garba et al. (Singapore Med. J. [2005] 46(11):632-634; U on form PTO-892).

Hillmen teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59. Hillmen teaches treating transfusion-dependent PNH patients with ECULIZUMAB, a humanized anti-C5 antibody 9see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter. The mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Conclusion

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
September 26, 2007

David A. Saunders
DAVID A. SAUNDERS
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/050,543	02/03/2005	Leonard Bell	ALXN-P02-114	2128

28120 7590 06/11/2007

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
06/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/050,543	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-130* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation-in-part of U.S. Application Serial Number 10/771,552.

Claims 1-130 are currently pending.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-19, 86-92 and 109-130, drawn to a method for treating a hemolytic disease in a subject comprising administering a complement-affecting compound to the subject, wherein the subject's need for transfusion is reduced or eliminated, classified in class 424, subclass 278.1.

II. Claims 20-35, drawn to a method for reducing abdominal pain in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

III. Claims 36-40, 51-55, 76-80, and 99-108, drawn to a method for treating a hemolytic disease comprising administering a complement-affecting compound to the subject wherein there is a reduction in hemoglobinuria, classified in class 424, subclass 278.1.

IV. Claims 41-45 and 81-85, drawn to a method for restoring nitric oxide homeostasis or reducing nitrous oxide deficiency in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

V. Claim46-50, drawn to a method for reducing hemolysis disease by reducing LDH levels in the bloodstream comprising administering a complement affecting compound to the subject, classified in class 424, subclass 278.1.

VI. Claims 56-60, drawn to a method for reducing dysphagia in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

VII. Claims 61-65, drawn to a method for reducing erectile dysfunction in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

VIII. Claims 66-70, drawn to a method for reducing thrombosis in a subject comprising administering a complement-affecting compound to the subject, classified in class 424, subclass 278.1.

IX. Claims 71-75, drawn to a method for increasing the proportion of Type III red blood cells in a subject's blood comprising administering a complement affecting compound to the subject, classified in class 424, subclass 278.1.

X. Claims 93-98, drawn to a method for treating a hemolytic disease in a subject comprising administering a complement affecting compound and a compound that increases hematopoiesis to the subject, classified in class 424, subclass 278.1.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I-X are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions use the same reagent for the treatment, but each of the conditions in Groups I-X has a different etiology and/or affects a different part of the body. The anti-C5 antibody is administered therefore to achieve different therapeutic goals in each invention.

3. These inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art due to their recognized divergent subject matter. Further, a prior art search requires a literature search. It is an undue burden for the Examiner to search more than one invention and restriction for examination purposes as indicated is proper.

4. This application contains claims directed to the following patentably distinct species:

a. antibodies,
b. soluble complement inhibitory compounds,
c. proteins, protein fragments, peptides,
d. small molecules,
e. RNA aptamers, L-RNA aptamers,
f. spiegelmers,
g. antisense compounds,
h. serine protease inhibitors,
i. double stranded RNA,
j. small interfering RNA,
k. locked nucleic acid inhibitors,
l. and peptide nucleic acid inhibitors.

The species are independent or distinct because each of the species has a different structure and different mode of action.

Irrespective of which group is chosen, Applicant is further required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no

generic claim is finally held to be allowable. Currently, claims 1, 2, 4, 6, 7, 9-20, 25-37, 39-42, 44-47, 49-52, 54-57, 59-62, 64-67, 69-72, 74-77, 79-82, 84-87, 89-94, 96-100, 102-105, 107-112, 115, and 117-130 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

5. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103(a) of the other invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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F. Pierre VanderVegt, Ph.D.
Patent Examiner
June 4, 2007

David A Saunders

DAVID A. SAUNDERS
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/595,118	11/08/2006	Leonard Bell	ALXN-P03-114	6763

28120 7590 01/21/2011

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
01/21/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	11/595,118	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) *1-163 and 168-191* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *164-167* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/09/2007, 01/25/2008, 01/05/2009, 01/20/2010, 11/03/2010*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group II (claims 164-167) for continued examination in the Response to Restriction Requirement, filed 11/03/2010 is acknowledged.

Applicant's indication that an election of species as it reads on Group II is not necessary (at this time) is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (see MPEP 818.03(a)).

Therefore, claims 164-167 being acted upon as the elected invention.

Claims 1-163 and 168-191 have been withdrawn as being drawn to the non-elected Group and its corresponding species

2. The effective filing date of the instant claims is deemed to be the filing date of the instant application USSN 11/595,118, filed 11/08/2206, as the previous priority applications do not provide sufficient written support for claims 164-167 as follows.

A method of determining whether a subject having a hemolytic disorder is susceptible to thrombosis comprising measuring the PNH granulocyte clone size of said subject, wherein if the clone size is greater than O. 1% then said subject is susceptible to thrombosis.

If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

3. If applicant desires priority under 35 U.S.C. 119(e) / 120 based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Applicant should update the status of the priority documents on page 1 of the instant specification.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate corrections are required

6. For examination purposes, it is noted the measuring the PNH granulocyte clone size refers to measuring the number or PNH granulocytes and not measuring the physical size of PNH granulocytes.

7. Claims 164-167 are objected to as "PNH" should be recited as "paroxysmal nocturnal hemoglobinuria" upon first time usage for clarity.

8. Claim 164-167 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 164-167 are indefinite in the recitation of "wherein the clone is greater than 0.1% / 1% / 10% / 50%" because a referenced control is not indicated.

Applicant is invited to consider amending the claims to include "of the total granulocyte count" as described on page 12, paragraph 4 of the instant specification to obviate this rejection.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 164-167 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The instant encompass "determining whether a subject is susceptible to thrombosis" based upon measuring the related clone size of PNH granulocytes" as follows.

164. A method of determining whether a subject having a hemolytic disorder is susceptible to thrombosis comprising measuring the PNH granulocyte clone size of said subject, wherein if the clone size is greater than 0.1% then said subject is susceptible to thrombosis.

165. The method of claim 164, wherein said clone size is greater than 1%.

166. The method of claim 164, wherein said clone size is greater than 10%.

167. The method of claim 164, wherein said clone size is greater than 50%.

Moyo et al. (British Journal of Haematology 126: 133-138, 2004) (1449; #CY) teach studied and evaluated patients with paroxysmal nocturnal hemoglobinuria (PNH) using sensitive and specific diagnostic assays and concluded that their data not only confirmed that the size of PNH clones, including PNH clones as measured in granulocytes, correlates with the risk of thrombosis, but also suggests a correlation of PNH clones to more symptomatic PNH (see entire document, including Abstract, Materials and Methods, Results, including Figures 1-4, and Discussion).

Moyo et al. found a strong association between PNH clones as measured in granulocytes and thrombosis, where the cutoff between the percentage of PNH granulocytes and thrombosis was 61% and the odds ratio for thrombosis was 1:64 for a 10% change in the size of the PNH granulocyte clones (e.g., see Results, particularly, page 135, column 2, paragraphs 1-2).

Such observations would indicate that there is a lack of correlation of measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size.

Therefore, there is a lack of predictability of correlating PNH granulocyte size and susceptibility of thrombosis when the clone is 0.1% , 1% , 10% or 50%" as recited in the instant claims.

In turn,, the specification does not enable one of skill in the art, at the time the invention was made, to practice the claimed methods of a lack of correlation of measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size.

Also, a medical diagnosis is a process of identifying a medical condition or disease by its signs, symptoms, and from the results of various diagnostic procedures.

Several variables are used in evaluating the predictability of detection or diagnostic assays.

These include diagnostic specificity and sensitivity and positive and negative predictive values.

The sensitivity of an assay reflects the fraction of those subjects with a specific disease that the assay correctly identifies as positive; while the specificity of an assay reflects the fraction of those subjects without the disease that the assay correctly identifies as negative.

The positive predictive value refers to the probability that an individual with a positive test result has the diseases; while the negative predictive value refers to the probability that an individual with a negative test result does not have the disease.

There is an inverse relationship between the sensitivity and specificity, which is related to the assigned cutoff value that is used for a particular test to segregate diseased populations from those with no disease.

In the absence of objective evidence to the contrary and keeping with the lack of predictability of a lack of correlating measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size as well as the differences and multiple variables associated with different hemolytic disorders wherein there is a susceptibility to thrombosis encompassed by the claimed methods,

there is insufficient disclosure on how to make and use the claimed methods to a lack of correlate measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size.

Given the unpredictability of the art in a lack of correlation of measuring the clone size of PNH granulocytes and thrombosis, when the clone size is less than 61% relative to total granulocyte size,

the experimentation left to those skilled in the art, would be unnecessarily, and improperly, extensive and undue.

In view of the lack of predictability of the art to which the invention pertains the lack of established protocols for correlating susceptibility to thrombosis based upon the presence alone of PNH granulocytes, undue experimentation would be required to practice the claimed methods of diagnosing / determining whether a subject is susceptible to thrombosis by determining PNH granulocytes of 0.1%-50% relative to controls with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for determining susceptibility to thrombosis based upon a broad range of PNH granulocyte sizes relative to control encompassed by the claimed methods.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 164-167 are rejected under 35 U.S.C. § 102(b) as anticipated by Moyo et al. (British Journal of Haematology 126: 133-138, 2004) (1449; #CY) (see entire document).

Moyo et al. teach studied and evaluated patients with paroxysmal nocturnal haemoglobinuria (PNH) using sensitive and specific diagnostic assays and concluded that their data not only confirmed that the size of PNH clones, including PNH clones as measured in granulocytes, correlates with the risk of thrombosis, but also suggests a correlation of PNH clones to more symptomatic PNH (see entire document, including Abstract, Materials and Methods, Results, including Figures 1-4, and Discussion).

Note, too, that Moyo et al. discuss validating the work of others, who showed that large PNH clones are predictive of thrombosis (see Discussion).

While Moyo et al. does not describe "wherein the clone is greater than 0.1% / 1% / 10% / 50%" explicitly,

Moyo et al. found a strong association between PNH clones as measured in granulocytes and thrombosis, where the cutoff between the percentage of PNH granulocytes and thrombosis was 61% and the odds ratio for thrombosis was 1:64 for a 10% change in the size of the PNH granulocyte clones (e.g., see Results, particularly, page 135, column 2, paragraphs 1-2).

These values anticipate the broad ranges encompasss the claimed limitation(s) "wherein the clone is greater than 0.1% / 1% / 10% / 50%".

Regarding the recitation of "identifying a subject having or being at risk of having a condition related to an excessive T cell mediated immune response",

it is noted that this "observing" step or clause does not recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or may be performed entirely in the human mind is obviously not tied to any machine and does not transform any article into a different state or thing.

Therefore, the "identifying a subject" step or clause simply recites or choosing the intended patient population for the claimed methods taught by the prior art, given the broadest reasonable interpretation of the claims.

13. No claim allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
January 18, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/595,118	11/08/2006	Leonard Bell	ALXN-P03-114	6763

28120 7590 10/05/2010

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
10/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/595,118	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2010*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-191* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *09/20/2010* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/595,118	11/08/2006	Leonard Bell	ALXN-P03-114	6763

28120 7590 07/07/2010

ROPES & GRAY LLP
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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
07/07/2010	PAPER

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	11/595,118	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

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Period for Reply

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- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2009*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-191* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

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4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. . The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Art Unit 1644

2. Applicant's Response to Restriction Requirement, filed 04/27/2009, is acknowledged.

However, upon a review of the instant specification, the previous Restriction Requirement, mailed 04/03/2009, has been withdrawn

From a review of the specification, it appears that all of the claims are drawn to methods of treating hemolytic diseases, which encompass various symptoms such as hemoglobinuria, anemia, dysphagia, fatigue, erectile dysfunction, recurrent abdominal pain and thrombosis (e.g., see pages 15-16 of the Detailed Description).

Therefore, setting forth the claimed invention in terms of Groups as done previously appears inconsistent with treating hemolytic diseases.

Claims 1-191 are pending and currently under Election of Species set forth herein.

The examiner apologizes for any inconvenience to applicant in this matter/

3. This application is directed to the following species.
   A) administering a compound as set forth in claims 2 and 7 for example alone or
   B) administering a compound as set forth in claims 2 and 7 for example *in combination with a second compound as set forth in claim 31 for example.*

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

The species are distinct because they require different methods steps, ingredients and endpoints.

Further, these species of first and second compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these molecules do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species of (A) or (B) AND elect a specific ultimate species of a first compound as set forth in (A) *(e.g., anti-C5 antibody or a specific RNA aptamer)* and a specific ultimate species a second compound of (B) *(e.g., EPO, antilymphocyte globin)* if elected herein for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. For example, claim 1 is generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

4. In addition to the election of species from Section 3;
then applicant is required to elect a species from the following.

This application contains claims directed to the following patentably distinct species of the claimed invention by electing a specific hemolytic disease and/or a specific symptom of a hemolytic disease.

From a review of the specification, the only hemolytic disease described appears to be paroxysmal nocturnal hemoglobinuria (PNH).
If other hemolytic diseases are described, then applicant should elected a specific hemolytic disease.

In addition, particularly if the only hemolytic disease described is PNH,
then applicant should elect a specific symptom of a hemolytic disease such as hemoglobinuria, anemia, dysphagia, fatigue, erectile dysfunction, recurrent abdominal pain and thrombosis either claimed or disclosed in the instant specification (e.g., see pages 15-16 of the Detailed Descrption).

Alternatively, if applicant deems that all of the symptoms are inherent or obvious in treating patients with treating hemolytic diseases,
Then this aspect of the election of species may be withdrawn.

At this point, it is not clear whether applicant is treating different diseases or patient populations. Applicant is invited to clarify this issue in the interest of compact prosecution.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species are distinct because these targeted hemolytic diseases and/or symptoms differ in etiologies and therapeutic endpoints. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed *species (e.g., PNH if electing a hemolytic disease AND anemia, erectile dysfunction for a symptom)* for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

5. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

6. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

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/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
July 6, 2010

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/595,118	11/08/2006	Leonard Bell	ALXN-P03-114	6763

28120 7590 04/03/2009

ROPES & GRAY LLP
PATENT DOCKETING 39/41
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	PAPER NUMBER
1644	

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04/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/595,118	BELL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-191* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-191* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-163, drawn to a method of reducing the occurrence of thrombosis in a subject, classified in class 514, subclass 2, for example.

II. Claims 164-167, drawn to a method of determining whether a subject having a hemolytic disorder is susceptible to thrombosis by measuring PNH granulocyte size, classified in class 435, subclass 7.1.

III. Claims 168-179, drawn to a method of increasing PNH red blood cell mass in a subject comprising inhibiting complement, classified in class 424, subclass 130.1, for example.

IV. Claims 180-191, drawn to a method for treating hemolytic anemia in a subject comprising inhibiting complement, classified in class 424, subclass 130.1 for example.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I, III, IV and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are drawn to methods of treatment in Groups I, III and IV, while Group II is drawn to a method of diagnosing a hemolytic disorder by measuring the size of the PNH granulocyte population in a subject. The diagnostic method does not require the practice of the treatment method and vice-versa.

3. Inventions I and III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions are drawn to methods for the treatment of different conditions, each of which would require a separate search of the literature.

4. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

5. **This application contains claims directed to the following patentably distinct species**:

IN GROUP I, there are three species elections required:

Applicant must elect a subject subset for search selected from the group consisting of patients with a higher than normal LDH level (claims 41-122) and patients with lower than normal nitric oxide level (123-163).

Applicant must further elect a complement inhibitor from the compounds enumerated in claims 7 OR 8.

Applicant must further elect a second compound for treatment of a subject selected from a compound that increases hematopoiesis and an anti-thrombotic compound.

6. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Should Applicant elect Group I, Applicant is further required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 11-6, 9-14 and 19-29 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571)272-0852. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D. /PV/
Patent Examiner
March 27, 2009

/Eileen B. O'Hara/
Supervisory Patent Examiner
Art Unit 1644

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/225,040	05/13/2009	Leonard Bell	ALXN-P04-114	5538

28120 7590 09/22/2011

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
ROGERS, JAMES L	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
09/22/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	12/225,040	BELL ET AL.	
	Examiner	Art Unit	
	JAMES ROGERS	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *93-108* is/are pending in the application.

5a) Of the above claim(s) *103-108* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *93-102* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/13/2009, 1/20/2010, 9/29/2010, 5/10/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 93-108 are pending.

2. Applicant's election with traverse of Group I, claims 93-102, drawn to a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody or a C5-binding fragment thereof, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof, and wherein the anti-C5 antibody or C5-binding fragment thereof inhibits cleavage of C5 into fragments C5a and C5b, filed on 07/21/11, is acknowledged.

Applicant's traversal is on the grounds that the cited reference of Hillmen et al. (N Engl J Med 2004; 350: 552-9) cited in the restriction requirement mailed on 6/1/2011 does not disclose or even suggest the instantly claimed pharmaceutical compositions or the use of the claimed compositions for treating patients afflicted with a hemolytic disease and thus Groups I and II are linked by a unifying inventive technical feature.

This argument was not found persuasive for the same reasons in the restriction requirement mailed 6/1/2011 and for the reasons in the obviousness rejection set forth below.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 103-108 (non-elected Groups II) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions/species.

4. Claims 93-102 are under consideration in the instant examination as they read on a method of pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody or a C5-binding fragment thereof, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof, and wherein the anti-C5 antibody or C5-binding fragment thereof inhibits cleavage of C5 into fragments C5a and C5b.

5. Applicant's IDSs, filed 5/13/2009, 1/20/2010, 9/29/2010 and 5/10/2010, are acknowledged. The foreign patent to Gotze EP0411306A1 listed on the information disclosure statement filed on 5/13/2009 fails to comply with 37 CFR 1.98(a)(3) because it does not include either a translation or a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information. Applicant is invited to provide a copy of the English translation or a statement of relevance.

The Listed U.S. Patent to Bell et al. (2005/0191298) listed on the information disclosure statement filed on 5/13/2009 does not contain the correct Patent document number.

The reference has been considered by the examiner and the correct patent document number listed on the attached Form 892.

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The non-patent literature document, Hillmen et al., listed on the information disclosure statement filed 9/29/2010 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of the non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. Applicant is invited to provide a copy of the reference to the examiner.

6. The first line of the specification should be amended to reflect that the current application is a national stage application of PCT/US07/06606 which claims priority to US provisional application 60/783/070.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 93, 95-97, and 99-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al., (N Engl J Med 2004; 350: 552-9, IDS Ref of 5/13/09).

Hillmen et al. teaches a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12. Hillmen et al. further discloses that the anti-C5 antibody binds specifically to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶)

Hillmen et al. differs from the claimed invention by not expressly reciting a single unit dosage form of 300 mg of the anti-C5 antibody, that the single unit dosage form has a volume of 30 mL and that the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody.

While the prior art reference is silent with respect to the limitations that the pharmaceutical composition comprise a single unit dosage form of 300 mg, that the single unit dosage form has a volume of 30 mL (claim 96) and comprises a 10 mg/mL solution of the anti-C5 antibody or C5-binding fragment thereof (claim 97), it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454, 456, 105 USPQ 233; 235 (CCPA 1955). See MPE §§2144.05 part IIA.

In the instant case, given that Hillmen et al. teaches administration of a 600 mg and 900 mg doses which can both be obtained simply by administering two or three separate single unit dosage forms of 300 mg of the instant claimed invention, respectively, the claimed dosage forms are simply a matter of convenience based upon the needs of the patient and involves only routine skill in the art. Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to supply the anti-C5 antibody or C5-binding fragment thereof in a composition comprising 300 mg single unit dosages as well as said dosages in a volume of 30 mL (i.e., 10 mg/mL).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 101-102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al., (N Engl J Med 2004; 350: 552-9, IDS Ref of 5/13/09), as applied to claims 93, 95-97 and 99-100 above, in view of Kaplan (Curr. Opin. Investig. Drugs, 3(7): 1017-23 (2002), IDS Ref of 5/13/09).

The teachings of Hillmen et al. have been discussed supra.

Hillmen et al. differs from the claimed invention by not reciting a C5-binding fragment which is pexelizumab.

Kaplan teaches the humanized single chain anti-C5 monoclonal antibody fragment, pexeizumab (p. 1018, 4th ¶) which was designed to have the advantage of enhanced tissue penetration.

Those of skill in the art would have had reason to use the anti-C5 binding fragment pexelizumab as a substitute for the anti-C5 antibody eculizumab in the administration to patients with PNH as taught by Hillmen et al. because Kaplan teaches that the antibody fragment has the advantage of enhanced tissue penetration. Substituting a known

element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claim 94 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al., (N Engl J Med 2004; 350: 552-9, IDS Ref of 5/13/09), as applied to claims 93, 95-97 and 99-100 above, and further in view of Tang et al. (Pharmaceutical Research, 21(2) (2004)).

The teachings of Hillmen et al. have been discussed supra.

Hillmen et al. differs from the claimed invention by not reciting that the pharmaceutical composition is lyophilized (claim 94).

Tang et al. teaches that lyophilization, also known as "freeze drying", is widely used for pharmaceuticals to improve the stability and long term storage stability of labile drugs, especially protein drugs (p. 191, 1st ¶).

It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the lyophilization procedure taught by Tang et al. with the anti-C5 antibody composition taught by Hillmen et al. One skilled in the art would be motivated to provide the single unit dosage form of anti-C5 antibody or a C5 binding fragment thereof in lyophilized form because Tang et al. teaches that lyophilization is commonly used to improve the stability and long term storage stability of labile drugs, especially protein drugs.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claim 98 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al., (N Engl J Med 2004; 350: 552-9, IDS Ref of 5/13/09), as applied to claims 93, 95-97 and 99-100 above, and further in view of Garcia et al. (Biologicals (2002) 30, 143-151).

The teachings of Hillmen et al. have been discussed supra.

Hillmen et al. differs from the claimed invention by not reciting that the pharmaceutical composition is a preservative free formulation (claim 98).

Garci et al. teaches that the influence of preservatives on the safety and stability of antivenoms may be involved in adverse reactions to antivenoms and is an issue that deserves careful consideration (p. 144, 2nd ¶; p. 149, last ¶).

It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to provide the composition taught by Hillmen et al. in a preservative free formulation. One skilled in the art would be motivated to provide the composition in a preservative free formulation because Garci et al. teaches that the presence of preservatives can be an important safety issue in that they may lead to adverse reactions when present in antibody compositions such as antivenoms.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Ram Shukla** can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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September 14, 2011

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner, Art Unit 1644

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/225,040	05/13/2009	Leonard Bell	ALXN-P04-114	5538

28120 7590 06/01/2011

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
ROGERS, JAMES L	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
06/01/2011	ELECTRONIC

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USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)
	12/225,040	BELL ET AL.
	Examiner	Art Unit
	JAMES ROGERS	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *93-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *93-108* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's preliminary amendment, filed on May 10, 2011, is acknowledged. Claims 93-108 are pending and being acted upon presently.

Election/Restrictions

2. Restriction is required under 35 USC 121 and 372. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

3. In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 93-102, drawn to a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody or a C5-binding fragment thereof, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof, and wherein the anti-C5 antibody or C5-binding fragment thereof inhibits cleavage of C5 into fragments C5a and C5b.

II. Claims 103-108, drawn to a method for treating a patient afflicted with a hemolytic disease, the method comprising administering to the patient a pharmaceutical composition comprising a single unit dosage form of an anti-C5 antibody or a C5-binding fragment thereof, wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody or C5-binding fragment thereof, and wherein the anti-C5 antibody or C5-binding fragment thereof inhibits cleavage of C5 into fragments C5a and C5b, in an amount and with a frequency effective to treat the hemolytic disease.

4. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 132, they lack the same or corresponding special technical features for the following reasons:

The invention of Group II was found to have no special technical feature that defined the contribution over the prior art of Hillmen et al.: "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria" N Engl J Med 2004; 350: 552-9.

Hillmen et al. teaches treating patients with a hemolytic disease with infusions of eculizumab (600 mg) every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12 (Abstract).

Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention.

5. Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143)**.**

6. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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May 24, 2011

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner,
Art Unit 1644

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28120 7590 04/11/2011

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
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	JAMES ROGERS	1644	

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- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25, 44, 68-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-25, 44, 68-92* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's preliminary amendment, filed on September 12, 2008, is acknowledged.

Claims 1-25, 44, and 68-92 are pending and being acted upon presently.

Species Election

2. Applicant is required under 35 US 121 (1) to elect a single disclosed species to which claims would be restricted if no generic claim is finally held to be allowable and (2) to list all claims readable thereon including those subsequently added.

A. Applicant is required to elect a particular assay for quality of life (e.g., FACIT-Fatigue score or EORTC QLQ-C30 score) such as one recited in claims 2 and 5. These species are distinct because the assays differ with respect to ingredients, method steps, and endpoints; thus each assay patentably distinct subject matter.

(i) If Applicant elects EORTC QLQ-C30 as an assay for quality of life, applicant is further required to elect a particular aspect of quality of life (e.g., global health status or insomnia) such as one recited in claims 7 and 8. These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter.

B. Applicant is required to elect a particular compound (e.g., CR1, K76 COOH, steroid, or antibody which blocks C5 cleavage) such as one recited in claims 9-17 and 80-85. These are distinct species because their structures and modes of action are different which, in turn, address different therapeutic endpoints.

C. Applicant is required to elect a particular type of disease (e.g., aplastic anemia, myelodysplastic syndrome, or paroxysmal nocturnal hemoglobinuria) such as one recited in claims 18, 74 and 90. These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter.

D. Applicant is required to elect a particular assay for health-adjusted life expectancy (e.g., Years of potential life lost or Years of healthy life) such as one recited in claim 75. These species are distinct because the pathological conditions differ in etiologies and therapeutic endpoints; thus each condition represents patentably distinct subject matter.

3. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species,** including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 4, 2011

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/902,617	10/12/2010	Leonard Bell	ALXN-P06-114	2376

28120 7590 06/23/2011

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/23/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)
	12/902,617	BELL ET AL.
	Examiner	Art Unit
	PHILLIP GAMBEL	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *131-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *131-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

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1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/04/2011*.	6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of the species (B) (methods of administering anti-C5 antibody and one or more additional compounds that increase hematopoiesis) and the species erythropoietin with traverse in the Response to the Election of Species Requirement, filed 05/04/2011, is acknowledged.

The traversal is on the grounds the Groups (A) and (B) are closely related and both species rely upon the recitation of "comprising" and, in turn, that searching would not imnpose an undue or substantial burden since the search would overlap.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

The following is noted from the Election of Species, mailed 04/04/2011.

These species of (A) and (B) are distinct because they rely upon different ingredients, methods steps and endpoints.
In turn, the steps rely upon ingredients and compounds that differ in their structures, physicochemical properties and modes of action that differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these ingredients and compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species

These species of compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species *(e.g., A or B and if B, then specific one or more compounds)* for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 131, 136 and 141 are generic, for example.
There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

This, applicant has not done.

The election of species is maintained for the reasons of record, which are reiterated herein for applicant's convenience.

Claims 131-145 are pending.

Claims 1-130 have been canceled previously.

Claims 131-145 are under consideration in the instant application as they read on the elected invention / species, including the combination of anti-C5 antibodies and erythropoietin.

3. Applicant should update the status of the priority documents on page 1 of the specification.

USSN 11/050,543 is now abandoned.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.
For example, see page 40 of the specification.

Appropriate corrections are required

5. Claims 132, 137 and 142 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 132, 137 and 142 are indefinite in the recitation of "h5G1.1" because its characteristics are not known. The use of "h5G1.1" as the sole means of identifying the claimed antibody renders the claims indefinite because it is merely 1 laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation to define completely distinct antibodies or biological materials.

Amending the claims to recite the appropriate ATCC Accession Numbers would obviate this rejection.

Providing the entire amino acid sequence the "h5G1.1" antibody would obviate this rejection.

Alternatively, applicant is invited to make the record clear whether satisfaction of the requirements under 35 USC 112, second paragraph, for this particular biological material has been satisfied in current U.S. Patent 6,355,245 (1449), as described on page 19 of the specification in order to make the record of the instant application complete.

Note that if applicant is relying upon the sequence of h5G1.1, it is the entire amino acid sequence that encodes h5G1.1. that is required.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 131-145 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.
The specification as originally filed does not provide support for the invention as now claimed:

The specification as originally filed does not provide support for the invention as now claimed:
"with a frequency effective to maintain a serum concentration of the antibody of about 35 μg/ml to thereby maintain serum complement activity in the patient at a level below 20% of the normal serum complement activity" and
"dosing schedule … at least once every 12 days".

Applicant's amendment, filed 10/12/2010, directs support for the newly added claims to page 19, lines 6-16; page 33, lines 20-23; page 36, lines 16 – page 37, line 9 and page 40, lines 1-7 and asserts no new matter has been filed.

However, with respect to the recitation of "with a frequency effective to maintain a serum concentration of the antibody of about 35 μg/ml to thereby maintain serum complement activity in the patient at a level below 20% of the normal serum complement activity",

applicant has relied upon the particulars of measuring the capacity of patient serum samples to lyse chicken erythrocytes in measuring serum hemolytic activity under certain conditions upon a particular dosage regimen(s) (e.g., see pages 39-40 of the specification).

In contrast, the claimed "frequency" is broader than that relied upon in the description of the specification as-filed.

In contrast, the claimed serum concentration is based upon any serum complement activity under any in vivo or in vitro conditions.

However, with respect to the recitation of "dosing schedule ... at least once every 12 days",
applicant has relied upon the particulars of "a reduction in the dosing interval from 14 to 12 days to maintain levels of eculizumab about 35 μg/ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients" (E.g., see page 37, lines 2-9 of the specification),
in which the change in dosing to 12 days was limited to the particulars of the two patients in the study,
wherein the switch to 12 days was subsequent to a particular dosing regimen and for a fixed period of time.

In contrast, the claimed dosing regimen encompasses a broader dosing range of "at least once every 12 days", which includes a 12 day regimen and more than once during a 12 day regimen,
as well as a serum activity endpoints, which has addressed above.
The claims have broaden the claimed functional readout of the dosing regimen as well as the claimed dosing regimens from that described in the specification as-filed.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.
See MPEP 714.02 and 2163.06.

8. Claims 132, 137 and 142 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that the h5G1.1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the appropriate cell line / hybridoma which produce this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Alternatively, applicant is invited to make the record clear whether satisfaction of the requirements under 35 USC 112, first paragraph, enablement for biological materials has been satisfied in current U.S. Patent 6,355,245 (1449), as described on page 19 of the specification in order to make the record of the instant application complete.

Note that if applicant is relying upon the sequence of h5G1.1, it is the entire amino acid sequence that encodes h5G1.1. that is required.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(f) or (g) prior art under 35 U.S.C. § 103(a).

11. Claims 131-140 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449) (see entire document).

Since the public availability of this document is not clear and given that certain claims are subject to a rejection under 35 USC 112, first paragraph, written description / new matter; this rejection is being applied under 35 U.S.C. § 102(a)(b).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 133 and 138) or effective amounts to maintain serum complement activity at a certain range (e.g., see claims 131 and 136),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab (tradename for h5G1.1 antibody) every other week,
the prior art teaches effective amounts of treatment with the h5G1.1 anti-C5 antibody occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

12. Claims 131-133, 136-139 and 141-143 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) dosea and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 133, 138 and 143) or effective amounts to maintain serum complement activity at a certain range (e.g., see claims 131, 136 and 141),

it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab (tradename for h5G1.1 antibody) every other week,

the prior art teaches effective amounts of treatment with the h5G1.1 anti-C5 antibody occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,

it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

13. Claims 131-145 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) (1449) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (1449) with respect to normal LDH levels.

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) dosea and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.
Hillmen (2002) does not teach treating a subject with EPO.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Given the prior art teachings of treating with 900 mg of eculizumab (tradename for h5G1.1 antibody) every other week,
the prior art teaches effective amounts of treatment with the h5G1.1 anti-C5 antibody occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters

(e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Futher, the mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors) and erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia).

In addition, as to the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations",
treating PNH patients characterized by the criteria of the proportion of type III red blood cells, platelet counts, type III granulocyte clone and serum complement activity are result effective variables of controlling hemolysis and reducing the risk of venous thrombosis with anti-C5 antibodies in the treatment of PNH patient populations who are characterized by intravascular hemolyisis, venous thrombosis and aplastic anemia.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d

1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As the nature of the dosing and therapeutic endpoints were known to the ordinary artisan, it would have been obvious to optimize the frequency of anti-C5 antibodies in order to control hemolysis and the risk of venous thrombosis in a variety of PNH patients.

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

14. Given copending applications encompassing similar subject matter and the restriction set forth herein, applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/

Primary Examiner
Technology Center 1600
Art Unit 1644
June 16, 2011

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/902,617	10/12/2010	Leonard Bell	ALXN-P06-114	2376

28120 7590 04/04/2011

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/04/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	12/902,617	BELL ET AL.	
	Examiner	Art Unit	
	PHILLIP GAMBEL	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2010*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *131-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *131-145* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 10/12/2010, has been entered.
Claims 1-130 have been canceled.
Claims 131-145 have been added.

Claims 131-145 are pending.

2. Applicant is required to elect
A) whether the claimed method do NOT comprise further administering one or more compounds that increase hematopoiesis OR
B) whether the claimed method do comprise further administering one or more compounds that increase hematopoiesis.

If applicant elects (B),
then applicant is required to elect a specific one or more compound that increase hematopoiesis from those recited in claims 135, 140 and 145 and more particularly from pages 8 and 12 of the instant specification.
If applicant elects *"one or more compounds"*, then applicant should clearly define the one or more compounds (e.g., cyclosporine, ATG, EPO derivatives, etc.).

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species of (A) and (B) are distinct because they rely upon different ingredients, methods steps and endpoints.
In turn, the steps rely upon ingredients and compounds that differ in their structures, physicochemical properties and modes of action that differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these indgredients and compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species

These species of compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species (e.g., A or B and if B, then specific one or more compounds) for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 131, 136 and 141 are generic, for example.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

3. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
March 26, 2011

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/335,518	12/22/2011	Leonard Bell	AXJ-114CPCN2RCE	4891

133485 7590 08/22/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
08/22/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 13/335,518	Applicant(s) BELL ET AL.	
	Examiner PHILLIP GAMBEL	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/12/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *131,133-136,138-141 and 143-146* is/are pending in the application.

5a) Of the above claim(s) *134,135,139,140,144 and 145* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *131,133,136,138,141, 143, 146* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/12/2015 has been entered.

Applicant's amendment, filed 03/12/2015, has been entered.

Claims 131, 136 and 141 have been amended.

Claims 152-153 have been added.

Claims 1-130, 132, 137, 142 and 147-153 have been canceled.
Claims 1-130, 132, 137, 142 and 148 have been canceled previously.

Claims 131, 133-136, 138-141 and 143-146 are pending.

As indicated previously, applicant's election of the species (A) (methods of administering anti-C5 antibody, where the claimed do not comprise further administering one or more compounds that increase hematopoiesis in the Response to Restriction Requirement, filed 12/09/2013, has been acknowledged.

Applicant's remarks concerning entitlement of claims to additional species upon allowance of a generic linking claim have been acknowledged.

Claims 131, 133, 136, 138, 141, 143 and 146 are under consideration in the instant application as they read on the elected species.

Claims 134, 135, 139, 140, 144 and 145 have been withdrawn as being drawn to the non-elected species.

3. The text of those sections of Title 35 USC not included in this Office Action can be found in a prior Office Action.

This Office Action will be in response to applicant's arguments and amendments, filed 03/12/2015.

The rejections of record can be found in the previous Office Action, mailed 09/12/2014.

4. Priority.

Applicant's arguments in conjunction with the amended claims, filed 03/12/2015, with respect to priority are acknowledged.

Given the amended claims, filed 03/12/2015, the following is noted.

Newly amended claims 131, 136 and 141 are set forth herein.

131. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising:
(1) identifying a PNH patient who experiences serum hemolytic activity on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks; and
(2) administering 900 mg of eculizumab to the patient once every 12 days to maintain a serum concentration of eculizumab of approximately 35 µg/ml to 50 µg/ml, thereby treating PNH in the patient.

136. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising:
(1) identifying a PNH patient who experiences serum hemolytic activity on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks; and
(2) administering 900 mg of eculizumab to the patient once every 12 days to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient.

141. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising administering eculizumab to the patient according to the following dosing schedule:
(i) 600 mg of eculizumab each week for four weeks;
(ii) 900 mg of eculizumab on the fifth week; and thereafter,
(iii) 900 mg of eculizumab ~~at least~~ once every 12 days,
wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient.

Note that not all current claims receive benefit of the previous priority applications.

The recitation of "identifying step" in claims 131 and 136,
"administering once every 12 days to maintain a serum concentration ... / administering once every 12 day to maintain in the patient a serum complement activity …", and
"to maintain a serum concentration of eculizumab of approximately 35 µg/ml to 50 µg/ml"
broadly recited in the newly amended / added claims do not appear to have sufficient written support in the specification as filed.

In addition, the recitation of "wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient" in claims 141 / 146 is not readily apparent in pages 36-37, overlapping paragraph of the specification (Examples).
The instant application does not particularly identify this particular combination of limitations.

Applicant's remarks, filed 03/12/2015, indicate that the support for the new and amended claims can be found throughout the specification and claims as originally filed.

The written support of the term "identifying" itself is not found in the specification as filed as well as the priority documents.

The written support of the claimed "identifying steps" is not found in the specification as filed as well as the priority documents.

Given the amended claims, it appears that applicant continues to rely upon the Examples to support the current amended claims.

While the term / step of identifying reads on establish or indicating who / someone or what / something is or associated with,

the Example discloses patients who participated in therapy trials to evaluate the effect of anti-C5 antibody on PNH in the absence of clearly disclosing "identifying step(s)" and in the absence of applicant's remarks clearly directing the written support of "identifying" / "identifying steps" in the specification.

Page 36, paragraph 3 of the specification (Examples) discloses the range of "35 µg/ml to *350* µg/ml", not "approximately 35 µg/ml to *50* µg/ml"

in the context of serum hemolytic activity in nine of the elven patients as being completely blocked throughout the 64 week treatment period of trough levels of eculizumab at equilibrium ranging …" rather "to maintain a serum concentration of eculizumab …" as currently claimed.

Pages 36-37, overlapping paragraph of the specification (Examples) disclosing that a reduction of eculizumab above 35 µg//ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients who did not sustain levels of eculizumab necessary to consistently block complement rather than "administering to the patient once every 12 days to maintain a serum complement activity at a level below 20% of the normal serum complement activity …" as currently claimed.

Applicant's reliance on generic disclosure and possibly certain observations in the instant Examples of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not provide sufficient written description nor direction and guidance to the "currently claimed limitations".

Note that the explicit recitation of the "limitations" cited above are not readily apparent in the specification as filed.

Note that applicant has amended the claims by relying upon certain observations of the eleven patients either in the treatment period or in an extension study under certain distinct dosing variable and time periods to broadly claim new limitations that departs from the instant disclosure as filed.

The instant disclosure of does not define nor set forth parameters" or provide for the metes and bounds of the "identifying steps".

Obviousness is not the standard for the addition new limitations to the disclosure as filed.
It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Applicant is claiming a subgenus not supported by the specification as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

It is also true that the written description requirement must still be met in some way so as to "describe the claimed invention so that one skilled in the art can recognize what is claimed".

A patent specification should set forth enough detail to allow a person or ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.

If applicant desires priority for the above-mentioned limitation / current claims prior to filing date of the instant application (12/22/2011);
applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

5. Claims 131, 133, 136 and 146 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 131, 133, 136 and 138 are indefinite in the recitation of "the identifying steps…" because these "limitations" are not clearly defined by the claim and the specification does not provide a sufficient standard for ascertaining the requisite degree or endpoints to reasonably apprise one of ordinary skill in the art of the metes and bounds of the invention.

For example, the specification does not set forth nor disclose the term "identifying" / "identifying steps" and does not define the metes and bounds nor the nature of the particular "identifying steps" encompassed by this claimed recitation.

While applicant's remarks, filed 03/12/2015 in response to the previous rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph relies upon the current amended claims to address the issue of positive steps by specifying the steps of (1) identifying and (2) administering,
applicant does not provide sufficient written description of the identifying steps in the specification (and priority documents) as filed.

It is noted that this "identifying steps" do not recite any additional active method steps, but simply state a characterization or conclusion of steps (not claimed) or may be performed entirely in the human mind is obviously not tied to any machine and do not transform any article into a different state or thing.
For example, the identifying steps read on mental steps which do not require positive steps.

The instant specification does not provide a sufficient definition nor description of the appropriate steps and readouts to apprise the ordinary artisan of the metes and bounds of the claimed "identifying limitations" indicated herein.

It is not clear as what positive steps, measures / parameters, etc., occur other than mental steps, including oral / written communications such as being informed by another or reading a report.

In the absence of a disclosure / description and/or a clear definition in the specification as filed,
the claimed recitation of the "identifying steps" is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06.

6. This is a written description rejection, new matter, under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Claims 131, 133, 136, 138, 141, 143 and 146 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 131, 136 and 141 are set forth herein.

131. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising:
(1) identifying a PNH patient who experiences serum hemolytic activity on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks; and
(2) administering 900 mg of eculizumab to the patient once every 12 days to maintain a serum concentration of eculizumab of approximately 35 µg/ml to 50 µg/ml, thereby treating PNH in the patient.

136. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising:
(1) identifying a PNH patient who experiences serum hemolytic activity on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks; and
(2) administering 900 mg of eculizumab to the patient once every 12 days to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient.

141. A method for treating paroxysmal nocturnal hemoglobinuria (PNH) in a patient, the method comprising administering eculizumab to the patient according to the following dosing schedule:
(i) 600 mg of eculizumab each week for four weeks;
(ii) 900 mg of eculizumab on the fifth week; and thereafter,
(iii) 900 mg of eculizumab ~~at least~~ once every 12 days,
wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient.

The recitation of "identifying step" in claims 131 and 136,
"administering once every 12 days to maintain a serum concentration ... / administering once every 12 day to maintain in the patient a serum complement activity …", and
"to maintain a serum concentration of eculizumab of approximately 35 µg/ml to 50 µg/ml"
broadly recited in the newly amended / added claims do not appear to have sufficient written support in the specification as filed.

In addition, the recitation of "wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient" in claims 141 / 146 is not readily apparent in pages 36-37, overlapping paragraph of the specification (Examples).
The instant application does not particularly identify this particular combination of limitations.

Applicant's remarks, filed 03/12/2015, indicate that the support for the new and amended claims can be found throughout the specification and claims as originally filed.

The written support of the term "identifying" itself is not found in the specification as filed as well as the priority documents.
The written support of the claimed "identifying steps" is not found in the specification as filed as well as the priority documents.

Given the amended claims, it appears that applicant continues to rely upon the Examples to support the current amended claims.

While the term / step of identifying reads on establish or indicating who / someone or what / something is or associated with,

the Example discloses patients who participated in therapy trials to evaluate the effect of anti-C5 antibody on PNH in the absence of clearly disclosing "identifying step(s)" and in the absence of applicant's remarks clearly directing the written support of "identifying" / "identifying steps" in the specification.

Page 36, paragraph 3 of the specification (Examples) discloses the range of "35 µg/ml to *350* µg/ml, not "approximately 35 µg/ml to *50* µg/ml"

in the context of serum hemolytic activity in nine of the elven patients as being completely blocked throughout the 64 week treatment period of trough levels of eculizumab at equilibrium ranging …" rather "to maintain a serum concentration of eculizumab …" as currently claimed.

Pages 36-37, overlapping paragraph of the specification (Examples) disclosing that a reduction of eculizumab above 35 µg//ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients who did not sustain levels of eculizumab necessary to consistently block complement rather than "administering to the patient once every 12 days to maintain a serum complement activity at a level below 20% of the normal serum complement activity …" as currently claimed.

In addition, the recitation of "wherein the dosing schedule is effective to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity, thereby treating PNH in the patient" in claims 141 / 146 is not readily apparent in pages 36-37, overlapping paragraph of the specification (Examples).

The instant application does not particularly identify this particular combination of limitations.

Applicant's reliance on generic disclosure and possibly certain observations in the instant Examples of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not provide sufficient written description nor direction and guidance to the "currently claimed limitations".

Note that the explicit recitation of the "limitations" cited above are not readily apparent in the specification as filed.

Note that applicant has amended the claims by relying upon certain observations of the eleven patients either in the treatment period or in an extension study under certain distinct dosing variable and time periods to broadly claim new limitations that departs from the instant disclosure as filed.

The instant disclosure of does not define nor set forth parameters" or provide for the metes and bounds of the "identifying steps".

Obviousness is not the standard for the addition new limitations to the disclosure as filed.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Applicant is claiming a subgenus not supported by the specification as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

It is also true that the written description requirement must still be met in some way so as to "describe the claimed invention so that one skilled in the art can recognize what is claimed".

A patent specification should set forth enough detail to allow a person or ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

7. Upon reconsideration of applicant's amended claims and arguments, filed 03/12/2015, the previous rejection rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) has been withdrawn in view of the recitation of an identifying step and an administering 900 mg eculizumab to the patient every 12 days step has been withdrawn.

8. Upon reconsideration of applicant's amended claims and arguments, filed 03/12/2015, the previous rejection rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) has been withdrawn in view of the recitation of an identifying step and an administering 900 mg eculizumab to the patient every 12 days step.

9. Upon reconsideration of applicant's amended claims and arguments, filed 03/12/2015, the previous rejection under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) (1449) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (1449) with respect to normal LDH levels has been withdrawn in view of the recitation of an identifying step and/or an administering 900 mg eculizumab to the patient every 12 days step.

10. New Grounds of Rejection

Claims 131, 133, 136, 138, 141, 143 and 146 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bell et al. US 2005/0191298) (1449) (see entire document).

Given the priority issues set forth above,
this rejection is set forth.

Bell et al. teach the methods of treating PNH with eculizumab, including the dosing regimens recited in the instant claims, including the characterization of the patients and serum complement activity in patents (see entire document, including Abstract, Background, Summary, Detailed Description, particularly paragraphs [0065]-[0067], Examples in paragraphs [0081]-[0096],Claims and Figures).

While Bell et al. teach the same methods as claims,
it is acknowledged that Bell et al. differs from the claims by not reciting the "identifying steps" per se.

However, it is noted that this "identifying steps" do not recite any additional active method steps, but simply state a characterization or conclusion of steps (not claimed) or may be performed entirely in the human mind is obviously not tied to any machine and do not transform any article into a different state or thing.
For example under the broadest reasonable interpretation of the claims,
the identifying steps read on mental steps which do not require positive steps.

Again, the referenced Examples teach the same methods as claimed and that the prior art teachings of the administering step would have been those patients identified / chosen / selected by the physicians in the clinical trials taught by the prior art.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure
In turn, the claimed limitations are explicitly or inherent in the prior art teachings.

11. New Ground of Rejection.

Claims 131, 133, 136, 138, 141, 143 and 146 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bell et al. US 2005/0191298) (1449) (see entire document).

Given the priority issues set forth above,
this rejection is set forth.

Bell et al. teach the methods of treating PNH with eculizumab, including the dosing regimens recited in the instant claims, including the characterization of the methods (see entire document, including Abstract, Background, Summary, Detailed Description, particularly paragraphs [0065]-[0067], Examples in paragraphs [0081]-[0096],Claims and Figures).

While Bell et al. teach the same methods as claims,
it is acknowledged that Bell et al. differs from the claims by not reciting the "identifying steps" per se.

However, it is noted that this "identifying steps" do not recite any additional active method steps, but simply state a characterization or conclusion of steps (not claimed) or may be performed entirely in the human mind is obviously not tied to any machine and do not transform any article into a different state or thing.
For example under the broadest reasonable interpretation of the claims,
the identifying steps read on mental steps which do not require positive steps.

Again, the referenced Examples teach the same methods as claimed and that the prior art teachings of the administering step would have been those patients identified / chosen / selected by the physicians in the clinical trials taught by the prior art.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure
In turn, the claim limitations are explicitly or inherent / intrinsic in the prior art teachings.

Alternatively, one of ordinary skill in the art at the time the invention was made would have been motivated identify those patients who were treated with the regimen in claims 131(1) and 136(1) as taught in the Examples and then administer 900 mg eculizumab once every 12 days also taught by the Examples to maintain eculizumab concentrations and/or to inhibit serum hemolytic activity in the treatment of PNH (e.g., see Examples, including paragraph [0088].

It does not appear that the claim language or limitations result in an unobvious manipulative difference in the method steps when compared to the prior art disclosure of providing 600 mg weekly for four (4) doses and 900 mg every other week of eculizumab a humanized anti-C5 antibody and maintenance doses in the treatment of patients with PNH at the time the invention was made.

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to identify / select / determine those patients who did not sustain levels of eculizmab necessary to consistenly block complement by administering 900 mg eculizumab once every 12 days also taught by the Examples to maintain eculizumab concentrations and/or to inhibit serum hemolytic activity in the treatment of PNH (e.g., see Examples, including paragraph [0088 select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time with an expectation of success.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007).

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
August 17, 2016

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/335,518	12/22/2011	Leonard Bell	AXJ-114CPCN2	4891

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NELSON MULLINS RILEY & SCARBOROUGH LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
09/12/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 13/335,518	Applicant(s) BELL ET AL.	
	Examiner PHILLIP GAMBEL	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/07/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *131,133-136,138-141,143-147 and 149-153* is/are pending in the application.

5a) Of the above claim(s) *134, 135, 139, 140, 144, 145, 150 and 151* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *131,133,136,138,141,143,146,147,149,152 and 153* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Applicant's amendment, filed 07/07/2014, has been entered.

Claims 131, 136, 141 and 147 have been amended.

Claims 152-153 have been added.

Claims 132, 137, 142 and 148 have been canceled.
Claims 1-130 have been canceled previously.

Claims 131, 133-136, 138-141, 143-147 and 149-153 are pending.

As indicated previously, applicant's election of the species (A) (methods of administering anti-C5 antibody, where the claimed do not comprise further administering one or more compounds that increase hematopoiesis in the Response to Restriction Requirement, filed 12/09/2013, has been acknowledged.

Applicant's remarks concerning entitlement of claims to additional species upon allowance of a generic linking claim have been acknowledged.

Claims 131, 133, 136, 138, 141, 143, 146, 147, 149, 152 and 153 are under consideration in the instant application as they read on the elected species.

Claims 134, 135, 139, 140, 144, 145, 150 and 151 have been withdrawn as being drawn to the non-elected species.

3. The text of those sections of Title 35 USC not included in this Office Action can be found in a prior Office Action.

This Office Action will be in response to applicant's arguments and amendments, filed 07/07/2014).

The rejections of record can be found in the previous Office Action, mailed 02/06/2014.

4. Priority.

Note that not all claims may receive benefit of the priority applications.

The recitation of "the method comprising administering eculizumab to a patient who has experienced complement-related serum hemolytic activity breakthrough ...",
"a method for preventing complement-related serum hemolytic activity breakthrough in a patient",
"with a frequency effective to maintain a serum concentration of eculizumab of at least 35 µg/ml",
"at least once every 12 days to maintain in the patient a serum complement activity at a level below 20% of the normal serum complement activity"
broadly recited in the newly amended / added claims do not appear to have sufficient written support in the specification as filed.

Applicant's remarks, filed 07/07/2014, indicate that the support for the new and amended claims can be found throughout the specification and claims as originally filed.

Applicant also relies upon the following with respect to Priority.

Applicants respectfully note that literal support for an administration regimen that comprises administration of an anti-C5 antibody at least once every 12 days can be found at least, for example, at page 36 (line 16) through page 37 (line 9) of the specification as originally filed. For the Examiner's convenience, the relevant section is reproduced below:

Serum hemolytic activity in nine of the eleven patients was completely blocked throughout the 64 week treatment period with trough levels of eculizumab at equilibrium ranging from approximately 35 µg/ml to 350 µg/ml. During the extension study, 2 patients did not sustain levels of eculizumab necessary to consistently block complement. This breakthrough in serum hemolytic activity occurred in the last 2 days of the 14 day dosing interval, a pattern that was repeated between multiple doses. In one of the patients, as seen in FIG. 4, break-through of complement blockade resulted in hemoglobinuria, dysphagia, and increased LDH and AST, which correlated with the return of serum hemolytic activity. At the next dose, symptoms resolved (FIG. 5) and reduction in the dosing interval from 900 mg every 14 days to 900 mg every 12 days resulted in a regain of complement control which was maintained over the extension study to 64 weeks in both patients. This patient showed a 24 hour resolution of dysphagia and hemoglobinuria. A reduction in the dosing interval from 14 to 12 days was sufficient to maintain levels of eculizumab above 35 µg/ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients (emphasis added).

Applicants also confirm that the present application is not a continuation-in- part of the prior application (USSN 12/902,617), but rather a continuation of USSN 12/902,617, which is a continuation of USSN 11/050,543, which is a continuation-in-part of USSN 10/771,552, as specified on the Application Data Sheet as filed with the application. Accordingly, the same support for "at least once every 12 days" that exists in the present specification can be found in each of the priority applications, including the earliest priority application, USSN 10/771,552 (see, e.g., paragraph [0078] of the corresponding published application, U.S. 2005/0169921).

Applicants, therefore, respectfully maintain that the presently pending claims are entitled to full priority.

Applicant's reliance on generic disclosure and possibly certain observations in the instant Example of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not provide sufficient written description nor direction and guidance to the "currently claimed limitations".

Note that the explicit recitation of the "limitations" cited above are not readily apparent in the specification as filed.

Note that applicant has amended the claims or added new claims by relying upon certain observations of the eleven patients either in the treatment period or in an extension study under certain distinct dosing variable and time periods to broadly claim new limitations.

Again, the recitation of "comprising administering to a patient with PNH an anti-C5 antibody at least once every 12 days to thereby maintain in the patient a serum complement activation at a level below 20% of the normal serum complement activity", "at least once every 12 days" and "at least 35 μg/mg/ml" are setting forth new limitations based upon certain observations of the Examples, including setting forth limitations with no upper limit that departs from the instant disclosure as filed.

The limited disclosure of "a breakthrough in serum hemolytic activity" does not define nor set forth parameters for the "breakthrough" or provide for the metes and bounds of said "breakthrough".

The specification as filed does not provide sufficient written description of a separate category of patients who has experience complement-related serum hemolytic breakthrough, nor prevent PNH in such patients based upon certain observations in the clinical trials of the Example.

Obviousness is not the standard for the addition new limitations to the disclosure as filed. It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Applicant is claiming a subgenus not supported by the specification as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

It is also true that the written description requirement must still be met in some way so as to "describe the claimed invention so that one skilled in the art can recognize what is claimed.

A patent specification should set forth enough detail to allow a person or ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.

If applicant desires priority for the above-mentioned limitation / current claims prior to filing date of the instant application (12/22/2011);
applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Therefore, this application repeats a substantial portion of prior USSN 12/902,617, filed 10/12/2010 and adds and claims additional disclosure not presented in the prior application, as indicated above.

Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application.

Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Therefore, applicant should amend the first line of the specification to indicate the status of the instant application as a continuation-in-part and file an Application Data Sheet reflecting the proper relationship of the instant application to its priority documents.

A claim as a whole has only one effective filing date.
See Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

Applicant's arguments, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

5. Upon reconsideration of applicant's amended claims, filed 07/07/2014, the previous rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, with respect to the "wherein clauses" have been withdrawn.

6. Claims 131, 133, 136, 138, 141, 143, 146, 149, 152 and 153 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 131-133, 136-138, 141-143 and 146-149 are indefinite in the recitation of "a patient who has experienced complement-related serum hemolytic activity breakthrough" to maintain a serum concentration of eculizumab" because it is not clear as to what are the parameters that define specific patient populations (e.g., to be treated or have already been treated) or defines other characteristics of the claimed methods of elements recited within the claimed methods (e.g., amounts and frequency) of the claimed methods.

Applicant's reliance on generic disclosure and possibly certain observations in the instant Example of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention to the "currently claimed limitations", as argued / asserted by applicant.

Other than relying upon the observations of the clinical and extend trails on pages 56-57 of the specification,
the specification does not define nor set forth the parameters of "a patient who has experienced complement-related serum hemolytic activity breakthrough".

Given the nature of the patients populations being treated (e.g., those with PNH or having symptoms associated with PNH) as well as applicant's reliance upon the Example for this limitation, wherein the Example describes certain patients undergoing treatment in clinical trials and extended trials,
it is unclear or indefinite as to the metes and bound of the claimed patient populations to be treated, that is, the broadest reasonable interpretation of the claims read on treating PNH patients, PNH patients undergoing treatment, who are PNH patients generally and/or patients with symptoms of PNH,
rather than being limited to patients identified as having experienced complement-related serum hemolytic activity breakthrough, as argued / asserted by applicant.

There is no positive step with regard to "identifying".

There is no clear definition, nor parameters as well as explicit recitation of "a patient who has experienced complement-related serum hemolytic activity breakthrough" or even "complement-related serum hemolytic activity breakthrough" in the specification as filed.

It is unclear whether the claimed methods necessarily limits the claimed patient population to a very well defined patient populations or simply states a characterization or conclusion of the results of those steps of patient populations being treated for PNH or having symptoms / manifestations such as hemolytic anemia associated with PNH with anti-C5 antibodies / eculizumab.

The claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

7. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(o). Correction of the following is required:

The recitation of "comprising administering to a patient with PNH an anti-C5 antibody at least once every 12 days to thereby maintain in the patient a serum complement activation at a level below 20% of the normal serum complement activity" and "at least once every 12 days" (e.g., see claims 136 and dependent claims thereof, claims 141 and dependent claims thereof).

Applicant's arguments, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

In contrast to applicant's reliance upon pages 36-37 of the instant specification based upon the specifics of eleven patients participating in therapy and extended trials evaluating the effects of anti-C5 antibody / eculizumab on PNH and symptoms associated therewith,
the claims associated with the preliminary amendment, filed 12/22/2011, including the recitation of "at least once every 12 days" is not readily apparent in the specification as-filed and broadens the instant disclosure as-filed.

Applicant's preliminary amendment, filed 12/22/2011, directs support for the newly added claims to various pages of the specification but does not provide clear direct support for the above-mentioned limitations encompassing administration regimens that includes the recitation of "at least once every 12 days".

The written support of administration regimen that includes the recitation of "at least once every 12 days" is not readily apparent in the specification as-filed.

Applicant's arguments have not been found persuasive.

Applicant is required to amend the specification to provide proper antecedent basis of the current claims in the specification.

Alternatively, applicant is invited to identify the written support for instant claims in the specification as filed.

8. This is a written description rejection, new matter under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Claims 131,133, 136, 138, 141, 143, 146, 147, 152 and 153 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

In contrast to applicant's reliance upon pages 36-37 of the instant specification based upon the specifics of eleven patients participating in therapy and extended trials evaluating the effects of anti-C5 antibody / eculizumab on PNH and symptoms associated therewith,
applicant's reliance on generic disclosure and possibly certain observations in the instant Example of eleven PNH patients who were transfusion-dependent and hemolytic in therapy trials and who were given a particular therapeutic regimen of eculizumab, including excerpt derived from pages 36-37 of the specification does not provide sufficient written description nor direction and guidance to the "currently claimed limitations".

Applicant relies upon the observations of treating a particular patient undergoing a particular dosing regimen on pages 36-37 of the specification to establish a new imitation.

A reduction in the dosing interval from 14 to 12 days was sufficient to maintain levels of eculizumab above 35 µg/ml and effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients.

Note that the explicit recitation of the "limitations" cited above are not readily apparent in the specification as filed.

Note that applicant has amended the claims or added new claims by relying upon certain observations of the eleven patients either in the treatment period or in an extension study under certain distinct dosing variable and time periods to broadly claim new limitations.

The specification as originally filed does not provide support for the invention as now claimed:

"at least 35 μg/ml" and "wherein the patient has experienced complement-related serum hemolytic activity breakthrough".

As indicated previously and consistent with current arguments,

applicant's amendment, filed 12/09/2013, directs support for the newly amended claims to paragraphs [0012], [0081], [0088] and [0093] of the corresponding US2012/0308559 and asserts no new matter has been filed.

Again, as noted previously, the specification as-filed appears to provide written description of "approximately 35 μg/ml to 50 μg/ml" and not an open-ended range of "at least 35 μg/ml" as currently recited (see pages 6-7, overlapping paragraph of the specification' paragraph [0088] of US2012/0308559).

Also, the specification as-filed appears to provide written description of "serum hemolytic activity" and not "complement-related serum hemolytic activity" as currently recited (see pages 6-7, overlapping paragraph of the specification' paragraph [0088] of US2012/0308559).

The newly amended "limitations" have broaden the written description of the Examples relied upon for the claimed "limitations" and, in turn, represent a departure of the specification / application as-filed.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.

See MPEP 714.02 and 2163.06.

Applicant's arguments have not been found persuasive.

9. Claims 131, 133, 136, 138, 146, 147, 149, 152 and 153 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449) (see entire document).

Applicant's arguments in conjunction with certain legal citations, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

In contrast to applicant's arguments that the prior art fails to identify a patient who has experience a complement related serum hemolytic activity breakthrough on a particular dosing regimen schedule, the following is noted.

Under the broadest reasonable interpretation of the claims,
the claims read on treating PNH in patient populations who are patients in need of being treated such as those patients who have a complement-related serum hemolytic activity, who are PNH patients who are undergoing treatment (e.g., treatment with anti-C5 antibody / eculizumab) and/or patients who have been undergoing treatment and who are determined to have complement-related serum hemolytic activity.

Note that the claims do not recite a specific positive step of identifying a patient who has experienced complement-related serum hemolytic activity breakthrough.

Note that PNH is characterized by hemolytic anemia (a decreased number of red blood cells) (e.g., see page 2, paragraph 2 of the specification) and serum hemolytic activity (i.e., the percentage of cell lysis) (e.g., see page 40, paragraph 1 of the specification).

The specification does not define, nor set forth the parameters of "complement-related serum hemolytic activity breakthrough".

Given the description of "breakthrough" on pages 36-37, overlapping paragraphs of the specification,
a breakthrough could read on serum hemolytic activity or serum hemolytic activity that is not consistently block by treatment and/or treatment by eculizumab.

The following is reiterated for applicant's convenience.

Since the public availability of this document is not clear and given that certain claims are subject to a rejection under 35 USC 112, first paragraph, written description / new matter;
this rejection is being applied under 35 U.S.C. § 102(a)(b).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

The prior art dosage administration regimen reads on the claimed methods.

Consistent with the rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, above and with respect to claim construction for prior art rejections, the following is noted.

Although applicant has amended the claims to avoid the previously recited "wherein clauses", the claims do not necessarily recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of or had symptoms / manifestations such as hemolytic anemia of PNH.

Therefore, under the broadest reasonable interpretation of the claims, the recitation a patient who has experienced complement-related serum hemolytic activity breakthrough" is not considered to further limit the method defined by the claim and has been given its proper weight in construing the claims of administering to a patient with PNH and/or manifestations of hemolytic anemia associated with PNH an anti-C5 antibody in an amount and with a frequency effective to maintain a serum concentration of at least 35 μg/ml.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) or effective amounts to maintain serum complement activity at a certain range, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab every other week, the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

Applicant's arguments have not been found persuasive.

10. Claims 131, 133, 136, 138, 146, 147, 149, 152 and 153 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) (see entire document).

Applicant's arguments in conjunction with certain legal citations, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record and that addressed above and reiterated herein.

In contrast to applicant's arguments that the prior art fails to identify a patient who has experience a complement related serum hemolytic activity breakthrough on a particular dosing regimen schedule, the following is noted.

Under the broadest reasonable interpretation of the claims,
the claims read on treating PNH in patient populations who are patients in need of being treated such as those patients who have a complement-related serum hemolytic activity, who are PNH patients who are undergoing treatment (e.g., treatment with anti-C5 antibody / eculizumab) and/or patients who have been undergoing treatment and who are determined to have complement-related serum hemolytic activity.

Note that the claims do not recite a specific positive step of identifying a patient who has experienced complement-related serum hemolytic activity breakthrough.

Note that PNH is characterized by hemolytic anemia (a decreased number of red blood cells) (e.g., see page 2, paragraph 2 of the specification) and serum hemolytic activity (i.e., the percentage of cell lysis) (e.g., see page 40, paragraph 1 of the specification).

The specification does not define, nor set forth the parameters of "complement-related serum hemolytic activity breakthrough".

Given the description of "breakthrough" on pages 36-37, overlapping paragraphs of the specification,
a breakthrough could read on serum hemolytic activity or serum hemolytic activity that is not consistently block by treatment and/or treatment by eculizumab.

The following of record is reiterated for applicant's convenience.

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) doses and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.
The prior art dosage administration regimen reads on the claimed methods

Consistent with the rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, above and with respect to claim construction for prior art rejections,
the following is noted.

Although applicant has amended the claims to avoid the previously recited "wherein clauses",
the claims do not necessarily recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of or had symptoms / manifestations such as hemolytic anemia of PNH.

Therefore, under the broadest reasonable interpretation of the claims,
the recitation a patient who has experienced complement-related serum hemolytic activity breakthrough" is not considered to further limit the method defined by the claim and has been given its proper weight in construing the claims of administering to a patient with PNH and/or manifestations of hemolytic anemia associated with PNH an anti-C5 antibody in an amount and with a frequency effective to maintain a serum concentration of at least 35 μg/ml.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) or effective amounts to maintain serum complement activity at a certain range,
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab every other week,
the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

Applicant's arguments have not been found persuasive.

11. Claims 131, 133, 136, 138, 141, 143, 146, 147, 149, 152 and 153 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) (1449) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (1449) with respect to normal LDH levels.

Applicant's arguments, filed 07/14/2014, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant argues the following.

The pending claims are based, at least in part, on the surprising discovery that for a subset of patients afflicted with PNH, the original, established dosing regimen for eculizumab was insufficient to maintain the blockade of systemic complement activity in these patients. As described in the specification, this "[b]reakthrough of complement blockade resulted in hemoglobinuria, dysphagia, and increased LDH and AST, which correlated with a return of serum hemolytic activity" (page 36 (line 22) through page 37 (line 2)). These breakthrough patients were treated with a new dosing schedule - 900 mg of eculizumab every 12 days. Applicants further appreciated that, in order to more effectively treat PNH patients, eculizumab should be administered to the patients in an amount and with a frequency effective to maintain a serum concentration of eculizumab of at least 35 ug/ml (claim 131) or to maintain the hemolytic activity potential of the patient' s serum at a level below 20% of the hemolytic activity of their serum prior to treatment with eculizumab (claims 136, 141, and 147). The serum hemolytic activity was measured using the total human serum complement hemolytic assay described in the working examples. As

described in the specification, patients whose serum hemolytic activity (as measured using the assay) rose above 20% of the pretreatment serum hemolytic activity experienced breakthrough. In other words, Applicants determined a therapeutic threshold for more effective treatment of PNH using eculizumab.

Applicants also discovered that administration of eculizumab every 12 days, as presently claimed, is the optimum regimen for these particular patients. Specifically, as shown in Figure 4, at day 0, i.e., before administration of eculizumab, pharmacodynamic (PD) levels were consistently high, indicating high levels of complement activity in the patient's serum, which in turn correlates with high levels of hemolysis. PD levels again were measured on days 9, 12 and 13 after administration of eculizumab. The measured PD levels consistently show that no hemolysis was found until day 12. However, on day 13, PD levels surprisingly increased dramatically, thereby indicating an abrupt relapse of hemolytic activity in the PNH patients. In particular, the PD levels as shown in the below excerpt from Figure 4 demonstrate the dramatic increase of serum hemolytic activity from day 12 to day 13:

Day 12	Day 13	Day 14 = day 0
PD 2	56	56

Accordingly, the optimal time window for administration of eculizumab is very narrow and a 12 day dosing interval, as recited in claims 136 and 141, is ideal.

None of the cited references teaches or suggests any particular therapeutic threshold for eculizumab, let alone a serum concentration of eculizumab of at least 35 µg/ml (claim 131) or a level which maintains in the patient a serum complement activity below 20% of the normal serum complement activity (claims 136, 141, and 147). Nor do the cited references teach or suggest any optimal window for administering eculizumab, let alone every 12 days (claims 136 and 141). Therefore, contrary to the Examiner's assertion, one of ordinary skill in the art would not have been motivated to have selected the particularly claimed treatment regimens based on the cited references. Specifically, Hillmen 2002, does not teach PNH breakthrough patients. While Hillmen 2003, mentions breakthrough patients, it does not teach the particularly claimed population of patients, as presently claimed (i. e., who experienced complement-related serum hemolytic activity breakthrough on the particular dosing schedule of eculizumab). Neither Hillmen 2002 nor Hillmen 2003 teach or suggest the 20% serum hemolytic activity threshold, the threshold serum concentration of eculizumab of at least 35 ug/ml, or the particular 12 day dosing schedule, as presently claimed.

Myers et al. and Garba et al., fail to cure the deficiencies of Hillmen 2002 and Hillmen 2002. Specifically neither of these references even discusses breakthrough of PNH patients, let alone a particular serum hemolytic activity threshold (e.g., 20%) or a threshold serum concentration of eculizumab (e.g., at least 35 ug/ml) or the optimal 12 day dosing schedule, as presently claimed.

In sum, none of the cited references would have provided motivation to have selected the presently claimed dosage regimens for preventing PNH breakthrough. Accordingly, the presently claimed methods are patentable over the cited references and Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Also, note the rebuttal above in terms of the broadest reasonable interpretation of the claims as follows.

In contrast to applicant's arguments that the prior art fails to identify a patient who has experience a complement related serum hemolytic activity breakthrough on a particular dosing regimen schedule, the following is noted.

Under the broadest reasonable interpretation of the claims,
the claims read on treating PNH in patient populations who are patients in need of being treated such as those patients who have a complement-related serum hemolytic activity, who are PNH patients who are undergoing treatment (e.g., treatment with anti-C5 antibody / eculizumab) and/or patients who have been undergoing treatment and who are determined to have complement-related serum hemolytic activity.

Note that the claims do not recite a specific positive step of identifying a patient who has experienced complement-related serum hemolytic activity breakthrough.

Note that PNH is characterized by hemolytic anemia (a decreased number of red blood cells) (e.g., see page 2, paragraph 2 of the specification) and serum hemolytic activity (i.e., the percentage of cell lysis) (e.g., see page 40, paragraph 1 of the specification).

The specification does not define, nor set forth the parameters of "complement-related serum hemolytic activity breakthrough".

Given the description of "breakthrough" on pages 36-37, overlapping paragraphs of the specification,
a breakthrough could read on serum hemolytic activity or serum hemolytic activity that is not consistently block by treatment and/or treatment by eculizumab.

Also, note that the prior art teach the same or nearly the same dosages and regimen consistent in the same or nearly the same clinical trials to treat PNH.

While applicant relies upon the instant Example, particularly pages 56-57 of the specification to assert unexpected results,
note that serum hemolytic activity of nine of the eleven patients was completely blocked by eculizumab at equilibrium ranging from approximately 35 µg/ml to 350 µg/ml and
that modifying the dosing interval was sufficient to active equilibrium and blocking hemolytic activity of administering eculizumab,
consistent with the result-effective variables of the prior art rejection relying upon treating the same or nearly the same patients with the same or nearly the same dosing /frequency at the time the invention was made.

The following is reiterated for applicant's convenience.

Hillmen et al. (2003) teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) doses and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

It does not appear that the claim language or limitations result in an unobvious manipulative difference in the method steps when compared to the prior art disclosure of providing 600 mg weekly for four (4) doses and 900 mg every other week of eculizumab a humanized anti-C5 antibody and maintenance doses in the treatment of patients with PNH at the time the invention was made.

Given the prior art teachings of treating with 900 mg of eculizumab every other week, the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days to achieve effective treatment or blocking of hemolytic activity in PNH patients at the time the invention was made.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Further, the mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors) and erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia).

In addition, as to the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations",
treating PNH patients characterized by the criteria of the proportion of type III red blood cells, platelet counts, type III granulocyte clone and serum complement activity are result effective variables of controlling hemolysis and reducing the risk of venous thrombosis with anti-C5 antibodies in the treatment of PNH patient populations who are characterized by intravascular hemolyisis, venous thrombosis and aplastic anemia.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As the nature of the dosing and therapeutic endpoints were known to the ordinary artisan, it would have been obvious to optimize the frequency of anti-C5 antibodies in order to control hemolysis and the risk of venous thrombosis in a variety of PNH patients.

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Applicant's arguments have not been found persuasive.

11. Given copending applications encompassing similar subject matter and the restriction set forth herein, applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

Applicant's submission of an Information Disclosure Statement to make of record related appliations as wella s Office Actions is acknowledged.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
September 8, 2014

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/335,518	12/22/2011	Leonard Bell	ALXN-P07-114	4891

959 7590 02/06/2014

NELSON MULLINS RILEY & SCARBOROUGH LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
02/06/2014	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 13/335,518	Applicant(s) BELL ET AL.	
	Examiner PHILLIP GAMBEL	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *131-151*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *131-151* is/are pending in the application.

5a) Of the above claim(s) *134,135,139,140,144,145,150 and 151* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *131-133,136-138,141-143 and 146-149* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *12/22/2011* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Applicant's amendment, filed 12/09/2013, has been entered.

Claims 131-133, 136, 137, 141, 142 and 146-149 have been amended.

Claims 131-151 are pending.

Claims 1-130 have been canceled previously.

3. Applicant's election of the species (A) (methods of administering anti-C5 antibody, where the claimed do not comprise further administering one or more compounds that increase hematopoiesis in the Response to Restriction Requirement, filed 12/09/2013, is acknowledged.

Applicant's remarks concerning entitlement of claims to additional species upon allowance of a generic linking claim are acknowledged.

Claims 131-133, 136-138, 141-143 and 146-149 are under consideration in the instant application as they read on the elected species.

Claims 134, 135, 139, 140, 144, 145, 150 and 151 have been withdrawn as being drawn to the non-elected species.

4. Priority.

A) Applicant should update the status of the priority documents on page 1 of the specification.

USSN 12/902,617 is now abandoned.

B) Note that not all claims may receive benefit of the priority applications.

The recitation of "comprising administering to a patient with PNH an anti-C5 antibody at least once every 12 days to thereby maintain in the patient a serum complement activation at a level below 20% of the normal serum complement activity" and "at least once every 12 days" (e.g., see claims 136 and dependent claims thereof, claims 141 and dependent claims thereof).

Applicant's preliminary amendment filed 12/22/2011, directs support for the newly added claims to various pages of the specification but does not provide clear direct support for the above-mentioned limitations encompassing administration regimens that includes the recitation of "at least once every 12 days".

The written support of administration regimen that includes the recitation of "at least once every 12 days" is not readily apparent in the specification as-filed.

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

If applicant desires priority for the above-mentioned limitation / current claims prior to filing date of the instant application (12/22/2011);
applicant is invited to point out and provide documentary support for the priority of the instant claims.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Therefore, this application repeats a substantial portion of prior USSN 12/902,617, filed 10/12/2010 and adds and claims additional disclosure not presented in the prior application, as indicated above.
Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application.

Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78.

Therefore, applicant should amend the first line of the specification to indicate the status of the instant application as a continuation-in-part and file an Application Data Sheet reflecting the proper relationship of the instant application to its priority documents.

A claim as a whole has only one effective filing date.
See Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP 608.01.

For example, see page 40 of the specification.

Appropriate corrections are required

6. The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 131-133, 136-138, 141-143 and 146-149 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 131-133, 136-138, 141-143 and 146-149 are indefinite in the recitation of the "wherein clause" in the independent claims ("wherein the patient has experienced complement activity breakthrough on a dosing schedule of eculizumab comprising: (i) 600 mg of eculizumab each week for four weeks; (ii) 900 mg of eculizumab on the fifth week; and thereafter, (iii) 900 mg of eculizumab once every two weeks, and wherein the anti-C5 antibody inhibits the cleavage of complement component C5 into fragments C5a and C5b") because it is not clear as to whether the wherein clause defines positive steps in the claimed methods, defines specific patient populations (e.g., to be treated or have already been treated) or defines other characteristics of the claimed methods of elements recited within the claimed methods (e.g., characteristics of the anti-C5 antibody or eculizumab, capabilities / possibilities of the claimed methods).

Given the recitation of "wherein the patient has experienced complement activity breakthrough on a dosing schedule",

it is unclear whether the "wherein clause" necessarily recites any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of possibly the characterization of the anti-C5 antibodies / eculizumab.

Note that the claim recites "wherein the patient has experienced complement activity breakthrough on a dosing schedule" in the past tense.

It is not clear whether or how the "wherein clause" further limits the claimed methods of treating PNH.

The intent, meaning and the metes and bounds of the claimed methods in view of the "wherein clause" are ambiguous and ill-defined.

The claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

8. The following is a quotation of 35 U.S.C. 112(a):
(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(o). Correction of the following is required:

The recitation of "comprising administering to a patient with PNH an anti-C5 antibody at least once every 12 days to thereby maintain in the patient a serum complement activation at a level below 20% of the normal serum complement activity" and "at least once every 12 days" (e.g., see claims 136 and dependent claims thereof, claims 141 and dependent claims thereof).

Applicant's preliminary amendment filed 12/22/2011, directs support for the newly added claims to various pages of the specification but does not provide clear direct support for the above-mentioned limitations encompassing administration regimens that includes the recitation of "at least once every 12 days".

The written support of administration regimen that includes the recitation of "at least once every 12 days" is not readily apparent in the specification as-filed.

Applicant is required to amend the specification to provide proper antecedent basis of claims 136 and dependent claims thereof and claims 141 and dependent claims thereof in the specification.

Alternatively, applicant is invited to identify the written support for instant claims in the specification as filed.

10. This is a written description rejection, new matter under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph.

Claims 131-133, 136-138, 141-143 and 146-149 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed:

The specification as originally filed does not provide support for the invention as now claimed:
"at least 35 μg/ml" and "wherein the patient has experienced complement activity breakthrough on a dosing schedule".

Applicant's amendment, filed 12/09/2013, directs support for the newly amended claims to paragraphs [0012], [0081], [0088] and [0093] of the corresponding US2012/0308559 and asserts no new matter has been filed.

However the specification as-filed appears to provide written description of "approximately 35 μg/ml to 50 μg/ml" and not an open-ended range of "at least 35 μg/ml" as currently recited (see pages 6-7, overlapping paragraph of the specification' paragraph [0088] of US2012/0308559).

Also, the specification as-filed appears to provide written description of "serum hemolytic activity" and not any/all "complement activity" as currently recited (see pages 6-7, overlapping paragraph of the specification' paragraph [0088] of US2012/0308559).

The newly amended "limitations" have broaden the written description of the Examples relied upon for the claimed "limitations" and, in turn, represent a departure of the specification / application as-filed.

The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above.
See MPEP 714.02 and 2163.06.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(f) or (g) prior art under 35 U.S.C. § 103(a).

13. Claims 131-133, 136-138 and 146-149 are rejected under 35 U.S.C. § 102(a)(b) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449) (see entire document).

Since the public availability of this document is not clear and given that certain claims are subject to a rejection under 35 USC 112, first paragraph, written description / new matter; this rejection is being applied under 35 U.S.C. § 102(a)(b).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

The prior art dosage administration regimen reads on the claimed methods.

Consistent with the rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, above and with respect to claim construction for prior art rejections, the following is noted.

Regarding the interpretive "wherein" clause recited in independent claims, the wherein clause does not necessarily recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of possibly the characterization of the anti-C5 antibodies / eculizumab.

Therefore, the "wherein clause" is not considered to further limit the method defined by the claim and has been given its proper weight in construing the claims of administering to a patient with PNH an anti-C5 antibody in an amount and with a frequency effective to maintain a serum concentration of at least 35 μg/ml.
It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 133, 138, 149) or effective amounts to maintain serum complement activity at a certain range (e.g., see claims 131, 136, 146), it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979).

Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab every other week, the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

14. Claims 131-133, 136-138 and 146-149 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) doses and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

The prior art dosage administration regimen reads on the claimed methods

Consistent with the rejection under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, above and with respect to claim construction for prior art rejections,
the following is noted.

Regarding the interpretive "wherein" clause recited in independent claims,
the wherein clause does not necessarily recite any additional active method steps, but simply states a characterization or conclusion of the results of those steps or the patient populations that have been treated of possibly the characterization of the anti-C5 antibodies / eculizumab.

Therefore, the "wherein clause" is not considered to further limit the method defined by the claim and has been given its proper weight in construing the claims of administering to a patient with PNH an anti-C5 antibody in an amount and with a frequency effective to maintain a serum concentration of at least 35 μg/ml.
It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 133, 138 and 149) or effective amounts to maintain serum complement activity at a certain range (e.g., see claims 131, 136 and 146),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Given the prior art teaching of treating with 900 mg of eculizumab every other week,
the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,

it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

15. Claims 131-133, 136-138, 141-143 and 146-149 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Hillmen (44th ASH Annual Meeting Abstract, Blood, Vol. 100, 2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) (1449) and as evidenced by Garba et al. (Singapore Med. J. 46(11):632-634, 2005) (1449) with respect to normal LDH levels.

Hillmen et al. (2003) teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with 900 mg eculizumab by i.v. infusion every other week for one year an anti-C5 antibody and completing 11 and 16 months of therapy and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH, PNH type III cells and complement activity (see entire document).

Hillmen (2002) teaches that paroxysmal nocturnal hemoglubinuria (PNH) is characterized by intravascular hemolysis and venous thrombosis. Hillmen teaches that the hemolysis is complement-mediated and due to the deficiency of complement regulatory proteins on red cells, particularly the terminal complement inhibitor CD59 (see entire document). Hillmen teaches treating transfusion-dependent PNH patients with 600 mg weekly for four (4) doses and 900 mg every other week of ECULIZUMAB, a humanized anti-C5 antibody (see entire publication). Hillmen teaches that the biological parameters of hemolysis dramatically improved or normalized for all patients within a week of starting therapy. Hillmen further teaches that mean LDH decreased greater than 50%, from 4494 +/- 3380 units/liter to 636 +/- 166 units/liter.

It does not appear that the claim language or limitations result in an unobvious manipulative difference in the method steps when compared to the prior art disclosure of providing 600 mg weekly for four (4) doses and 900 mg every other week of eculizumab a humanized anti-C5 antibody and maintenance doses in the treatment of patients with PNH at the time the invention was made.

Given the prior art teachings of treating with 900 mg of eculizumab every other week,

the prior art teaches effective amounts of treatment with the anti-C5 antibody eculizumab occurs in a dosing regimen at least once every 12 days.

On this record, it is reasonable to conclude that the same PNH patients are being administered the same active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., LDH, complement activity and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Further, the mean level of LDH in the PNH patients was more than 1.5 times the upper limit of a normal LDH level in a person, as evidenced by Garba, who discloses that normal LDH in a person is 247.10 +/- 19.0 units/liter (Abstract in particular). The prior art teaching clearly anticipates the claimed invention.

Regarding the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations" recited in the claims,
it is noted that these limitations do not recite any additional active method steps, but simply states a characterization, an intended result or a conclusion of a process step or patient populations positively recited.

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors) and erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia).

In addition, as to the "frequencies to maintaining serum concentrations of antibodies" and "patient characterizations",
treating PNH patients characterized by the criteria of the proportion of type III red blood cells, platelet counts, type III granulocyte clone and serum complement activity are result effective variables of controlling hemolysis and reducing the risk of venous thrombosis with anti-C5 antibodies in the treatment of PNH patient populations who are characterized by intravascular hemolyisis, venous thrombosis and aplastic anemia.

It is well settled that "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). See also Merck & Co. v. Biocraft Labs. Inc., 874 F.2d 804, 809, 10 USPQ2d 1843, 1847-48 (Fed. Cir. 1989) (determination of suitable dosage amounts in diuretic compositions considered a matter of routine experimentation and therefore obvious).

As the nature of the dosing and therapeutic endpoints were known to the ordinary artisan, it would have been obvious to optimize the frequency of anti-C5 antibodies in order to control hemolysis and the risk of venous thrombosis in a variety of PNH patients.

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select and combine both anti-C5 antibodies and erythropoietin to address and manage the clinical manifestations of PNH over time. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

16. Given copending applications encompassing similar subject matter and the restriction set forth herein, applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/

Primary Examiner
Technology Center 1600
Art Unit 1644
February 4, 2014

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/335,518	12/22/2011	Leonard Bell	ALXN-P07-114	4891

28120 7590 11/07/2013

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/07/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No. 13/335,518	Applicant(s) BELL ET AL.	
	Examiner PHILLIP GAMBEL	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/22/2011, 10/03/2012*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *131-151* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *131-151* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Applicant's amendment, filed 12/22/2011, has been entered.
Claims 1-130 have been canceled.
Claims 131-145 have been added.

Applicant's amendment, filed 10/03/2012, has been entered.
Claim 131 has been amended.
Claims 146-151 have been added.

Claims 131-151 are pending.

3. Applicant is required to elect
A) whether the claimed method do NOT comprise further administering one or more compounds that increase hematopoiesis **OR**
B) whether the claimed method do comprise further administering one or more compounds that increase hematopoiesis.

If applicant elects (B),
then applicant is required to elect a specific one or more compound that increase hematopoiesis from those recited in claims 135, 140 and 145 and more particularly from pages 8-9, 12 and 21-22 of the instant specification.
If applicant elects "one or more compounds", then applicant should clearly define the one or more compounds *(e.g., iron, antithymocyte globulin, cyclosporine, ATG, EPO derivatives, etc.).*

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species of (A) and (B) are distinct because they rely upon different ingredients, methods steps and endpoints.

In turn, the steps rely upon ingredients and compounds that differ in their structures, physicochemical properties and modes of action that differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these ingredients and compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species

These species of compounds are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these compounds do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species (*e.g., A or B and if B, then specify one or more compounds)* for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 131, 136 and 141 are generic, for example.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

4. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

5. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
November 4, 2013

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114	8851

28120 7590 01/27/2014

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

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01/27/2014	ELECTRONIC

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The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No. 13/426,973	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/23/2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *91,98,100-106,110-113 and 115* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *91,98,100-106,110-113 and 115* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *05/14/2013, 10/23/2013, and 01/08/2014*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Claims 91, 98, 100-106, 110-113 and 115 are pending.

3. Applicant's IDSs, filed 05/14/2013, 10/23/2013, and 01/08/2014, are acknowledged. The references on the two IDSs submitted on 05/14/2013 have been striked-through because the references are duplicates of the references listed on the IDS, also filed on 05/14/2013 and previously considered in the prior 05/31/2013 OA.

In view of the Response filed 10/23/2013, the following rejections are maintained.

Response to Arguments

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 91, 98, 100-106, and 112-113 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as is evidenced by the current specification at p. 16, lines 20-25.

Applicant's arguments filed 10/23/2013 were fully considered but were not considered persuasive.

Applicant asserts that the genus of potential dosage forms for eculizumab vary widely in volume, concentration and quantity whereas the instant claims are drawn to a distinct species in which the volume, concentration, and quantity are defined. Applicant further asserts that the examiner has relied nearly exclusively on general knowledge to supply the requisite reasons for the obviousness finding which is, in essence, “convenience” (p. 3 of the response). Applicant further asserts that weekly or biweekly injections of the 154, 210 or 350 mg doses of eculizumab would require the use of multiple 300 mg vials of the instantly claimed formulation or multiple uses of the same via which would be contrary to best practices for safe injection (p. 4 of the response).

This argument was not considered persuasive because while the examiner acknowledges that the ‘245 patent does not recite the specific species claimed by applicant (i.e., a single unit dosage form comprising 300 mg of the anti-C5 antibody, wherein the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody in a volume of 30 mL), the ‘245 patent does teach low doses of eculizumab which is the anti-C5 antibody are therapeutically effective (see p. 5 of the prior OA). The primary art reference Hill also teaches treating the same patient population afflicted with the same disease which is PNH by administering the same anti-C5 antibody, albeit at a higher dose of 600 mg (see p.3 of the prior OA). Those of skill in the art would look to the ‘245 patent for guidance in arriving at lower dosage amounts such as a single unit 300 mg or 10 mg/ml solution wherein the single unit dosage form has a volume of 30 mL as currently recited by applicant because the '245 teaches that lower dosages are also therapeutically effective. Where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454, 456, 105 USPQ 233; 235 (CCPA 1955). See MPE §§2144.05 part IIA. It remains the examiners position that given the teachings of Hill with respect to treating the exact same patient population and the same disease with the same antibody, that arriving at applicants' dosage would have amounted to no more than routine skill in the art in light of the ‘245 patent teachings that eculizumab is also effective at lower concentrations than the 600 mg dose taught by Hill.

In short, applicant is attempting to remove from the public domain methods of treating a specific disease with a specific therapeutic at a specific dose. The only difference between what is now claimed and what was known in the prior art is the single unit dosage size recited in the claims. The same therapeutic (eculizumab) was already known to be effective for treating the same disease (PNH). While the reference by Hillmen discloses methods of administering higher doses than are now claimed, Hill indicates that it would be effective at a range of doses including those now claimed. Applicant is requesting a 20-year right to exclude others from practicing the invention as claimed, on the theory that putting the therapeutic antibody in 30 ml at 10 mg/ml represents a non-obvious contribution over the art. The examiner is of the position that this difference could have easily been arrived at by one of ordinary skill in the art and does not merit a 20-year right to exclude others.

6. Claims 91, 98, 100-106, 110 and 112-113 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as applied to claims 91, 98, 100-106, and 112-113 above, in further view of Garcia et al. (Biologicals (2002) 30, 143-151, of record in the prior 08/20/2012 office action).

As applicant has not made any arguments with respect to the claimed difference that the composition is preservative free as in claim 110, the rejection from the prior OA is maintained.

7. Claims 91, 98, 100-106, 111-113 and 115 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as applied to claims 91,98, 100-106, and 112-113 above, in further view of Rosse et al. (Hematology Am Soc Hematol Edc. Program, 2004, 48-62, of record in the prior 08/20/2012 office action).

As applicant has not made any arguments with respect to the claimed difference concerning the treatment schedule set forth in claim 111, the rejection from the prior OA is maintained.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 17, 2014

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/
Supervisory Patent Examiner, Art Unit 1644
January 21, 2014

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114	8851

28120 7590 05/31/2013

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
05/31/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No. 13/426,973	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *91,98,100-106,110-113 and 115* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *91,98,100-106,110-113 and 115* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/22/2013, 5/14/2013*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 01/22/2013 is acknowledged.

Claims 91, 98, 100-106, 110-113, and 115 are pending and under consideration in the instant examination as they read on a method for treating a patient that (i) is afflicted with a hemolytic disease and (ii) has been vaccinated against Neisseria meningitides, the method comprising administering to the patient an effective amount of an anti-C5 antibody that inhibits cleavage of C5 into C5a and C5b.

2. The examiner acknowledges a conversation with Anita Varma on May 14, 2013 about the possible allowance of claims 91, 98, 100-106, 110 and 112-113. Upon further consideration, however, a new rejection under 35 USC 103 is set forth infra.

3. Applicant's amendment, filed 01/22/2013, has overcome the enablement rejection under 35 USC 112, 1st paragraph and the rejections under 35 USC 102(b) which were of the previous office action mailed on 08/20/2012.

4. Applicant's IDSs, filed on 01/22/2013 and 05/14/2013, are acknowledged and have been considered.

5. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the first paragraph of 35 U.S.C. 112 (pre-AIA). See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, US Provisional Application No. 60/783,070, fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph for one or more claims of this application. In particular, the claims as currently amended recite administration of "a pharmaceutical composition comprising a single unit dosage form ... wherein the single unit dosage form comprises 300 mg of the anti-C5 antibody, wherein the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody, wherein the single unit dosage form has a volume of 30 mL, and wherein the anti-C5 antibody is eculizumab".

Accordingly, the priority date of the instant claims of the current application is considered to be 3/15/2007, the filing date of PCT/US2007/006606.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 91, 98, 100-106, and 112-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as is evidenced by the current specification at p. 16, lines 20-25.

With respect to claims 91, 112-113 and 115, Hillmen teaches a method for treating a patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen further teaches that patients were vaccinated against N. meningitides before treatment (p. 554, lines 2-4).

In a particular embodiment, Hillmen further teaches a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12.

While Hillmen does not specifically recite that the patient afflicted with PNH is "due to a C3b-mediated vascular clearance of PNH erythrocytes through the reticuloendothelial system" as in claim 103, the prior art of treating the same PNH populations with the same composition (anti-C5 antibody) to achieve the same therapeutic effect does not differ from the claimed methods. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. As is further evidenced by Jasinski, moreover, mice studies indicate that the shortened survival of PIGA negative RBCs which causes PNH is mediated by macrophage clearance (clearance of PNH erythrocytes through the reticuloendothelial system) (abstract).

With respect to claim 104, Hillmen teaches that PNH is characterized by hemolytic anemia which renders the patient transfusion dependent and that patients continued to receive transfusion when they had symptoms of anemia (p. 554, 1st¶ under "Investigations" and p. 557, 1st ¶ under "Discussion"). Hillmen further teaches that Type III erythrocytes increased significantly but less than 100% ("from a mean of 36.7 +5.9 to 59.2+8.0 percent") (p. 556, 3rd ¶). Thus the recitation "wherein the patient is anemic and the anemia results at least in part from extravascular hemolysis, and wherein the patient remains anemic following treatment with the anti-C5 antibody" is considered to be inherently taught by Hillmen.

With respect to claim 105, Hillmen teaches that the patient population included men and women of 18 years of age and older who had received a diagnosis of PNH at least 6 months earlier and had received at least 4 red cell transfusions in the preceding 12 months (p. 553, last ¶) and that the percentage of type III erythrocytes increased from a mean of 36.7 +5.9 percent before treatment to 49.2 +8.0 percent at the end of 12 weeks of treatment (the patient is at least 18 years of age and has (i) a PNH type III erythrocyte population of greater than 10%) (p. 556, 2nd ¶).

Hill also teaches treating patients afflicted with PNH by administering eculizumab that specifically targets C5 (anti-C5 antibody), blocking the generation of C5a and the formation of C5b-9 (inhibits cleavage of C5 into fragments C5a and C5b) (abstract; p. 2559, 3rd l[) .

With respect to claim 98, Hill teaches that sustained efficacy and safety of eculizamab in a 1 -year study (anti-C5 antibody is administered to the patient for at least 6 months) (p. 2564, 1st ¶).

With respect to claims 100-102, Hill teaches a hemoglobin level of 10.0 + 0.4 prior to treatment with eculizumab (patient has a hemoglobin level less than 12-14 g/dL if a man or 10-12 g/dL is a woman).

With respect to claim 106, Hill (I) teaches a patient with a history of PNH and aplastic anemia (p. 2563, last I[).

The prior art references differ from the claimed invention in the recitation that the pharmaceutical composition of eculizumab comprises a single unit dosage form of 300 mg comprising 30 mL at 10 mg/mL.

However, the '245 patent teaches antibody 5G1.1, which is the same as eculizumab (see present specification, p. 16 lines 20-25), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human ('245 patent, column 16 lines 10-30). '245 patent also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). '245 teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). The reference teaches sterile formulations are known in the art and can include various pharmaceutical excipients, etc. (col 18 lines 30-45).

However neither Hillmen nor '245 teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen and Hill to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since '245 patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as '245 teaches that the antibody exerts its effect at low doses.

Finally, US 2005/0271660 teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed at pgs. 8-9 of the 01/22/2013 response have been fully considered but were not deemed persuasive.

Applicant asserts that it is well known in the art that the dose of an antibody will vary depending on such factors as the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient and the judgment of the prescribing physician. Applicant further asserts that in order to produce a solution of eculizumab at 10 mg/mL, the inventors had to know that eculizumab was sufficiently soluble for a 10 mg/mL formulation.

This argument was not considered persuasive because the '245 patent teaches that optimal dosing of eculizumab is within the skill of an artisan, particularly a physician, as noted above. In addition, the '660 publication teaches that eculizumab is highly soluble, including at up to 30 mg per ml providing a reasonable expectation of success in making a 10 mg/ml solution of the antibody as is also noted above. Given the additional teachings of the '245 patent that eculizumab is effective at lower doses, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to arrive at the lower single unit dosage form as currently claimed.

8. Claims 91, 98, 100-106, 110 and 112-113 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as applied to claims 91, 98, 100-106, and 112-113 above, in further view of Garcia et al. (Biologicals (2002) 30, 143-151, of record in the prior 08/20/2012 office action).

The prior art teachings of Hillmen, Hill, the '245 patent and the '660 publication are discussed supra.

The reference teachings differ from the claimed invention by not reciting that the pharmaceutical composition is a preservative free formulation as in claim 110.

Garci et al. teaches that the influence of preservatives on the safety and stability of antivenoms may be involved in adverse reactions to antivenoms and is an issue that deserves careful consideration (p. 144, 2nd ¶; p. 149, last ¶).

It would have been obvious to one of ordinary skill in the art at the time applicant's invention was made to provide the composition taught by the primary references in a preservative free formulation. One skilled in the art would be motivated to provide the composition in a preservative free formulation because Garci teaches that the presence

of preservatives can be an important safety issue in that they may lead to adverse reactions when present in antibody compositions such as antivenoms.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 91, 98, 100-106, 111-113 and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9, of record in the prior 08/20/2012 office action) and Hill et al. (Haematologica 2005, of record in the prior 08/20/2012 office action), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002) and Wang (US 2005/0271660), as applied to claims 91, 98, 100-106, and 112-113 above, in further view of Rosse et al. (Hematology Am Soc Hematol Edc. Program, 2004, 48-62, of record in the prior 08/20/2012 office action).

The prior art teachings of Hillmen, Hill, the '245 patent and the '660 publication are discussed supra.

The reference teachings differs from the claimed invention by not reciting the specific treatment schedule set forth in claim 111, "(i) 600 mg of the antibody every 7 ±2 days for the first 4 weeks, (ii) 900 mg of the antibody for the fifth dose 7 ± days after 9i), and (iii) 900 mg of the antibody every 14 ± 2 days thereafter, wherein the administration occurs via 25 to 45 minute intravenous infusion" as in claims 111 and 115.

Nevertheless, it would have been obvious to one of ordinary skill in the art to administer eculizumab according to the claimed recited treatment schedule above because, as stated supra, Hillman teaches a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12.

Rosse also teaches therapeutic treatment of patients with transfusion-dependent paroxysmal nocturnal hemoglobinuria (PNH), by administering to the patients an effective amount of eculizumab, which blocks cleavage of C5 into C5a and C5b (Fig. 4; p. 48, 1 st ¶; p. 53, 2nd column, lines 16-18).

In a specific treatment schedule, Rosse further teaches the exact same treatment regimen where eculizumab (anti-C5 antibody) was given at a dose of 600 mg every week for 4 weeks (600 mg of the antibody every 7 + 2 days for the first 4 weeks) and then at a dose of 900 mg every other week (900 mg of the antibody for the fifth dose 7 + 2 days after and 900 mg of the antibody every 14 + 2 days thereafter). Rosse further

teaches that the drug is given by intravenous infusion over 30 minutes (administration of the antibody to the patient is to occur via 25 to 45 minutes intravenous infusion).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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May 20, 2013

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/
Supervisory Patent Examiner, Art Unit 1644
May 24, 2013

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/426,973	03/22/2012	Leonard Bell	ALXN-P08-114	8851

28120 7590 08/20/2012

ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
ROGERS, JAMES L	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
08/20/2012	ELECTRONIC

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Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	13/426,973	BELL ET AL.	
	Examiner	Art Unit	
	JAMES ROGERS	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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Status

1)☒ Responsive to communication(s) filed on *22 March 2012*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *91-115* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *91-115* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/13/2012*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 91-115 are pending.

2. Claims 91-115 are under consideration in the instant examination as they read on a method for treating a patient that (i) is afflicted with a hemolytic disease and (ii) has been vaccinated against Neisseria meningitides, the method comprising administering to the patient an effective amount of an anti-C5 antibody that inhibits cleavage of C5 into C5a and C5b.

3. Applicant's IDS, filed 8/13/2012, is acknowledged and has been considered.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

5. Claims 91-98 and 106-115 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treatment of paroxysmal nocturnal hemoglobinuria (PNH) by administering to a patient an effective amount of an anti-C5 antibody, does not reasonably provide enablement for a method for treatment of **any hemolytic disease** by administering an anti-C5 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

Claims 91-98 and 106-115 are genus claims which encompass a method for treating a patient who suffers from **any type of hemolytic disease** by administering to the patient an effective amount of an anti-C5 antibody.

While the claims encompass treating a patient suffering from any type of hemolytic disease, the specification discloses a phase III study which evaluated the effect of eculizumab (an anti-C5 antibody) on a cohort of 87 transfusion dependent patients suffering from a single type of hemolytic disease, paroxysmal nocturnal hemoglobinuria (PNH) (p. 2, 1st ¶)

As evidenced by the specification, PNH is a disease which is characterized by hemolysis due to the absence of the GPI-anchored complement regulatory protein CD59 which blocks the formation of the terminal complement complex on the cell surface (p. 2, 2nd ¶). However, other hemolytic diseases do not share the same etiology as PNH. For example, sickle cell disease, which is also characterized by intravascular hemolysis" is caused by a mutation in the β-globin chain of hemoglobin (Kato, Blood Reviews, 2007, p. 38, 1st ¶Fig. 1), and at least one study has not identified any complement abnormality in sickle cell disease (Strauss, Pediat. Res. 11(4), 1997, abstract). In addition, as is stated by Stuart et al., sickle cell disease "is a systemic disease of monumental complexity" (Lancet, 364, 2004, p. 1357, last ¶)

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Because the current claims encompass a large number of different hemolytic diseases, each with potentially different pathophysiological mechanisms, it is not clear that reliance upon a method for treating a single type of hemolytic disease (i.e., PNH) accurately reflects the relative mammal efficacy of the claimed therapeutic strategy for any type of hemolytic disease.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) *the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

7. Claims 113-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosse et al. (hematology Am Soc Hematol Edc. Program, 2004, 48-62).

Rosse teaches therapeutic treatment of patients with transfusion-dependent paroxysmal nocturnal hemoglobinuria (PNH), which is characterized by chronic intravascular hemolysis (method for treating a patient that is afflicted with a hemolytic disease) by administering to the patients an effective amount of eculizumab, which is a humanized chimeric anti-C5 antibody (whole antibody) which blocks cleavage of C5 into C5a and C5b (Fig. 4; p. 48, 1st ¶; p. 53, 2nd column, lines 16-18).

Rosse further teaches that eculizumab (anti-C5 antibody) has a completely nonfunctional Fc domain (p. 53, lines 10-13). Because the constant region is nonfunctional, eculizumab would necessarily have decreased effector function with respect to antibody-dependent cell mediated cytotoxity (ADCC) and complement dependent cytotoxicity (CDC) relative to the corresponding native constant region.

With respect to claim 115, Rosse further teaches that eculizumab (anti-C5 antibody) was given at a dose of 600 mg every week for 4 weeks (600 mg of the antibody every 7 ± 2 days for the first 4 weeks) and then at a dose of 900 mg every other week (900 mg of the antibody for the fifth dose 7 ± 2 days after and 900 mg of the antibody every 14 ± 2 days thereafter). Rosse further teaches that the drug is given by intravenous infusion over 30 minutes (administration of the antibody to the patient is to occur via 25 to 45 minutes intravenous infusion).

The reference teachings anticipate the claimed invention.

8. Claims 91-93, 96-97, 99, 103-105, and 112-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9), as is evidenced by Jasinski (Blood, 103, 2004, 2827-2834) and Rosse et al. (hematology Am Soc Hematol Edc. Program, 2004, 48-62).

With respect to claims 91-93, 99, and 112-115, Hillmen teaches a method for treating a patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) which is a disease characterized by hemolytic anemia (patient afflicted with a hemolytic disease) (p. 557, 2nd ¶) by administering to the patient an effective amount of eculizumab (whole antibody) (p. 552, “methods”) which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen further teaches that patients were vaccinated against *N. meningitides* before treatment (p. 554, lines 2-4). As is evidenced by Rosse, eculizumab (anti-C5 antibody) has a completely nonfunctional Fc domain (p. 53, lines 10-13). Because the constant region is nonfunctional, eculizumab would necessarily have decreased effector function with respect to antibody-dependent cell mediated cytotoxity (ADCC) and complement dependent cytotoxicity (CDC) relative to the corresponding native constant region.

Claim 103 is included because while Hillmen does not specifically recite that the patient afflicted with PNH is “due to a C3b-mediated vascular clearance of PNH erythrocytes through the reticuloendothelial system”, the prior art of treating the same PNH populations with the same composition (anti-C5 antibody) to achieve the same therapeutic effect does not differ from the claimed methods. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or

obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. As is further evidenced by Jasinski, moreover, mice studies indicate that the shortened survival of PIGA negative RBCs which causes PNH is mediated by macrophage clearance (clearance of PNH erythrocytes through the reticuloendothelial system) (abstract).

Claim 104 is included because Hillmen teaches that PNH is characterized by hemolytic anemia which renders the patient transfusion dependent and that patients continued to receive transfusion when they had symptoms of anemia (p. 554, 1st under "Investigations" and p. 557, 1st ¶ under "Discussion"). Hillmen further teaches that Type III erythrocytes increased significantly but less than 100% ("from a mean of 36.7 ±5.9 to 59.2±8.0 percent") (p. 556, 3rd ¶). Thus the recitation "wherein the patient is anemic and the anemia results at least in part from extravascular hemolysis, and wherein the patient remains anemic following treatment with the anti-C5 antibody" is considered to be inherently taught by Hillmen.

Claim 105 is included because Hillmen teaches that the patient population included men and women of 18 years of age and older who had received a diagnosis of PNH at least 6 months earlier and had received at least 4 red cell transfusions in the preceding 12 months (p. 553, last ¶) and that the percentage of type III erythrocytes increased from a mean of 36.7 ±5.9 percent before treatment to 49.2 ±8.0 percent at the end of 12 weeks of treatment (the patient is at least 18 years of age and has (i) a PNH type III erythrocyte population of greater than 10%) (p. 556, 2nd ¶).

The reference teachings anticipate the claimed invention.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 91-93, 96-106 and 111-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosse et al. (Hematology 2004) OR Hill (Blood, 2005, hereafter "Hill (I)") OR Hill et al. ((Haematologica 2005, hereafter "Hill (II)"), each in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), as is evidenced by Jasinski (Blood, 103, 2004, 2827-2834).

With respect to claims 91-93, 99, and 112, Rosse teaches therapeutic treatment of patients with transfusion-dependent paroxysmal nocturnal hemoglobinuria (PNH), which is characterized by chronic intravascular hemolysis (method for treating a patient that is afflicted with a hemolytic disease) by administering to the patients an effective amount of eculizumab, which is a humanized chimeric anti-C5 antibody (whole antibody) which blocks cleavage of C5 into C5a and C5b (Fig. 4; p. 48, 1st ¶; p. 53, 2nd column, lines 16-18).

With respect to claims 96-97, 113 and 114, Rosse further teaches that eculizumab (anti-C5 antibody) has a completely nonfunctional Fc domain (p. 53, lines 10-13). Because the constant region is nonfunctional, eculizumab would necessarily have decreased effector function with respect to antibody-dependent cell mediated cytotoxity (ADCC) and complement dependent cytotoxicity (CDC) relative to the corresponding native constant region.

With respect to claims 111 and 115, Rosse teaches that eculizumab (anti-C5 antibody) was given at a dose of 600 mg every week for 4 weeks (600 mg of the antibody every 7 ± 2 days for the first 4 weeks) and then at a dose of 900 mg every other week (900 mg of the antibody for the fifth dose 7 ± 2 days after and 900 mg of the antibody every 14 ± 2 days thereafter). Rosse further teaches that the drug is given by intravenous infusion over 30 minutes (administration of the antibody to the patient is to occur via 25 to 45 minutes intravenous infusion).

Rosse further teaches that deficiency of complement molecules after C5 remarkably have little phenotype with the exception of an increased risk by encapsulated organisms such as *Neisseria meningitides* (p. 53, lines 1-3).

With respect to claims 91-93, Hill (I) teaches treating patients afflicted with PNH by administering eculizumab which is a humanized monoclonal antibody (whole antibody) that specifically targets C5 (anti-C5 antibody), blocking the generation of C5a and the formation of C5b-9 (inhibits cleavage of C5 into fragments C5a and C5b) (abstract; p. 2559, 3rd ¶)

With respect to claim 98, Hill (I) teaches that sustained efficacy and safety of eculizamab in a 1-year study (anti-C5 antibody is administered to the patient for at least 6 months) (p. 2564, 1st ¶).

With respect to claims 100-102, Hill (I) teaches a hemoglobin level of 10.0 ± 0.4 prior to treatment with eculizumab (patient has a hemoglobin level less than 12-14 g/dL if a man or 10-12 g/dL is a woman).

Claim 104 is included because Hill(I) teaches that the trigger for transfusion before and during the study remained unchanged for each patient and was based on the occurrence of symptoms resulting from anemia, hemolysis, or both (p. 2560 under "clinical investigations"). Thus the recitation "wherein the patient is anemic and the anemia results at least in part from extravascular hemolysis, and wherein the patient remains anemic following treatment with the anti-C5 antibody" is considered to be inherently taught by Hill(I).

With respect to claim 106, Hill (I) teaches a patient with a history of PNH and aplastic anemia (p. 2563, last ¶).

With respect to claim 99, and 101, Hill II teaches treatment of two PNH patients (patient afflicted with a hemolytic disease) by administering eculizumab (anti-C5 antibody) (abstract).

With respect to claim 105, Hill II further teaches that the first 27 year old (patient is at least 18 years of age) during the one year period prior to eculizumab treatment hematological parameters including 47% type III PNH RBCs at baseline (a PNH type II erythrocyte population of greater than 10 %) and that since being diagnosed with PNH in 1998 to treatment in July 2002, the patient was transfusion dependent receiving about 1-2 units/month (received at least 4 transfusion during the 12 months immediately preceding the first treatment with the anti-C5 antibody) (p. e111, 3rd ¶).

Claim 103 is included because while the prior art references do not specifically recite that the patient afflicted with PNH is "due to a C3b-mediated vascular clearance of PNH erythrocytes through the reticuloendothelial system", the prior art of treating the same PNH populations with the same composition (anti-C5 antibody) to achieve the same therapeutic effect does not differ from the claimed methods. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. As is further evidenced by Jasinski, moreover, mice studies indicate that the shortened survival of PIGA negative RBCs which causes PNH is mediated by macrophage clearance (clearance of PNH erythrocytes through the reticuloendothelial system) (abstract).

The prior art references differ from the claimed invention by the recitation that the patient has been vaccinated against Neisseria meningitides.

With respect to claims 91-93, 99, and 112, Hillmen teaches a method for treating a patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) which is a disease characterized by hemolytic anemia (patient afflicted with a hemolytic disease) (p. 557, 2nd ¶) by administering to the patient an effective amount of eculizumab (whole antibody) (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen further teaches that patients were vaccinated against *N. meningitides* before treatment (p. 554, lines 2-4).

It would be obvious and within the skill of one in the art at the time the invention was made to vaccinate against *Neisseria meningitides* as taught by Hillmen in a method of treating PNH by administration of an anti-C5 antibody such as eculizamab as taught by either Rosse, Hill I or Hill II.

One of ordinary skill in the art at the time the invention was made would have been motivated to because eculizamab targets C5 thereby preventing cleavage of C5, and Rosse teaches that deficiency of complement molecules after C5 result in an increased risk by encapsulated organisms such as *Neisseria meningitides* (p. 53, lines 1-3). Thus, vaccination against *N. meningitides* prior to administration of eculizamab (anti-C5 antibody) for the treatment of PNH as taught by Hillmen would be a prudent measure against the risk of infection from *N. meningitides* in any method where an anti-C5 antibody is administered to a patient.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 107-110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosse et al. (Hematology 2004) OR Hill (Blood, 2005, hereafter "Hill (I)") OR Hill et al. ((Haematologica 2005, hereafter "Hill (II)") in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), as applied to claims 91-93, 96-102, 105-106 and 111-115 above, and further in view of Garcia et al. (Biologicals (2002) 30, 143-151).

The teachings of Rosse, Hill(I), Hill(II) and Hillmen have been discussed supra.

Hillmen further teaches a pharmaceutical composition comprising eculizumab (anti-C5 monoclonal antibody) which was administered to patients with PNH at 600 mg every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12.

The prior art references differ from the claimed invention by not expressly reciting a single unit dosage form of 300 mg of the anti-C5 antibody, that the single unit dosage form has a volume of 30 mL and that the single unit dosage form comprises a 10 mg/mL solution of the anti-C5 antibody as in claims 107-109.

The reference teachings also differ from the claimed invention by not reciting that the pharmaceutical composition is a preservative free formulation as in claim 110.

Garci et al. teaches that the influence of preservatives on the safety and stability of antivenoms may be involved in adverse reactions to antivenoms and is an issue that deserves careful consideration (p. 144, 2nd ¶; p. 149, last ¶).

It would have been obvious to one of ordinary skill in the art at the time applicant's invention was made to provide the composition taught by the primary references in a preservative free formulation. One skilled in the art would be motivated to provide the composition in a preservative free formulation because Garci teaches that the presence of preservatives can be an important safety issue in that they may lead to adverse reactions when present in antibody compositions such as antivenoms.

While the prior art references are silent with respect to the limitations that the pharmaceutical composition comprise a single unit dosage form of 300 mg, that the single unit dosage form has a volume of 30 mL (claim 96) and comprises a 10 mg/mL solution of the anti-C5 antibody or C5-binding fragment thereof (claim 97), it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454, 456, 105 USPQ 233; 235 (CCPA 1955). See MPE §§2144.05 part IIA.

In the instant case, given that Hillmen teaches administration of a 600 mg and 900 mg doses which can both be obtained simply by administering two or three separate single unit dosage forms of 300 mg of the instant claimed invention, respectively, the claimed dosage forms are simply a matter of convenience based upon the needs of the patient and involves only routine skill in the art. Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to supply the anti-C5 antibody or C5-binding fragment thereof in a composition comprising 300 mg single unit dosages as well as said dosages in a volume of 30 mL (i.e., 10 mg/mL).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 94-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosse et al. (Hematology 2004) and Hill (Blood, 2005, hereafter "Hill (I)") and Hill et al. ((Haematologica 2005, hereafter "Hill (II)") and Hillmen et al. (N Engl J Med 2004; 350: 552-9), as applied to claims 91-93, 96-102, 105-106 and 111-115 above, and further in view of Kaplan (Curr. Opin. Investig. Drugs, 3(7): 1017-23 (2002), IDS Ref of 5/13/09).

The teachings of Rosse, Hill(I), Hill (II), and Hillmen have been discussed supra.

The prior art references differ from the claimed invention by not reciting that the anti-C5 antibody is a C5-binding fragment such as an scFv as in claim 94 and that the anti-C5 antibody is pexelizumab as in claim 95.

Kaplan teaches the humanized single chain (scFv) anti-C5 monoclonal antibody fragment, pexelizumab (p. 1018, 4th ¶) which was designed to have the advantage of enhanced tissue penetration.

Those of skill in the art would have had reason to use the anti-C5 binding fragment pexelizumab as a substitute for the anti-C5 antibody eculizumab in the administration to patients with PNH as taught by the prior art references because Kaplan teaches that the antibody fragment has the advantage of enhanced tissue penetration. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

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August 15, 2012

/JAMES ROGERS/
Examiner, Art Unit 1644

/Maher M. Haddad/
Primary Examiner, Art Unit 1644

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133485 7590 06/07/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER
ROGERS, JAMES L

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/07/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2	3159

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/07/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

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III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

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(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2	3159

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/07/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
ROGERS, JAMES L	1644	424-133100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
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2. For printing on the patent front page, list
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- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Samsung Bioepis Exhibit No. 1002
Page 334

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2	3159

133485 7590 06/07/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER
ROGERS, JAMES L

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/07/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/148,839	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *5/12/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-3*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5/12/2017
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JAMES ROGERS/ Examiner, Art Unit 1644	/DANIEL E. KOLKER/ Supervisory Patent Examiner, Art Unit 1644

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Applicant's Response, filed 5/12/2017, is acknowledged.

3. Applicant's IDS, filed 5/12/2017, is acknowledged and has been considered.

REASONS FOR ALLOWANCE

4. The following is an Examiner's Statement of Reasons for Allowance:

The claims are drawn to a pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH) where the composition is a sterile, preservative free, 300 mg single use dosage form comprising 30 ml of a 10 mg/ml antibody solution and wherein the antibody comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

Applicant's arguments in the Response of 5/12/2017 to the outstanding Non-final OA of 4/4/2017 which included rejections under 35 USC 102, 35 USC 103 and double patenting rejections as well as a Request for Additional Information Under 37 CFR 1.105 in conjunction with the Declaration Pursuant to 37 CFR 1.132 by Dr. Laural Boone, dated May 11, 2017, is persuasive to overcome all of the rejections for the following reasons:

(a) None of the applied references in the rejections recite using an antibody which comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently recited and one of skill in the art would not have been easily guided to making antibodies with these recited sequences.

(b) Applicant's Response to the Request for Additional Information is considered sufficient and persuasive to conclude that each of the clinical trials conducted by applicant referenced in the Request did not constitute "public use" under 35 USC 102(b) of the claimed invention as they were not accessible to the public. As applicant notes in the response, factors which are used to determine if an invention is accessible to the public are set out by the Federal Circuit in *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.*, (No. 2012-1428, Fed. Cir. May 20, 2013). The factual circumstances cited by applicant considered by the examiner as being most persuasive to negate any determination that the referenced clinical trials constituted "public use" is the use by applicant of confidentiality provisions (see p. 11 of the response for the 16 clinical studies subject to interrogatories A-F of the Request and pp. 2-3 and p.5 (including sample confidentiality provision" of the Declaration) for the studies and the fact that neither doctors nor

patients had any knowledge of the currently claimed sequences of the antibody used in the studies (see p. 5 of the Response). Other factual evidence presented by applicant includes the declaration by Laural S. Boone that strict control over the eculizumab drug was exercised for each clinical trial referenced (see p. 6 of the Declaration).

(c) The Double Patenting rejections have been overcome in light of applicant's approved TDs of 5/12/2017 over the '601, '340, '980, '263, '035, '102, '176 and '235 patents and '290, 464 and 491' Patent Applications.

As to the remaining two applications (15/243,386 and 11/127,438), the '386 application is now abandoned. The '438 application, as noted by applicant in the Response, recites an aerosol composition comprising an antibody which does not include the currently claimed sequences.

Accordingly, claims 1-3, are deemed allowable.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel E. Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 19, 2017

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/
Supervisory Patent Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/148,839	05/06/2016	Leonard BELL	AXJ-114BUSCN2	3159

133485 7590 04/04/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/04/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/148,839	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/15/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-3* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3 are pending and under consideration in the instant examination and read on a compositions which is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml sterile, preservative free solution.

2. Applicant's two IDSs submitted on 2/15/2017 are acknowledged and have been considered.

Priority

3. The examiner acknowledges applicant's corrected priority claim to 3/15/2007. A Corrected Filing Receipt was mailed from the office on 2/21/2017, Reflecting that the earliest priority date for which priority is claimed is 3/15/2007, the filing date of PCT /US2007 /006606.

Claim Rejections - 35 USC§ 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -
(b) the invention was patented or described in a *printed publication in this or* a *foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

5. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9, IDS Ref. of 10/21/2016), as is evidenced by applicant's specification as filed at p.44 and Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996).

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd paragraph).

While Hillmen does not specifically recite that the antibody that binds CS comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID N0:4, the specification as filed at p. 44 discloses that SEQ ID NO: 2 and SEQ ID NO: 4 constitute the H and L chains for "eculizumab" and Hillmen, as noted supra, teaches administering "eculizumab". Hillmen further teaches that "eculizumab" is a recombinant humanized antibody that binds to C5 (p. 553, 3rd ~) and cites Thomas which in turn describes in detail humanization of the clone referred to as "5G1 .1" arrive at the humanized h5G1 .1 which retain both the affinity and blocking functions of the murine 5g1 .1 antibody (abstract). Accordingly and in absence of evidence to the contrary, the currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the Land H chains of "eculizumab" are considered to be

inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Hillmen.

The reference teachings anticipate the claimed invention.

To the extent that applicant will argue that Hillmen names eculizumab but does not teach the precise sequences being currently claimed, please note the following:

35 USC 102(b) states:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States,

While it is true that if the antibody was unknown prior, then a reference which names it does not enable that antibody. See MPEP 2121.02 sections I and II. See also 2121.01, "the stated test is whether a reference contains an 'enabling disclosure' " In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an asserted anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." And ... "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)."

In the instant case, applicant's position is that the mere naming is insufficient. However, the extensive number of both patent literature and NPL documents as well as clinical trials indicates that eculizumab was widespread and well-known. As evidence of the availability and use of eculizumab the examiner refers applicant to the following documents, some of which are part of the Request for additional Information which is also part of this OA:

A) Exhibit A: from clinicalTrials.govClinicaltrials.gov (studies 41-60).

B) Exhibit B: (printout for NCT00005571), in particular page 3 indicating that the trial was ongoing in Bethesda MD, and bottom of page 1 indicating that the drug used was eculizumab.

C) Exhibit C: Clinicaltrials.gov from 6/23/2005 for NCT00098280

D) Exhibit D: Kaplan 2002. Current Opinion in Investigational Drugs 3(7): 10107-1023

E) Exhibit E: Appel et al. Kidney International 2006 70:S45-S50, in particular the paragraph spanning pp. S48-S49.

F) Wang (US 2005/0271660). The reference is a US Patent Application Publication claiming methods of using eculizumab (see claim 7), and is presumed to be enabled.

G) Rother (WO 2005/110481). See for example claims 10, 44-45, 79-80, 123, 125, 130 as well as page 17 line 26 - p. 18 line 12 (noting that the antibody from US Patent 6355245 is now named eculizumab).

H) Rother (US 2009/0028850). This is the publication of the national-stage entry of the '481 application above. Note that the underlying application (11/596382) contains claims to methods of using eculizumab; the office has considered these claims to be enabled. Note that the case recently was decided by the PTAB, and the Board agreed that claims drawn to administering eculizumab were obvious (and thus presumably enabled and operative) as of the filing date of that underlying application, 5/16/2005.

In re Antor Media Corp (CAFC, 2012) states that subject matter disclosed in a reference, whether it is a patent claim, other parts of a patent, or non-patent literature, is presumed to be enabling absent evidence to the contrary. Accordingly, it is the examiner's position that eculizumab was effectively in the public domain.

6. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by **Appel et al.** (Kidney International 70, S45-S50, 2006).

Appel teaches that eculizumab is a humanized monoclonal antibody that prevents the activation of complement component C5. Appel further teaches a randomized trial in 200 patients with eculizumab (S48 and spanning to S49)).

While Appel does not specifically recite that the antibody that binds CS comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID N0:4, in absence of evidence to the contrary, the currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the Land H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Appel.

The reference teachings anticipate the claimed invention.

7. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by **Wang** (US2005/0271660).

Wang teaches an eculizumab that inhibits activation of the complement system (¶s11, 67, 171).

While Wang does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID N0:4, in absence of evidence to the contrary, the currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the Land H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Wang.

The reference teachings anticipate the claimed invention.

Claim Rejections -35 USC§ 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 5S2-9), in view of Evans et al. (US 6,355,245 81, issued 3/12/2002), Wang (US 200S/0271660), as is evidenced by the parent specification of US Patent Application No. 13/426,973 at p. 16, lines 20-25.

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen teaches that patients received infusions 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 (p. 554 under "treatment schedule").

The prior art references differ from the claimed invention in the recitation that the composition is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml sterile, preservative free solution as in claims 1 and 3.

However, Evans teaches antibody 5G1.1, which is the same as eculizumab (see parent specification US Patent Application No. 13/426,973, p. 16 lines 20-25), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human ('245 patent, column 16 lines 10-30). Evans also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a

reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 1 5-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

However neither Hillmen nor '245 teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

Finally, **Wang** teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (1[71) sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 2/15/2107 were fully considered but were not considered persuasive.

Applicant asserts that prior to the 3/15/2007 effective filing date of the present application, the complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public. Applicant asserts that neither Hillmen, Wang nor Evans teach or suggest the currently claimed sequence.

This argument was not considered persuasive for the following reasons because eculizumab is considered to have been in public use or on sale in this country more than one year prior to applicant's invention for the reasons stated supra in the anticipation rejection. Note the preponderance of evidence indicates that the antibody was in public use. The public availability of eculizumab is accordingly considered sufficient to have placed one of skill in the art in possession of applicant's currently claimed sequences for eculizumab.

Request for Additional Information Under 37 CFR 1.105

10. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

11. In response to this requirement, please provide answers to each of the following interrogatories eliciting factual information:

(a) Studies #41-60 in the attached Exhibit A provide prima facie evidence that the methods now claimed were in use in this country more than a year before the document Exhibit A, please answer the following questions:

(i) Which is any of these studies disclose the same antibody sequences for eculizumab encompassed by the claims of the current application (i.e., SEQ ID NO: 2 and SEQ ID: 4)?

(ii) Whether any of the researcher(s) at each of the study sites identified in (i) above was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers for the study(s) identified in (i) above acting solely at the direction of the present inventors?

(b) the study entitled "Safety and Effectiveness of h5G 1.1-mAb for Dermatomyositis" listed on the attached Exhibit B please answer the following questions:

(i) Does this study disclose the same antibody sequences for eculizumab encompassed by the claims of the current application (i.e., SEQ ID NO: 2 and SEQ ID: 4)?

(ii) Whether any of the researcher(s) at the study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (i) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(C) For the study entitled "View of NCT00098280 on 2005_06_23" attached as exhibit C, please answer the following questions:

(i) Does this study disclose the same antibody sequences for eculizumab encompassed

by the claims of the current application (i.e., SEQ ID NO: 2 and SEQ ID: 4)?

(ii) Whether any of the researcher(s) the study sites was under any

confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (i) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(D) Exhibit D: "Eculizumab Alexion –Mariana Kaplan: please answer the following questions with respect to the study (445382) reference on p. 1018, 2nd ¶:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at the study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (i) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(E) Exhibit E (Appel "new approaches to the treatment of glomerular diseases), please answer the following questions with respect to the randomized, placebo-controlled trial in 200 patients referenced at the end of p. S48:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(F) With respect to the IDS submitted on 2/15/2017 which lists NPL literature, please answer the following questions:

(i) Do any of the studies referenced by the NPL documents disclose the same antibody sequences for eculizumab encompassed by the claims of the current application (i.e., SEQ ID NO: 2 and SEQ ID: 4)?

(ii) If the answer to (i) is in the affirmative, were any of the researcher(s) at each of the study sites was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(G) On what date was eculizumab as encompassed by the current claims (i.e., SEQ ID Nos: 2 and 4) first offered for sale?

12. The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *Jn re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *Jn re Goodman,* 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(1)(1) - 706.02(1)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321 (b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/e TD-info-1.jsp.

14. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of **US Patent No. 9,494,601,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '601 claim eculizumab (see claim 10 of the '601) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

15. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of **US Patent No. 8,999,340,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '340 claim eculizumab (see claim 27 of the '340) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

16. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of **US Patent No. 9,409,980,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '980 claim eculizumab (see claim 5 of the '980). The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

17. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 3-14 of **US Patent No. 9,556,263,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '263 claim eculizumab (see claims 2 and 4 of the '263) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml

anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

18. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of **US Patent No. 9,352,035,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '035 claim eculizumab (see claim 1 of the '035) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

19. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of **US Patent No. 9,415,102,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '102 claim eculizumab (see claim 15 of the '102) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

20. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of **US Patent No. 9,409,980,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '980 claim eculizumab (see claim 3 of the '980). The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

21. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4 of **US Patent No. 9,447,176,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '176 claim eculizumab (see claim 1 of the

'176) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

22. Claims 1-3 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5,7, 9-16 of US Patent No. 9,388,235, in view of Hillmen et al. (N Engl J Med 2004; 3SO: S52-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '23S claim eculizumab (see claim 31 of the '235) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

25. Claims 1-3 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 15-17, 58-59 of US Patent Application No: 11/127,438, in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '438 claim eculizumab (while not recited in the claims it is clearly a preferred embodiment; as the claim covers the product eculizumab this rejection is proper). The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-CS antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

25. Claims 1-3 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4 of **US Patent Application No: 15/243,386,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '386 claim eculizumab (see claim 1 of the '386) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5

antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

26. Claims 1-3 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4 of **US Patent Application No: 15/243,290,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '290 claim eculizumab (see claim 1 of the '290) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

27. Claims 1-3 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 94, 97-98 of **US Patent Application No: 15/282,464,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245 81, issued 3/12/2002) and Wang (US 2005/0271660).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '464 claim eculizumab (see claim 94 of the '464) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5 antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

28. Claims 1-3 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 129 – 138 of **US Patent Application No: 15/148,491,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Evans et al. (US 6,355,245, issued 3/12/2002) and Wang (US 2005/0271660).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '491 claim eculizumab (see claim 129 of the '491) The difference between the two applications concern the dosages (i.e., 30 ml of a 10 mg/ml antibody and 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml anti-C5

antibody solution) and the limitation "sterile, preservative free" which would be obvious in view of Hillmen, Evans and Wang as discussed supra.

29. No claim is allowed.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270- 5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 21, 2017

/JAMES ROGERS/

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

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Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
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NOTIFICATION DATE	DELIVERY MODE
08/16/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/148,839	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/6/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *5/6/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claim 1 is pending and under consideration in the instant examination and reads on a compositions which is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml sterile, preservative free solution.

2. Applicant's IDSs, filed on 05/06/2016, are acknowledged and have been considered.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of 35 U.S.C. 112(a) or the first paragraph of 35 U.S.C. 112 (pre-AIA). See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, US Provisional Application No. 60/783,070, fails to provide adequate support or enablement in the manner provided by 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph for one or more claims of this application. In particular, the claim recites a composition which is a 300 mg eculizumab single-use dosage comprising 30 ml of a 10 mg eculizumab/ml steril, preservative free solution.

Accordingly, the priority date of the instant claims of the current application is considered to be **3/15/2007**, the filing date of PCT/US2007/006606.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter

pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002), Wang (US 2005/0271660), as is evidenced by the parent specification of US Patent Application No. 13/426,973 at p. 16, lines 20-25.

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen teaches that patients received infusions 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 (p. 554 under “treatment schedule”).

The prior art references differ from the claimed invention in the recitation that the composition is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml steril, preservative free solution.

However, Evans teaches antibody 5G1.1, which is the same as eculizumab (see parent specification US Patent Application No. 13/426,973, p. 16 lines 20-25), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human (‘245 patent, column 16 lines 10-30). Evans also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

However neither Hillmen nor '245 teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

Finally, Wang teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71) (sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 9, 2016

/JAMES ROGERS/

Examiner, Art Unit 1644

/SHARON WEN/
Primary Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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NOTICE OF ALLOWANCE AND FEE(S) DUE

133485 7590 06/28/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER
ROGERS, JAMES L

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/28/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/28/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

133485 7590 06/28/2017
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/28/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
ROGERS, JAMES L	1644	424-133100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
❑ Issue Fee
❑ Publication Fee (No small entity discount permitted)
❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
❑ A check is enclosed.
❑ Payment by credit card. Form PTO-2038 is attached.
❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
❑ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Samsung Bioepis Exhibit No. 1002
Page 362

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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133485 7590 06/28/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/28/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *6/13/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-10*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JAMES ROGERS/ Examiner, Art Unit 1644	/DANIEL E. KOLKER/ Supervisory Patent Examiner, Art Unit 1644

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Applicant's Amendment/Response, filed 6/13/2017, is acknowledged.

3. Applicant's IDSs, filed 6/13/2017, are acknowledged and have been considered.

REASONS FOR ALLOWANCE

4. The following is an Examiner's Statement of Reasons for Allowance:

The claims are drawn to a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient 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.

Applicant's arguments in the Response of 6/13/2017 to the outstanding Non-final OA of 4/11/2017 which included rejections under 35 USC 102, 35 USC 103 and double patenting rejections as well as a Request for Additional Information Under 37 CFR 1.105 in conjunction with the Declaration Pursuant to 37 CFR 1.132 by Dr. Laural Boone, dated May 11, 2017 (previously submitted in a related case 15/148,839), is persuasive to overcome all of the rejections for the following reasons:

(a) None of the applied references in the rejections recite using an antibody which comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently recited and one of skill in the art would not have been easily guided to making antibodies with these recited sequences.

(b) Applicant's Response to the Request for Additional Information is considered sufficient and persuasive to conclude that each of the clinical trials conducted by applicant referenced in the Request did not constitute "public use" under 35 USC 102(b) of the claimed invention as they were not accessible to the public. As applicant notes in the response, factors which are used to determine if an invention is accessible to the public are set out by the Federal Circuit in *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.*, (No. 2012-1428, Fed. Cir. May 20, 2013). The factual circumstances cited by applicant considered by the examiner as being most persuasive to negate any determination that the referenced clinical trials constituted "public use" is the use by applicant of confidentiality provisions and the fact that neither doctors nor patients had any knowledge of the currently claimed sequences of the antibody used in the studies. Other factual evidence presented by applicant includes the declaration by Laural S. Boone that strict control over the eculizumab drug was exercised for each clinical trial referenced (see p. 6 of the Declaration).

(c) The Double Patenting rejections have been overcome in light of applicant's approved TDs of 6/13/2017 over the '601, '980 and '263 patents.

Accordingly, claims 1-10, are deemed allowable.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel E. Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 21, 2017

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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133485 7590 04/11/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
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Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/11/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/19/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

In view of the Response filed 1/19/2017, the following rejections are maintained.

Response to Arguments

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) *the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

4. Claims 1-2 and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9, IDS Ref. of 10/21/2016), as is evidenced by applicant's specification as filed at p.44 and Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996).

With respect to base claim 1, Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶).

While Hillmen does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO:4, the specification as filed at p. 44 discloses that SEQ ID NO: 2 and SEQ ID NO: 4 constitute the H and L chains for "eculizumab" and Hillmen, as noted supra, teaches administering "eculizumab". Hillmen further teaches that "eculizumab" is a recombinant humanized antibody that binds to C5 (p. 553, 3rd ¶) and cites Thomas which in turn describes in detail humanization of the clone referred to as "5G1.1" arrive at the humanized h5G1.1 which retain both the affinity and blocking functions of the murine 5g1.1 antibody (abstract). Accordingly and in absence of evidence to the contrary, the currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the L and H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Hillmen.

Claim 2 is included because Hillmen teaches that the patients received eculizumab by infusion (p. 554 under “Treatment Schedule").

Claim 7 is included because Hillmen teaches that the patients had previously been diagnosed of aplastic anemia (p. 555, 1st ¶).

Claim 8 is included because Hillmen teaches that patients received infusions of eculizumab (600 mg) every week 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 (p. 552 under “methods” and p. 554 under “treatment schedule”).

Claims 9-10 are included because Hillmen teaches that a decrease in lactate dehydrogenase began after a single dose of eculizumab (immediate decrease occurs within 1 week of administration of the antibody) in all patients and remained within or just above the normal range for the duration of the study (sustained decrease in mean levels of LDH) (p. 555, last ¶).

The reference teachings anticipate the claimed invention.

Applicant’s arguments submitted on 1/19/2017 were fully considered but were not considered persuasive.

Applicant has submitted a declaration by Dr. Leonard Bell that prior to March 15, 2007 effective filing date of the present application, the complete structure of eculizumab was not disclosed in the prior art; nor was it available to the public and that Hillmen fails to teach any part of the sequence of eculizumab (p. 4 of the Response).

This argument was not considered persuasive for the following reasons:

The Bell declaration submitted on 1/19/2017 states that clinical trials were conducted “but only under strict control and conditions of confidentiality”. However the declaration does not provide any evidence that the experiments conducted in the HILLMEN reference were under any condition of confidentiality, nor does it provide any evidence that the authors of that study were working under the direction of the present inventors.

It remains the examiner’s position that there is substantial evidence that eculizumab was in use more than a year before applicant filed for the patent.

As noted supra, 35 USC 102(b) states:

A person shall be entitled to a patent unless —

(b) the invention was patented or described in a printed publication in this or a foreign country **or in public use or on sale in this country**, more than one year prior to the date of the application for patent in the United States,

While it is true that if the antibody was unknown prior, then a reference which names it does not enable that antibody. See MPEP 2121.02 sections I and II. See also 2121.01, "the stated test is whether a reference contains an 'enabling disclosure'... ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an asserted anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." And … "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)."

In the instant case, applicant's position is that the mere naming is insufficient. However, the extensive number of both patent literature and NPL documents as well as clinical trials indicates that eculizumab was widespread and well-known. As evidence of the availability and use of eculizumab the examiner refers applicant to the following documents, some of which (exhibits A-E) are part of the Request for additional Information which is also part of this OA:

A) **Exhibit A:** from ClinicalTrails.gov (studies 41-60).
B) **Exhibit B:** Clinicaltrials.gov from 6/23/2005 for NCT00098280
C) **Exhibit C:** "Safety and Effectiveness of h5G1.1-mAb for dermatomyositis" clinical Trials.gov identifier NCT00005571
D) **Exhibit D:** Kaplan 2002. Current Opinion in Investigational Drugs 3(7):1017-1023.
E) **Exhibit E:** Appel et al. Kidney International 2006 70:S45-S50, in particular the paragraph spanning pp. S48-S49 (http://www.kidney-international.org/article/S0085-2538(15)51857-7/pdf)
F) **Wang (US 2005/0271660)**, which references pexelizumab or eculizumab as an antibody therapeutic (¶s4 , claim 7) and is presumed to be enabled.
G) **Rother (WO 2005/110481)**. See for example claims 10, 44-45, 79-80, 123, 125, 130 as well as page 17 line 26 – p. 18 line 12 (noting that the antibody from US Patent 6355245 is now named eculizumab).
H) **Rother (US 2009/0028850)**. This is the publication of the national-stage entry of the '481 application above. Note that the underlying application (11/596382) contains claims to methods of using eculizumab; the office has considered these claims to be enabled. Note that the case recently was decided by the PTAB, and the Board agreed that claims drawn to administering eculizumab were obvious (and thus presumably enabled and operative) as of the filing date of that underlying application, 5/16/2005.

In re Antor Media Corp (CAFC, 2012) states that subject matter disclosed in a reference, whether it is a patent claim, other parts of a patent, or non-patent literature, is presumed to be enabling absent evidence to the contrary.

It remains the examiner's position that eculizumab was effectively in the public domain over a year prior to the filing of this application, as indicated by the preponderance of evidence.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996) and of Evans et al. (US 6,355,245 B1, issued 3/12/2002), and further in view of Wang (US 2005/0271660).

The prior art teachings of Hillmen are discussed supra. The prior art teachings of Thomas and the '245 patent were discussed in the prior OA.

The prior art teachings differ from the claimed invention in the recitation that the antibody is administered at a dosage level of between 5-50 mg/kg per patient per treatment as in claim 3, that the composition is in a single unit dosage form as in claim 4 and that the single unit dosage form is a 300 mg single unit dosage form as in claim 5.

The prior art teachings further differ in the recitation that the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution as in claim 6.

The ‘245 patent further teaches antibody 5G1.1, which is the same as eculizumab (discussion supra), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human (‘245 patent, column 16 lines 10-30). Evans (the ‘245 patent) also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

Neither Hillmen nor the ‘245 patent (Evans) teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

It is further noted, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). “Only if the ‘results of optimizing a variable’ are ‘unexpectedly good’ can a patent be obtained for the claimed critical range.” In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). “[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.” In re Boesch, 617 F.2d 272, 276 (CCPA 1980).

Finally, **Wang** teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71) (sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 1/19/2017 were fully considered but were not considered persuasive.

Applicant's arguments mirror applicant's arguments with respect to the 35 USC 102(b) rejection over Hillmen supra. Accordingly, the examiner refers applicant to the examiner's rebuttal supra.

Request for Additional Information Under 37 CFR 1.105

7. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

8. In response to this requirement, please provide answers to each of the following interrogatories eliciting factual information:

(A) **Studies #41-60 in the attached Exhibit A** provide prima facie evidence that the methods now claimed were in use in this country more than a year before the application for patent was filed. Therefore for each of studies #41-60 in the attached document Exhibit A, please answer the following questions:

(i) Whether any of the trials (#s41-60) used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at each of the study sites identified in (i) above for which the same sequences currently claimed was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers for those trials identified in (i) acting solely at the direction of the present inventors?

(B) **the study entitled "Safety and Effectiveness of h5G1.1-mAb for Dermatomyositis" listed on the attached Exhibit B** please answer the following questions:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at each the study sites was under any confidentiality agreement?

(ii) What was the nature of such confidentiality agreement in (ii) above?

(iii) Were the researchers acting solely at the direction of the present inventors?

(C) **Exhibit D: "Eculizumab Alexion –Mariana Kaplan**: please answer the following questions with respect to the study (445382) reference on p. 1018, 2nd ¶:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at the study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (i) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(D) **Exhibit E (Appel "new approaches to the treatment of glomerular diseases)**, please answer the following questions with respect to the randomized, placebo-controlled trial in 200 patients referenced at the end of p. S48:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(E) On what date was eculizumab as encompassed by the currently claimed invention (i.e., H chains SEQ ID NO: 2 and L chain SEQ ID NO: 4) first offered for sale?

9. The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *Jn re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *Jn re Goodman,* 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(1)(1) - 706.02(1)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321 (b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

11. Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of **US Patent No. 9,494,601,** view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Thomas et al. (Molecular Immunology, 33 (17/18), pp. 1389-1401), Evans et al. (US 6,355,245 81, issued 3/12/2002) and Wang (US 2005/0271660)**.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '601 claim eculizumab (see claim 10 of the '601).

The differences between the claimed invention and ‘601 (treatment of a patient suffering from PNH and recited doses) would be obvious in view of Hillmen, Thomas, Evan and Wang as discussed supra.

12. Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of **US Patent No. 9,409,980,** in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Thomas et al. (Molecular Immunology, 33 (17/18), pp. 1389-1401), Evans et al. (US 6,355,245 81, issued 3/12/2002) and Wang (US 2005/0271660).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '980 claim eculizumab (see claim 5 of the '980).

The differences between the claimed invention and ‘980 (treatment of a patient suffering from PNH and recited doses) would be obvious in view of Hillmen, Thomas, Evan and Wang as discussed supra.

13. Claims 1-10 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of **US Patent No. 9,556,263,** view of Hillmen et al. (N Engl J Med 2004; 350: 552-9), Thomas et al. (Molecular Immunology, 33 (17/18), pp. 1389-1401), Evans et al. (US 6,355,245 81, issued 3/12/2002) and Wang (US 2005/0271660)**.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '263 claim eculizumab (see claims 2 and 4 of the '263).

The differences between the claimed invention and ‘263 (treatment of a patient suffering from PNH and recited doses) would be obvious in view of Hillmen, Thomas, Evan and Wang as discussed supra.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 30, 2017 /JAMES ROGERS/
Art Unit 1644

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 12/22/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
12/22/2016	ELECTRONIC

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chris.schlauch@nelsonmullins.com
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	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

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Status

1)☒ Responsive to communication(s) filed on *11/4/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

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Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

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Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/21/2016, 11/4/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

3. Applicant's IDSs filed on 10/21/2016 and 11/4/2016 are acknowledged and have been considered.

4. Applicant has overcome the ODP rejections which were in the prior OA mailed on 11/4/2016 given applicant's approved TD over US Patent Application 15/148,839 (Note: applicant's has also filed an approved TD over US Patent application 15/284,015).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) *the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

6. Claims 1-2 and 7-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9, IDS Ref. of 10/21/2016), as is evidenced by applicant's specification as filed at p.44 and Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996).

With respect to base claim 1, Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶).

While Hillmen does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO:4, the specification as filed at p. 44 discloses that SEQ ID NO: 2 and SEQ ID NO: 4 constitute the H and L chains for "eculizumab" and Hillmen, as noted supra, teaches administering "eculizumab". Hillmen further teaches that "eculizumab" is a recombinant humanized antibody that binds to C5 (p. 553, 3rd ¶) and cites Thomas which in turn describes in detail humanization of the clone referred to as "5G1.1" arrive at the humanized h5G1.1 which retain both the affinity and blocking functions of the murine 5g1.1 antibody (abstract). Accordingly and in absence of evidence to the contrary, the

currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the L and H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Hillmen.

Claim 2 is included because Hillmen teaches that the patients received eculizumab by infusion (p. 554 under "Treatment Schedule").

Claim 7 is included because Hillmen teaches that the patients had previously been diagnosed of aplastic anemia (p. 555, 1st ¶).

Claim 8 is included because Hillmen teaches that patients received infusions of eculizumab (600 mg) every week 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 (p. 552 under "methods" and p. 554 under "treatment schedule").

Claims 9-10 are included because Hillmen teaches that a decrease in lactate dehydrogenase began after a single dose of eculizumab (immediate decrease occurs within 1 week of administration of the antibody) in all patients and remained within or just above the normal range for the duration of the study (sustained decrease in mean levels of LDH) (p. 555, last ¶).

The reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained even though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-4 and 7-10 rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996) and of Evans et al. (US 6,355,245 B1, issued 3/12/2002).

The prior art teachings of Hillmen are discussed above.

To the extent that applicant intends to argue that Hillmen on its own does not constitute an enabling references because it does not explicitly place the eculizumab antibody in the public domain by not enabling one of ordinary skill in the art to make and use eculizumab comprising SEQ ID NO: 2 and 4 as currently claimed, Hillmen discloses (p. 553, 3rd¶) that eculizumab is a recombinant human antibody that binds to C5, and refers to reference number 15 (Thomas) as disclosing more information about eculizumab. Thomas in turn discloses that eculizumab is the humanized antibody h5G1.1. The '245 patent further discloses and claims the antibody made by hybridoma 5G1.1 (see for example claims 20-21) and thus places the 5G1.1 hybridoma and the antibody produced by it into the public domain.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to follow the teachings of Hillmen, Thomas and the ‘245 patent to arrive at the currently claimed invention. Hillmen and Thomas collectively teach that the 5G1.1 antibody can be used to treat PNH, and the ‘245 patent provides the public with this antibody. Thus one of ordinary skill in the art would have found it obvious to use this publicly available antibody in the methods disclosed by Hillmen.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen et al. (N Engl J Med 2004; 350: 552-9), in view of Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996) and of Evans et al. (US 6,355,245 B1, issued 3/12/2002), as applied to claims 1-4 and 7-10 above, and further in view of Wang (US 2005/0271660).

The prior art teachings of Hillmen, Thomas and the ‘245 patent are discussed supra.

The prior art teachings differ from the claimed invention in the recitation that the antibody is administered at a dosage level of between 5-50 mg/kg per patient per

treatment as in claim 3, that the composition is in a single unit dosage form as in claim 4 and that the single unit dosage form is a 300 mg single unit dosage form as in claim 5.

The prior art teachings further differ in the recitation that the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution as in claim 6.

The ‘245 patent further teaches antibody 5G1.1, which is the same as eculizumab (discussion supra), is effective at doses of 2.2, 3, or 5 mg per kg body weight; this corresponds to 154, 210, or 350 mg of antibody for a 70kg adult human (‘245 patent, column 16 lines 10-30). Evans (the ‘245 patent) also teaches that eculizumab is therapeutically effective when as little as 210 mg are present (column 16 lines 10-15). Evans teaches that the antibodies are particularly advantageous in that they are highly active even when administered in low doses (col 8 lines 25-32), providing a reasonable expectation of success in treating PHN with a dose less than what was disclosed by Hillmen. The reference teaches that it is within the skill of an artisan, particularly a physician, to determine the optimal dose (column 18 lines 15-30). Evans teaches formulations of the anti-C5 antibodies may be formulated in a pharmaceutically effective carrier such saline, which is considered to be a "preservative free solution". (col 18 lines 30-45).

Neither Hillmen nor the ‘245 patent (Evans) teaches a 300 mg single unit dosage as recited in the claims.

Nevertheless it would have been obvious to one of ordinary skill in the art to modify the teachings of Hillmen to administer 300 mg single unit dosages. Hillmen teaches that both 600 and 900 mg dosages can be used, and since Evans patent teaches that 210 or 350 mg of antibody would be expected to be therapeutically effective, arriving at the 300 mg dosage would be routine, convenient and obvious. One of ordinary skill in the art would have a reasonable expectation of success, as Evans teaches that the antibody exerts its effect at low doses.

It is further noted, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). “Only if the ‘results of optimizing a variable’ are ‘unexpectedly good’ can a patent be obtained for the claimed critical range.” In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). “[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.” In re Boesch, 617 F.2d 272, 276 (CCPA 1980).

Finally, **Wang** teaches that eculizumab is highly soluble, including at up to 30 mg per ml (paragraph 0171, Figure 10). Wang further teaches that pharmaceutically acceptable carriers include pyrogen-free water may be used in formulation of the antibody (¶71)

(sterile, preservative free solution). Therefore the artisan of ordinary skill would have had a reasonable expectation of success in making a 10 mg / ml solution of the antibody sterile, preservative free solution.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

December 5, 2016 /JAMES ROGERS/
Art Unit 1644

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

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15/260,888	09/09/2016	Leonard BELL	AXJ-114BUSCN3	2558

133485 7590 10/27/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
10/27/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/260,888	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/9/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/21/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

4. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 15/148,839, in view of Hillmen et al. (N Engl J Med 2004; 350: 552-9).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '839 application claims a pharmaceutical composition for use in treating a patient afflicted with PNH. The specification of the '516 at ¶158 defines eculizumab as having a heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4 which is 100% identical in amino acid sequence to the currently claimed SEQ IDs NO: 2 and 4. (see alignment below).

SEQ ID NO: 2 alignment

```
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60

Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120

Qy        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180

Qy        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Qy        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300

Qy        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360

Qy        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420

Qy        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
              ||||||||||||||||||||||||||||
Db        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
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SEQ ID NO: 4 alignment

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Qy          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
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                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60

Qy         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120

Qy        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180
                 ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180

Qy        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
                 |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

While the ‘839 does not specifically recite that the patient is anemic or that the antibody is administered to the patient at a dosage level of between 5-50 mg per kg per patient per treatment, in a single unit dosage form of the other various dosage schedules currently recited (e.g, 600 m/900/900 mg), Hillman teaches administration of the anti-C5 antibody eculizumab to an anemic patient (p. 555 under “demographic characteristics” at a dosing schedule of 600 mg 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 (p. 554, under “treatment schedule”). In addition, [I]t is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456 (CCPA 1955); see also In re Peterson, 315 F.3d 1325 (Fed. Cir. 2003). “Only if the ‘results of optimizing a variable’ are ‘unexpectedly good’ can a patent be obtained for the claimed critical range.” In re Geisler, 116 F.3d 1465, 1469 (Fed. Cir. 1997) (quoting In re Antonie, 559 F.2d 618, 620 (CCPA 1977)). “[Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.” In re Boesch, 617 F.2d 272, 276 (CCPA 1980). Given the teachings of Hillman one of skill in the art would regard administration of the anti-C5 antibody recited in '839 as an optimization variable.

5. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 91, 98, 100-106, 110-113, and 115 of copending Application No. 15/148,839.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the ‘973 application claims a method for treating a patient afflicted with PNH by administration of an anti-C5 antibody in single unit dosage form and at a dosing schedule of 600 for the first 4 weeks, 900 mg for the fifth and 900 mg every 14 days thereafter. The specification of the ‘839 (¶s 20, 158) defines an anti-C5 antibody as having a heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4 which is 100% identical in amino acid sequence to the currently claimed SEQ IDs NO: 2 and 4. (see alignment below).

SEQ ID NO: 2 alignment

```
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60

Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120

Qy        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180

Qy        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Qy        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300

Qy        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360

Qy        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420

Qy        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
              ||||||||||||||||||||||||||||
Db        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
```

SEQ ID NO: 4 alignment

```
Qy          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60

Qy         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120

Qy        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180

Qy        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

6. The closest prior art was regarded to be Hillmen et al. (N Engl J Med 2004; 350: 552-9). Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of

eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). Hillmen teaches that patients received infusions of 600 mg 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 (p. 554 under “treatment schedule”). However, Hillmen does not teach the specific anti-C5 antibody recited by the current application. As evidenced by Report from Alexion Pharma K.K. eculizumab has a H and L chain sequence (p. 3 of the Report) which when compared to the H and L chains of the currently recited anti-C5 antibody are not the same (see sequence alignment below ExPASy (userSeq1 is the imputed sequence of eculizumab and userSeq2 is the amino acid sequence for the H chain of the currently recited claims).

```
98.9% identity in 448 residues overlap; Score: 2364.0; Gap frequency: 0.0%

UserSeq1       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
UserSeq2       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
                 ************************************************************

UserSeq1      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
UserSeq2      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
                 ************************************************************

UserSeq1     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
UserSeq2     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
                 ************************************************************

UserSeq1     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
UserSeq2     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
                 ************************************************************

UserSeq1     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
UserSeq2     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHANKTKPREEQFNST
                 ********************************************  ************

UserSeq1     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPEPEQVYTLPPSQEEMT
                 ******************************************   *************

UserSeq1     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                 ************************************************************

UserSeq1     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                 ****************************
```

One of skill in the art would not have been easily guided to using the currently claimed anti-C5 antibody for treating a patient suffering from PNH given the teachings of Hillmen.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 20, 2016

/JAMES ROGERS/

/SHARON WEN/
Primary Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

133485 7590 07/03/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER
ROGERS, JAMES L

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/03/2017

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/284,015	10/03/2016	Leonard BELL	AXJ-114BUSCN4	1040

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	10/03/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

133485 7590 07/03/2017
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/284,015	10/03/2016	Leonard BELL	AXJ-114BUSCN4	1040

TITLE OF INVENTION: TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	10/03/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
ROGERS, JAMES L	1644	424-133100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Samsung Bioepis Exhibit No. 1002
Page 396

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/284,015	10/03/2016	Leonard BELL	AXJ-114BUSCN4	1040

133485 7590 07/03/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/03/2017

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/284,015	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *6/13/2017*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/JAMES ROGERS/ Examiner, Art Unit 1644	/DANIEL E. KOLKER/ Supervisory Patent Examiner, Art Unit 1644

DETAILED ACTION

1. The present application is being examined under the pre-AIA first to invent provisions.

2. Applicant's Amendment/Response, filed 6/13/2017, is acknowledged.

3. Applicant's IDSs, filed 6/13/2017, are acknowledged and have been considered.

REASONS FOR ALLOWANCE

4. The following is an Examiner's Statement of Reasons for Allowance:

The claims are drawn to an antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

Applicant's arguments in the Response of 6/13/2017 to the outstanding Non-final OA of 4/11/2017 which included rejections under 35 USC 102, 35 USC 103 and double patenting rejections as well as a Request for Additional Information Under 37 CFR 1.105 in conjunction with the Declaration Pursuant to 37 CFR 1.132 by Dr. Laural Boone, dated May 11, 2017 (previously submitted in a related case 15/148,839), is persuasive to overcome all of the rejections for the following reasons:

(a) None of the applied references in the rejections recite using an antibody which comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently recited and one of skill in the art would not have been easily guided to making antibodies with these recited sequences.

(b) Applicant's Response to the Request for Additional Information is considered sufficient and persuasive to conclude that each of the clinical trials conducted by applicant referenced in the Request did not constitute "public use" under 35 USC 102(b) of the claimed invention as they were not accessible to the public. As applicant notes in the response, factors which are used to determine if an invention is accessible to the public are set out by the Federal Circuit in *Dey, L.P. v. Sunovion Pharmaceuticals, Inc.*, (No. 2012-1428, Fed. Cir. May 20, 2013). The factual circumstances cited by applicant considered by the examiner as being most persuasive to negate any determination that the referenced clinical trials constituted "public use" is the use by applicant of confidentiality provisions and the fact that neither doctors nor patients had any knowledge of the currently claimed sequences of the antibody used in the studies. Other factual evidence presented by applicant includes the declaration by Laural S. Boone that strict control over the eculizumab drug was exercised for each clinical trial referenced (see p. 6 of the Declaration).

(c) The Double Patenting rejections have been overcome in light of applicant's approved TDs over the 601', 340', 980', 263', 035', 102', 176' and 235' Patents and the '290, 464, 491 applications. With respect to the US Patent Application No: 15/243,386, the patent was abandoned on 5/26/2017. The remaining ODP rejection over US Patent Application No: 11/127,438 is withdrawn in light of applicant's arguments on p. 9 of the Response which were considered persuasive.

Accordingly, claim 1 is deemed allowable.

5. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel E. Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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June 21, 2017

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/284,015	10/03/2016	Leonard BELL	AXJ-114BUSCN4	1040

133485 7590 04/11/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/11/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/284,015	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
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Status

1)☒ Responsive to communication(s) filed on *2/1/2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

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Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

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Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *2/1/2017*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 is pending and under consideration in the instant examination and reads On an antibody that binds C5 comprising a H chain SEQ ID NO: 2 and a L chain SEQ ID NO: 4.

2. Applicant's two IDSs submitted on 2/1/2017 are acknowledged and have been considered.

3. Applicant has overcome the outstanding double patenting rejection from the prior OA in light of applicant's approved TDs over 15/148,839 and 15/260,888, filed 2/1/2017.

Claim Rejections - 35 USC§ 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen et al. (N Engl J Med 2004; 350: 552-9, IDS Ref. of 10/21/2016), as is evidenced by applicant's specification as filed at p.44 and Thomas et al. (Molecular Immunology, 33(17/18), pp.1389-1401, 1996).

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶).

While Hillmen does not specifically recite that the antibody that binds CS comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID N0:4, the specification as filed at p. 44 discloses that SEQ ID NO: 2 and SEQ ID NO: 4 constitute the H and L chains for "eculizumab" and Hillmen, as noted supra, teaches administering "eculizumab". Hillmen further teaches that "eculizumab" is a recombinant humanized antibody that binds to C5 (p. 553, 3rd paragraph) and cites Thomas which in turn describes in detail humanization of the clone referred to as "5G1 .1" arrive at the humanized h5G1 .1 which retain both the affinity and blocking functions of the murine 5g1 .1 antibody (abstract). Accordingly and in absence of evidence to the contrary, the currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the Land H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Hillmen.

The reference teachings anticipate the claimed invention.

To the extent that applicant will argue that Hillmen names eculizumab but does not teach the precise sequences being currently claimed, please note the following:
35 USC 102(b) states:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States,

While it is true that if the antibody was unknown prior, then a reference which names it does not enable that antibody. See MPEP 2121.02 sections I and II. See also 2121.01, "the stated test is whether a reference contains an 'enabling disclosure' .... " In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an asserted anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." And ... "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985)."

In the instant case, applicant's position is that the mere naming is insufficient. However, the extensive number of both patent literature and NPL documents as well as clinical trials indicates that eculizumab was widespread and well-known. As evidence of the availability and use of eculizumab the examiner refers applicant to the following documents, some of which are part of the Request for additional Information which is also part of this OA:

A) Exhibit A: from clinicalTrials.govClinicaltrials.gov (studies 41-60).

B) Exhibit B: (printout for NCT00005571), in particular page 3 indicating that the trial was ongoing in Bethesda MD, and bottom of page 1 indicating that the drug used was eculizumab.

C) Exhibit C: Clinicaltrials.gov from 6/23/2005 for NCT00098280

D) Exhibit D: Kaplan 2002. Current opinion in Investigation Drugs 3(7): 1017-1023

E) Exhibit E: Appel et al. Kidney International 2006 70:S45-S50, in particular the paragraph spanning pp. S48-S49.

F) Wang (US 2005/0271660). The reference is a US Patent Application Publication claiming methods of using eculizumab (see claim 7), and is presumed to be enabled.

G) Rother (WO 2005/110481). See for example claims 10, 44-45, 79-80, 123, 125, 130 as well as page 17 line 26 - p. 18 line 12 (noting that the antibody from US Patent 6355245 is now named eculizumab).

H) Rother (US 2009/0028850). This is the publication of the national-stage entry of the '481 application above. Note that the underlying application (11/596382) contains claims to methods of using eculizumab; the office has considered these claims to be enabled. Note that the case recently was decided by the PTAB, and the Board agreed that claims drawn to administering eculizumab were obvious (and thus presumably enabled and operative) as of the filing date of that underlying application, 5/16/2005.

In re Antor Media Corp (CAFC, 2012) states that subject matter disclosed in a reference, whether it is a patent claim, other parts of a patent, or non-patent literature, is presumed to be enabling absent evidence to the contrary.

Accordingly, it is the examiner's position that eculizumab was effectively in the public domain.

6. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by **Appel et al.** (Kidney International 70, S45-S50, 2006).

Appel teaches that eculizumab is a humanized monoclonal antibody that prevents the activation of complement component C5. Appel further teaches a randomized trial in 200 patients with eculizumab (S48 and spanning to S49)).

While Appel does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID N0:4, in absence of evidence to the contrary, the currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the Land H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Appel.

The reference teachings anticipate the claimed invention.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by **Wang** (US2005/0271660).

Wang teaches an eculizumab that inhibits activation of the complement system (¶s11, 67, 171).

While Wang does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID N0:4, in absence of evidence to the contrary, the currently recited SEQ ID NO: 2 and SEQ ID NO: 4 which constitute the Land H chains of "eculizumab" are considered to be inherent properties of the "eculizumab" anti-C5 humanized monoclonal antibody taught by Wang.

The reference teachings anticipate the claimed invention. Note that the reference claims eculizumab.

Request for Additional Information Under 37 CFR 1.105

8. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.

9. In response to this requirement, please provide answers to each of the following interrogatories eliciting factual information:

(a) Studies #41-60 in the attached Exhibit A provide prima facie evidence that the methods now claimed were in use in this country more than a year before the document Exhibit A, please answer the following questions:

(i) Which is any of these studies disclose the same antibody sequences for eculizumab encompassed by the claims of the current application (i.e., SEQ ID NO: 2 and SEQ ID NO: 4)?

(ii) Whether any of the researcher(s) at each of the study sites for which eculizumab covered by the current claims in (i) above was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers in (i) above acting solely at the direction of the present inventors?

(b) the study entitled "Safety and Effectiveness of h5G 1.1-mAb for Dermatomyositis" listed on the **attached Exhibit B** please answer the following questions:

(i) Does this study disclose the same antibody sequences for eculizumab encompassed by the claims of the current application (i.e., SEQ ID NO: 2 and SEQ ID: 4)?

(ii) Whether any of the researcher(s) at the study site for any study identified in (i) above was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers for any study identified in (i) above acting solely at the direction of the present inventors?

(C) For the study entitled "View of NCT00098280 on 2005_06_23" attached as exhibit C, please answer the following questions:

(i) Does this study disclose the same antibody sequences for eculizumab encompassed by the claims of the current application (i.e., SEQ ID NO: 2 and SEQ ID: 4)?

(ii) Whether any of the researcher(s) the study site identified in (i) above was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers for any study identified in (i) above acting solely at the direction of the present inventors?

(D) Exhibit D: "Eculizumab Alexion –Mariana Kaplan: please answer the following questions with respect to the study (445382) reference on p. 1018, 2nd ¶:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at the study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (i) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(E) Exhibit E (Appel "new approaches to the treatment of glomerular diseases), please answer the following questions with respect to the randomized, placebo-controlled trial in 200 patients referenced at the end of p. S48:

(i) Whether the trial used the same sequences for eculizumab as currently claimed (i.e., SEQ ID 2 and 4).

(ii) Whether any of the researcher(s) at study site was under any confidentiality agreement?

(iii) What was the nature of such confidentiality agreement in (ii) above?

(iv) Were the researchers acting solely at the direction of the present inventors?

(F) On what date was eculizumab which is encompassed by the current claimed (i.e., SEQ ID NOs: 2 and 4) first offered for sale?

10. The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *Jn re Berg,* 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *Jn re Goodman,* 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(1)(1) - 706.02(1)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321 (b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/e TD-info-1.jsp.

12. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 7, 9, and 10 of **US Patent No. 9,494,601.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '601 claim eculizumab (see claim 10 of the '601)

13. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-18 of **US Patent No. 8,999,340.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '340 claim eculizumab (see claim

9 of the '34 patent0).

14. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of **US Patent No. 9,409,980.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '980 claim eculizumab (see claim 5 of the '980).

15. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of **US Patent No. 9,556,263.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '263 claim eculizumab (see claims 2 and 4 of the '263)

16. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of **US Patent No. 9,352,035.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '035 claim eculizumab (see claim 1 of the '035).

17. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-15 of **US Patent No. 9,415,102.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '102 claim eculizumab (see for example claims 4 and 15 of the '102).

18. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of **US Patent No. 9,409,980**.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '980 claim eculizumab (see claims 3-4 of the '980).

19. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4 of **US Patent No. 9,447,176**.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '176 claim eculizumab (see claim 1 of the '176).

20. Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5, 7, and 9-16 of **US Patent No. 9,388,235**.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '235 claim eculizumab (see claim 5 of the '235).

21. Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 15-17, 59 of **US Patent Application No: 11/127,438**.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '438 claim eculizumab (note the specification of the ‘438 application clearly encompasses eculizumab as one of the preferred antibodies).

22. Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4 of **US Patent Application No: 15/243,386.**

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '386 claim eculizumab (see claim 1 of the '386).

23. Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-4 of **US Patent Application No: 15/243,290.**

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '290 claim eculizumab (see claim 1 of the '290).

24. Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 94 and 97-98 of **US Patent Application No: 15/282,464**.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.
Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '464 claim eculizumab (see claim 94 of the '464)

25. Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 129 – 138 of **US Patent Application No: 15/148,491**.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '491 claim eculizumab (see claim 129 of the '491)

27. No claim is allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Kolker can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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March 21, 2017

/JAMES ROGERS/

/DANIEL E. KOLKER/

Supervisory Patent Examiner, Art Unit 1644

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/284,015	10/03/2016	Leonard BELL	AXJ-114BUSCN4	1040

133485 7590 11/01/2016

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
11/01/2016	ELECTRONIC

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ipboston.docketing@nelsonmullins.com
chris.schlauch@nelsonmullins.com
ipqualityassuranceboston@nelsonmullins.com

Office Action Summary	Application No. 15/284,015	Applicant(s) BELL ET AL.	
	Examiner JAMES ROGERS	Art Unit 1644	AIA (First Inventor to File) Status No

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Status

1)☒ Responsive to communication(s) filed on *10/3/2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

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Disposition of Claims*

5)☒ Claim(s) *1* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1* is/are rejected.

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Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

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Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *10/21/2016*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

1. Claim 1 is pending and under consideration in the instant examination.

2. The present application is being examined under the pre-AIA first to invent provisions.

3. Applicant's IDS's, filed 10/21/2016, are acknowledged and have been considered.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

5. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of copending **Application No. 15/148,839**.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the specification of the '839 at ¶158 defines eculizumab as having a heavy chain SEQ ID NO: 2 and light chain SEQ ID NO: 4 which is 100% identical in amino acid sequence to the currently claimed SEQ IDs NO: 2 and 4. (see alignment below).

SEQ ID NO: 2 alignment

```
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60

Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV 120

Qy        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ 180

Qy        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS 240

Qy        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST 300

Qy        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT 360

Qy        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 420

Qy        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
              ||||||||||||||||||||||||||||
Db        421 GNVFSCSVMHEALHNHYTQKSLSLSLGK 448
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SEQ ID NO: 4 alignment

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Qy          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQ 60
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Qy          61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          61 KPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTF 120

Qy         121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180
               ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         121 GQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN 180

Qy         181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
               |||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         181 SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
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6. The closest prior art was regarded to be Hillmen et al. (N Engl J Med 2004; 350: 552-9). Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patient an effective amount of eculizumab (p. 552, "methods") which specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b (p. 553, 3rd ¶). However, Hillmen does not teach the specific anti-C5 antibody recited by the current application. As evidenced by Report from Alexion Pharma K.K. eculizumab has a H and L chain sequence (p. 3 of the Report) which when compared to the H and L chains of the currently recited anti-C5 antibody are not the same (see sequence alignment below ExPASy (userSeq1 is the imputed sequence of eculizumab and userSeq2 is the amino acid sequence for the H chain of the currently recited claims).

```
98.9% identity in 448 residues overlap; Score: 2364.0; Gap frequency: 0.0%

UserSeq1       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
UserSeq2       1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
                 ************************************************************

UserSeq1      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
UserSeq2      61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
                 ************************************************************

UserSeq1     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
UserSeq2     121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
                 ************************************************************

UserSeq1     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
UserSeq2     181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
                 ************************************************************

UserSeq1     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
UserSeq2     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHANKTKPREEQFNST
                 ********************************************  ************

UserSeq1     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPEPEQVYTLPPSQEEMT
                 ********************************************   *************

UserSeq1     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                 ************************************************************

UserSeq1     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
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UserSeq2      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                  ****************************
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One of skill in the art would not have been easily guided to using the currently claimed anti-C5 antibody for treating a patient suffering from PNH given the teachings of Hillmen.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Rogers whose telephone number is (571) 270-5374. The examiner can normally be reached Monday through Friday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Daniel Kolker** can be reached on (571) 272-3181. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 26, 2016

/JAMES ROGERS/
Patent Examiner, AU 1644

/SHARON WEN/
Primary Examiner, Art Unit 1644

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(71) Applicant *(for all designated States except US)*: **ALEXION PHARMACEUTICALS, INC.** [US/US]; 352 Knotter Drive, Cheshire, CT 06410 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BELL, Leonard** [US/US]; 59 Tumblebrook Road, Woodbridge, CT 06525 (US). **ROTHER, Russell, P.** [US/US]; 25 Blue Trail Drive, Prospect, CT 06712 (US).

(74) Agent: **VARMA, Anita**; Fish & Neave IP Group, Ropes & Gray LLP, One International Place, Boston, MA 02110-2624 (US).

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

(57) Abstract: Eculizumab, a humanized monoclonal antibody against C5 that inhibits terminal complement activation, showed activity in a preliminary 12-week open-label trial in a small cohort of patients with paroxysmal nocturnal hemoglobinuria (PNH). The present study examined whether chronic eculizumab therapy could reduce intravascular hemolysis, stabilize hemoglobin levels, reduce transfusion requirements, and improve quality of life in a double-blind, randomized, placebo-controlled, multi-center global Phase III trial. It has been found that eculizumab stabilized hemoglobin levels, decreased the need for transfusions, and improved quality of life in PNH patients via reduced intravascular hemolysis. Chronic eculizumab treatment appears to be a safe and effective therapy for PNH.

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disease that results from clonal expansion of hematopoietic stem cells with somatic mutations in the X-linked gene called PIG-A.[1,2] Mutations in PIG-A lead to an early block in the synthesis of glycosylphosphatidylinositol (GPI)-anchors, which are required to tether many proteins to the cell surface. Consequently, PNH blood cells have a partial (type II) or complete (type III) deficiency of GPI-anchored proteins.

Intravascular hemolysis is a prominent feature of PNH and a direct result of the absence of the GPI-anchored complement regulatory protein CD59.[3,4] Under normal circumstances, CD59 blocks the formation of the terminal complement complex (also called the membrane attack complex) on the cell surface, thereby preventing erythrocyte lysis and platelet activation.[5-8] Excessive or persistent intravascular hemolysis in PNH patients not only results in anemia (normal ranges of hemoglobin are 14-18 g/dL for men and 12-16 g/dL for women, and persons with lower levels are considered to be anemic), but also hemoglobinuria and clinical sequelae related to the release of the erythrocyte contents into the circulation: fatigue, thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9,10,21,22] Indeed, impaired quality of life in PNH is disproportionate to the degree of anemia. Many PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels. There have been no therapies that effectively reduce intravascular hemolysis and improve the associated clinical morbidities in PNH.

Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5.[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

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SUMMARY

The present pivotal, phase III study, Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH), evaluated the effect of eculizumab on the stabilization of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of 87 transfusion-dependent PNH patients. Measures of intravascular hemolysis and quality of life were also assessed. This is the first placebo controlled study of a PNH patient population to control hemolysis and to differentiate between the effects due to hemolysis and the effects due to anemia.

It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits

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intravascular hemolysis. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method of prolonging the health-adjusted life expectancy of a patient comprising administering to said patient in need thereof a compound which inhibits formation of C5b-9. In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman. In certain embodiments, said patient suffers from paroxysmal nocturnal hemoglobinuria.

In certain aspects, the application provides a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria by administering a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system

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include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

In certain embodiments, said quality of life is measured by a FACIT-Fatigue score. In certain embodiments, the FACIT-Fatigue score increases by at least 3 points. In certain embodiments, the FACIT-Fatigue score increases by ≥ 4 points.

In certain embodiments, said quality of life is measured by an EORTC QLQ-C30 score. In certain embodiments, said EORTC QLQ-C30 score improves by $\geq 10\%$ of the pretreatment score. In certain embodiments, said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia. In certain embodiments, said aspect of quality of life is fatigue.

In certain embodiments, said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. In certain embodiments, said compound is a steroid that suppresses complement.

In certain embodiments, said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors. In certain embodiments, said compound is an antibody or an active antibody fragment. In certain embodiments, said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

In certain embodiments, said antibody or an active antibody fragment thereof binds C5. In certain embodiments, said antibody or active antibody fragment blocks C5 cleavage. In certain embodiments, said antibody or active antibody fragment inhibits the formation of C5b-9. In certain embodiments, said antibody is eculizumab. In certain embodiments, said antibody or active antibody fragment is administered for at least 6

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months. In certain embodiments, said patient has aplastic anemia or myelodysplastic syndrome.

In certain embodiments, said antibody that binds C5 or an active antibody fragment thereof is administered in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the single unit dosage form is lyophilized. In certain embodiments, the single unit dosage form is a sterile solution. In certain embodiments, the single unit dosage form is a preservative free formulation. In certain embodiments, the 300 mg single-use dosage form comprises 30 ml of a 10 mg/ml sterile, preservative free solution.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises an altered constant region, wherein said antibody or antigen-binding fragment exhibits decreased effector function relative to an anti-CDCP1 antibody with a native constant region. In certain embodiments, decreased effector function comprises one or more properties of the following group: a) decreased antibody-dependent cell-mediated cytotoxicity (ADCC), and b) decreased complement dependent cytotoxicity (CDC), compared to an anti-CDCP1 antibody with a native constant region. In certain embodiments, the altered constant region comprises a G2/G4 construct in place of the G1 domain.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 1 and the light chain variable region consists of SEQ ID NO: 3. In certain embodiments, the pharmaceutical composition comprises eculizumab. In certain embodiments, the pharmaceutical composition comprises pexelizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ ID NO: 4.

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In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

In certain embodiments, said health-adjusted life expectancy is measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one day. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least week. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one month. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one year.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the pharmaceutical composition comprises an antibody that binds C5 or an active antibody fragment thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-B show that eculizumab treatment decreases intravascular hemolysis and increases PNH type III erythrocytes. Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels. Figure 1B shows the mean proportion of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients.

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Figure 2 shows the effect of eculizumab treatment on transfusion requirements in PNH patients. This is a Kaplan-Meier plot of time to first transfusion for eculizumab- and placebo-treated patients from baseline through week 26. The P value is from the log rank analysis.

Figure 3 shows the effect of eculizumab on fatigue assessed by the FACIT-Fatigue Instrument. Quality of Life scores were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. Values for change from baseline to 26 weeks represent least-square means. A positive change indicates an improvement and a negative change indicates deterioration in the FACIT-Fatigue measures of quality of life.

DETAILED DESCRIPTION

I. Definitions

The term "derived from" means "obtained from" or "produced by" or "descending from".

The term "genetically altered antibodies" means antibodies wherein the amino acid sequence has been varied from that of a native antibody. Because of the relevance of recombinant DNA techniques to this application, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. The possible variations are many and range from the changing of just one or a few amino acids to the complete redesign of, for example, the variable or constant region. Changes in the constant region will, in general, be made in order to improve or alter characteristics, such as complement fixation, interaction with membranes and other effector functions. Changes in the variable region will be made in order to improve the antigen binding characteristics.

The term "an antigen-binding fragment of an antibody" refers to any portion of an antibody that retains the binding utility to the antigen. An exemplary antigen-binding fragment of an antibody is the heavy chain and/or light chain CDR, or the heavy and/or light chain variable region.

The term "homologous," in the context of two nucleic acids or polypeptides refers to two or more sequences or subsequences that have at least about 85%, at least 90%, at least 95%, or higher nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using the following sequence comparison

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method and/or by visual inspection. In certain embodiments, the "homolog" exists over a region of the sequences that is about 50 residues in length, at least about 100 residues, at least about 150 residues, or over the full length of the two sequences to be compared.

Methods of determining percent identity are known in the art. "Percent (%) sequence identity" with respect to a specified subject sequence, or a specified portion thereof, may be defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul et al., J. Mol. Biol. 215:403-410 (1997); http://blast.wustl.edu/blast/README.htm- l) with search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A "% identity value" is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported.

II. Overview

The present disclosure relates to a method of treating paroxysmal nocturnal hemoglobinuria ("PNH"), more specifically to improving certain aspects of quality of life which are impaired in PNH patients, and other hemolytic diseases in mammals. Specifically, the methods of treating hemolytic diseases, which are described herein, involve using compounds which bind to or otherwise block the generation and/or activity of one or more complement components. The present methods have been found to provide surprising results. For instance, hemolysis rapidly ceases upon administration of the compound which binds to or otherwise blocks the generation and/or activity of one or more complement components, with hemoglobinuria being significantly reduced after treatment. Also, hemolytic patients can be rendered less dependent on transfusions or transfusion-independent for extended periods (twelve months or more), well beyond the 120 day life cycle of red blood cells. In addition, type III red blood cell count can be increased dramatically in the midst of other mechanisms of red blood cell lysis (non-complement mediated and/or earlier complement component mediated e.g., Cb3). Another example of a surprising result is that symptoms resolved, indicating that NO serum levels were increased

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enough even in the presence of other mechanisms of red blood cell lysis. These and other results reported herein are unexpected and could not be predicted from prior treatments of hemolytic diseases.

III The Complement System

The complement system, useful complement inhibitors, and use of these inhibitors to treat PNH and other patients are more fully described in PCT Patent Application PCT/US2005/003225 filed February 3, 2005 and published as International Publication Number WO 2005/074607 A2 on August 18, 2005, the contents of which are incorporated herein by reference in their entirety.

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most

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important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment

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(Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction.

IV Measures of Quality of Life

Various measurements exist to assess quality of life and the effect of medical interventions on quality of life for example the Mini-Mental State Examination (MMSE), the Short Test of Mental Status, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the FACIT questionnaires and subscales including fatigue and anemia, the Likert Scale, and Borg Scale (Tombaugh, et al., J. Am. Geriatr. Soc. 40:922, 1992; Cummings, JAMA. 269(18):2420, 1993; Crum, et al., JAMA. 269(18):2386, 1993; Folstein, et al., J. Psychiat. Res. 12:189,1975; Kokmen, et al., Mayo Clin. Proc. 62:281, 1987; Tang-Wai, et al., Arch. Neurol. 60:1777, 2003; Tamburini, Ann.

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Oncol. 12(Suppl. 3):S7, 2001; Webster et al., Health and Quality of Life Outcomes. 1:79, 2003, www.hqlo.com/content/I/I/79; Grant, et al., Chest. 116:1208, 1999; and www.qolid.org). Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. In certain embodiments, improvement in quality of life is measured by: a) full scales; b) stand-alone subscales; and c) symptom indices.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by a European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. In certain embodiments, the EORTC questionnaire is the QLQ-C30.

In certain embodiments, improvement in quality of life is measured by the health-adjusted life expectancy (HALE) index as described in Wilkins, R. and Adams, OB., Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein MC and Stason WB, N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

In certain embodiments, improvement in quality of life is measured by the following instruments: Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, and Years of healthy life. These measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods improve the quality of life of a patient for at least one day, at least one week, at least two weeks, at least three weeks, at least one

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month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years, or the duration of treatment.

In certain embodiments, the symptoms used to measure quality of life are scaled for intensity. In certain embodiments, the symptoms are scaled for frequency. In certain embodiments, the symptoms are scaled for intensity and frequency.

In certain aspects, the application provides a method for prolonging the health-adjusted life expectancy of a subject comprising administering to the subject a compound which inhibits complement or inhibits formation of C5b-9. The above measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality-adjusted life expectancy due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods prolong the health-adjusted life expectancy in a subject by at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years as measured by the health-adjusted life expectancy (HALE) index as described in Wilkins et al. Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein et al., N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

V Inhibitors of the Complement Cascade

In certain embodiments, any compound which binds to or otherwise blocks the generation and/or activity of one or more complement components can be used in the present methods. In certain embodiments, a complement inhibitor may be a small molecule (up to 6,000 Da in molecular weight), a nucleic acid or nucleic acid analog, a peptidomimetic, or a macromolecule that is not a nucleic acid, a serine protease inhibitor, or a protein. These agents include, but are not limited to, small organic molecules, RNA

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aptamers including ARC187 (which is commercially available from Archemix Corp., Cambridge, Mass.), L-RNA aptamers, Spiegelmers, antisense compounds, molecules which may be utilized in RNA interference (RNAi) such as double stranded RNA including small interfering RNA (siRNA), locked nucleic acid (LNA) inhibitors, peptide nucleic acid (PNA) inhibitors.

In certain embodiments, a complement inhibitor may be a protein or protein fragment. Proteins are known which inhibit the complement cascade, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated neural injury, and C3a and C5a production. In certain embodiments, a complement inhibitor may be naturally occurring or soluble forms of complement inhibitory compounds such as CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

In certain embodiments, a complement inhibitor may be an antibody capable of inhibiting complement, such as an antibody that can block the formation of MAC. For example, an antibody complement inhibitor may include an antibody that binds C5. Such anti-C5 antibodies may directly interact with C5 and/or C5b, so as to inhibit the formation of and/or physiologic function of C5b.

Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

The concentration and/or physiologic activity of C5a and C5b in a body fluid can be measured by methods well known in the art. For C5a such methods include chemotaxis assays, RIAs, or ELISAs (see, for example, Ward and Zvaifler, J Clin Invest. 1971 Mar;50(3):606-16; Wurzner, et al., Complement Inflamm. 8:328-340, 1991). For C5b, hemolytic assays or assays for soluble C5b-9 as discussed herein can be used. Other assays

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known in the art can also be used. Using assays of these or other suitable types, candidate antibodies capable of inhibiting complement such as anti-C5 antibodies, now known or subsequently identified, can be screened in order to 1) identify compounds that are useful in the practice of the application and 2) determine the appropriate dosage levels of such compounds.

An antibody capable of inhibiting complement such as an antibody that binds C5 affecting C5b is preferably used at concentrations providing substantial reduction (i.e., reduction by at least about 25% as compared to that in the absence of the antibody that binds C5) in the C5b levels present in at least one blood-derived fluid of the patient following activation of complement within the fluid. Such concentrations can be conveniently determined by measuring the cell-lysing ability (e.g., hemolytic activity) of complement present in the fluid or the levels of soluble C5b-9 present in the fluid. Accordingly, a specific concentration for an antibody that affects C5b is one that results in a substantial reduction (i.e., a reduction by at least about 25%) in the cell-lysing ability of the complement present in at least one of the patient's blood-derived fluids. Reductions of the cell-lysing ability of complement present in the patient's body fluids can be measured by methods well known in the art such as, for example, by a conventional hemolytic assay such as the hemolysis assay described by Kabat and Mayer (eds), "Experimental Immunochemistry, 2d Edition", 135-240, Springfield, IL, CC Thomas (1961), pages 135-139, or a conventional variation of that assay such as the chicken erythrocyte hemolysis method described below.

Specific antibodies capable of inhibiting complement, such as an antibody that binds C5, are relatively specific and do not block the functions of early complement components. In particular, such specific agents will not substantially impair the opsonization functions associated with complement component C3b, which functions provide a means for clearance of foreign particles and substances from the body.

C3b is generated by the cleavage of C3, which is carried out by classical and/or alternative C3 convertases and results in the generation of both C3a and C3b. Therefore, in order not to impair the opsonization functions associated with C3b, specific antibodies capable of inhibiting complement such as an antibody that binds C5 do not substantially interfere with the cleavage of complement component C3 in a body fluid of the patient (e.g., serum) into C3a and C3b. Such interference with the cleavage of C3 can be detected by measuring body fluid levels of C3a and/or C3b, which are produced in equimolar ratios

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by the actions of the C3 convertases. Such measurements are informative because C3a and C3b levels will be reduced (compared to a matched sample without the antibody capable of inhibiting complement such as an antibody that binds C5) if cleavage is interfered with by an antibody capable of inhibiting complement such as an antibody that binds C5.

In practice, the quantitative measurement of such cleavage is generally more accurate when carried out by the measurement of body fluid C3a levels rather than of body fluid C3b levels, since C3a remains in the fluid phase whereas C3b is rapidly cleared. C3a levels in a body fluid can be measured by methods well known in the art such as, for example, by using a commercially available C3a EIA kit, e.g., that sold by Quidel Corporation, San Diego, Calif., according to the manufacturer's specifications. Particularly specific antibodies capable of inhibiting complement such as an antibody that binds C5 produce essentially no reduction in body fluid C3a levels following complement activation when tested in such assays.

Certain antibodies of the disclosure will prevent the cleavage of C5 to form C5a and C5b, thus preventing the generation of the anaphylatoxic activity associated with C5a and preventing the assembly of the membrane attack complex associated with C5b. As discussed above, in a particular embodiment, these anti-C5 antibodies will not impair the opsonization function associated with the action of C3b.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include a preferred whole antibody (now named eculizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)). Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, single-chain antibody, and Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., Nature 321:522-5 (1986)), chimerized, or deimmunized. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies.

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In specific embodiments, a therapeutic agent of the disclosure comprises an antibody or antibody fragment. Antibodies and fragments thereof may be made by any conventional method, such as those methods described herein. Antibodies are found in multiple forms, e.g., IgA, IgG, IgM, etc. Additionally, antibodies can be engineered in numerous ways. They can be made as single-chain antibodies (including small modular immunopharmaceuticals or SMIPs™), Fab and $F(ab')_2$ fragments, etc. Antibodies can be humanized, chimerized, deimmunized, or fully human. Numerous publications set forth the many types of antibodies and the methods of engineering such antibodies. For example, see U.S. Patent Nos. 6,355,245; 6,180,370; 5,693,762; 6,407,213; 6,548,640; 5,565,332; 5,225,539; 6,103,889; and 5,260,203.

This invention provides fragments of anti-C5 antibodies, which may comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8:1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment of an antibody yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" refers to the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although likely at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a

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free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the scFv to form the desired structure for antigen binding. For a review of scFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

SMIPs are a class of single-chain peptide engineered to include a target binding region, effector domain (CH2 and CH3 domains). *See, e.g.*, U.S. Patent Application Publication No. 20050238646. The target binding region may be derived from the variable region or CDRs of an antibody, e.g., an antibody that binds C5 of the application. Alternatively, the target binding region is derived from a protein that binds C5.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

It is well known that the binding to a molecule (or a pathogen) of antibodies with an Fc region assists in the processing and clearance of the molecule (or pathogen). The Fc portions of antibodies are recognized by specialized receptors expressed by immune effector cells. The Fc portions of IgG1 and IgG3 antibodies are recognized by Fc receptors present on the surface of phagocytic cells such as macrophages and neutrophils, which can thereby bind and engulf the molecules or pathogens coated with antibodies of these isotypes (C. A. Janeway et al., Immunobiology 5th edition, page 147, Garland Publishing (New York, 2001)).

This disclosure also provides monoclonal anti-C5 antibodies. A monoclonal antibody can be obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal

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antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are often synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. Monoclonal antibodies may also be produced in transfected cells, such as CHO cells and NS0 cells. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and does not require production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler et al., Nature 256:495-497 (1975), or may be made by recombinant DNA methods (*see, e.g.*, U.S. Patent Nos. 4,816,567 and 6,331,415). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature 352:624-628 (1991) and Marks et al., J. Mol. Biol. 222:581-597 (1991), for example.

A description of the preparation of a mouse anti-human-C5 monoclonal antibody with specific binding characteristics is presented in U.S. Patent Application Publication No. 20050226870. Wurzner et al., Complement Inflamm. 8:328-340 (1991), describe the preparation of other mouse anti-human-C5 monoclonal antibodies referred to as N19-8 and N20-9.

Other antibodies specifically contemplated are "oligoclonal" antibodies. As used herein, the term "oligoclonal" antibodies" refers to a predetermined mixture of distinct monoclonal antibodies. *See, e.g.*, PCT publication WO 95/20401; U.S. Patent Nos. 5,789,208 and 6,335,163. In one embodiment, oligoclonal antibodies consisting of a predetermined mixture of antibodies against one or more epitopes are generated in a single cell. In other embodiments, oligoclonal antibodies comprise a plurality of heavy chains capable of pairing with a common light chain to generate antibodies with multiple specificities (*e.g.*, PCT publication WO 04/009618). Oligoclonal antibodies are particularly useful when it is desired to target multiple epitopes on a single target molecule (*e.g.*, C5). In view of the assays and epitopes disclosed herein, those skilled in the art can generate or select antibodies or mixtures of antibodies that are applicable for an intended purpose and desired need.

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In certain embodiments that include a humanized and/or chimeric antibody, one or more of the CDRs are derived from an anti-human C5 antibody. In a specific embodiment, all of the CDRs are derived from an anti-human C5 antibody. In another specific embodiment, the CDRs from more than one anti-human C5 antibody are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first anti-human C5 antibody combined with CDR2 and CDR3 from the light chain of a second anti-human C5 antibody, and the CDRs from the heavy chain may be derived from a third anti-human C5 antibody. Further, the framework regions may be derived from one of the same anti-human C5 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. Human or humanized antibodies are specific for administration to human patients.

In certain embodiments, single chain antibodies, and chimeric, humanized or primatized (CDR-grafted) antibodies, as well as chimeric or CDR-grafted single chain antibodies, comprising portions derived from different species, are also encompassed by the present disclosure as antigen-binding fragments of an antibody. The various portions of these antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, nucleic acids encoding a chimeric or humanized chain can be expressed to produce a contiguous protein. See, e.g., U.S. Pat. Nos. 4,816,567 and 6,331,415; U.S. Pat. No. 4,816,397; European Patent No. 0,120,694; WO 86/01533; European Patent No. 0,194,276 B1; U.S. Pat. No. 5,225,539; and European Patent No. 0,239,400 B1. See also, Newman et al., BioTechnology 10:1455-1460 (1992), regarding primatized antibody. See, e.g., Ladner et al., U.S. Pat. No. 4,946,778; and Bird et al., Science 242:423-426 (1988), regarding single chain antibodies.

In addition, functional fragments of antibodies, including fragments of chimeric, humanized, primatized or single chain antibodies, can also be produced. Functional fragments of the subject antibodies retain at least one binding function and/or modulation function of the full-length antibody from which they are derived. Preferred functional fragments retain an antigen-binding function of a corresponding full-length antibody (such as for example, ability of antibody that binds C5 to bind C5).

General methods for the immunization of animals (in this case with C5 and/or C5b, etc.), isolation of antibody producing cells, fusion of such cells with immortal cells (e.g., myeloma cells) to generate hybridomas secreting monoclonal antibodies, screening of

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hybridoma supernatants for reactivity of secreted monoclonal antibodies with a desired antigen (in this case the immunogen or a molecule containing the immunogen), the preparation of quantities of such antibodies in hybridoma supernatants or ascites fluids, and for the purification and storage of such monoclonal antibodies, can be found in numerous publications. These include: Coligan, et al., eds. Current Protocols In Immunology, John Wiley & Sons, New York, 1992; Harlow and Lane, Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Liddell and Cryer, A Practical Guide To Monoclonal Antibodies, John Wiley & Sons, Chichester, West Sussex, England, 1991; Montz et al., Cellular Immunol. 127:337-351 (1990); Wurzner et al., Complement Inflamm. 8:328-340 (1991); and Mollnes et al., Scand. J. Immunol. 28:307-312 (1988).

VI Methods of Treatment

Methods of the application may be used to treat paroxysmal nocturnal hemoglobinuria associated symptoms. Methods of the application may be used to treat anemia associated symptoms. Treatment of paroxysmal nocturnal hemoglobinuria and/or anemia may be administered by standard means. Treatments of the application may be used in combination with other treatments of the application or known treatments for paroxysmal nocturnal hemoglobinuria and/or anemia. Treatments of the application may be co-administered with other treatments that treat symptoms of paroxysmal nocturnal hemoglobinuria and/or anemia.

VII Pharmaceutical Formulations and Uses

Methods of administration of small molecules, proteins, and nucleic acids are well-known to those of skill in the art. Methods of administration of antibodies are well-known to those of skill in the art. To achieve the desired inhibition, the antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab fragments will also require differing dosages than the equivalent intact immunoglobulins, as they are of considerably smaller mass than intact immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood. The dose will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing

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physician. Dosage levels of the antibodies for human subjects are generally between about 1 mg per kg and about 100 mg per kg per patient per treatment, and preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment. In terms of plasma concentrations, the antibody concentrations are preferably in the range from about 25 μg/mL to about 500 μg/mL. However, greater amounts may be required for extreme cases and smaller amounts may be sufficient for milder cases.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the antibody is administered according to the following protocol:

600 mg via 25 to 45 minute IV infusion every 7 ± 2 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 ± 2 days later, then 900 mg every 14 ± 2 days thereafter. Antibody is administered via IV infusion over 25 to 45 minute.

Administration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection. Other routes of administration may be used if desired but an intravenous route will be the most preferable. Formulations suitable for injection are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985). Such formulations must be sterile and non-pyrogenic, and generally will include a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The formulations may contain pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like. In certain embodiments, complement inhibitors such as eculizumab may be administered via IV infusion and diluted to a final concentration of 5 mg/ml prior to administration.

Administration of the antibodies capable of inhibiting complement such as an antibody that binds C5 will generally be performed by a parenteral route, typically via injection such as intra-articular or intravascular injection (e.g., intravenous infusion) or intramuscular injection. Other routes of administration, e.g., oral (p.o.), may be used if

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desired and practicable for the particular antibody capable of inhibiting complement to be administered. Antibodies capable of inhibiting complement such as an antibody that binds C5 can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and in vivo half-life of the particular antibody capable of inhibiting complement being administered. Doses of antibodies capable of inhibiting complement such as an antibody that binds C5 will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

In certain embodiments, a typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints with the dosage levels adjusted as needed to achieve the desired clinical outcome. In certain embodiments, treatment is administered in multiple dosages over at least a week. In certain embodiments, treatment is administered in multiple dosages over at least a month. In certain embodiments, treatment is administered in multiple dosages over at least a year. In certain embodiments, treatment is administered in multiple dosages over the remainder of the patient's life.

The frequency of administration may also be adjusted according to various parameters. These include the clinical response, the plasma half-life of the therapeutic of the disclosure, and the levels of the antibody in a body fluid, such as, blood, plasma, serum, or synovial fluid. To guide adjustment of the frequency of administration, levels of the therapeutic of the disclosure in the body fluid may be monitored during the course of treatment.

In certain embodiments, the frequency of administration may be adjusted according to an assay measuring cell-lysing ability of complement present in one or more of the patient's body fluids. The cell-lysing ability can be measured as percent hemolysis in hemolytic assays of the types described herein. A 10% or 25% or 50% reduction in the cell-lysing ability of complement present in a body fluid after treatment with the antibody capable of inhibiting complement used in the practice of the application means that the percent hemolysis after treatment is 90, 75, or 50 percent, respectively, of the percent hemolysis before treatment.

For the treatment of hemolytic diseases such as PNH by systemic administration of an antibody capable of inhibiting complement such as an antibody that binds C5 (as opposed to local administration), administration of a large initial dose is specific, i.e., a

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single initial dose sufficient to yield a substantial reduction, and more preferably an at least about 50% reduction, in the hemolytic activity of the patient's serum. Such a large initial dose is preferably followed by regularly repeated administration of tapered doses as needed to maintain substantial reductions of serum hemolytic titer. In another embodiment, the initial dose is given by both local and systemic routes, followed by repeated systemic administration of tapered doses as described above.

Formulations particularly useful for antibody-based therapeutic agents are also described in U.S. Patent App. Publication Nos. 20030202972, 20040091490 and 20050158316. In certain embodiments, the liquid formulations of the application are substantially free of surfactant and/or inorganic salts. In another specific embodiment, the liquid formulations have a pH ranging from about 5.0 to about 7.0. In yet another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from about 1 mM to about 100 mM. In still another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from 1 mM to 100 mM. It is also contemplated that the liquid formulations may further comprise one or more excipients such as a saccharide, an amino acid (e.g., arginine, lysine, and methionine) and a polyol. Additional descriptions and methods of preparing and analyzing liquid formulations can be found, for example, in PCT publications WO 03/106644, WO 04/066957, and WO 04/091658.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the application.

In certain embodiments, formulations of the subject antibodies are pyrogen-free formulations which are substantially free of endotoxins and/or related pyrogenic substances. Endotoxins include toxins that are confined inside microorganisms and are released when the microorganisms are broken down or die. Pyrogenic substances also include fever-inducing, thermostable substances (glycoproteins) from the outer membrane of bacteria and other microorganisms. Both of these substances can cause fever, hypotension and shock if administered to humans. Due to the potential harmful effects, it is advantageous to remove even low amounts of endotoxins from intravenously administered pharmaceutical drug solutions. The Food & Drug Administration ("FDA") has set an upper limit of 5 endotoxin units (EU) per dose per kilogram body weight in a

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single one hour period for intravenous drug applications (The United States Pharmacopeial Convention, Pharmacopeial Forum 26 (1):223 (2000)). When therapeutic proteins are administered in amounts of several hundred or thousand milligrams per kilogram body weight, as can be the case with monoclonal antibodies, it is advantageous to remove even trace amounts of endotoxin.

Formulations of the subject antibodies include those suitable for oral, dietary, topical, parenteral (e.g., intravenous, intraarterial, intramuscular, subcutaneous injection), ophthalmologic (e.g., topical or intraocular), inhalation (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops), rectal, and/or intravaginal administration. Other suitable methods of administration can also include rechargeable or biodegradable devices and controlled release polymeric devices. Stents, in particular, may be coated with a controlled release polymer mixed with an agent of the application. The pharmaceutical compositions of this disclosure can also be administered as part of a combinatorial therapy with other agents (either in the same formulation or in a separate formulation).

The amount of the formulation which will be therapeutically effective can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. The dosage of the compositions to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. For example, the actual patient body weight may be used to calculate the dose of the formulations in milliliters (mL) to be administered. There may be no downward adjustment to "ideal" weight. In such a situation, an appropriate dose may be calculated by the following formula: Dose (mL) = [patient weight (kg) x dose level (mg/kg)/ drug concentration (mg/mL)]

To achieve the desired treatment results, anti-C5 antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require

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different dosage levels. Antibodies prepared as Fab' fragments or single chain antibodies will also require differing dosages than the equivalent native immunoglobulins, as they are of considerably smaller mass than native immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood.

Other therapeutics of the disclosure can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and *in vivo* half-life of the particular therapeutic being administered.

Doses of therapeutics of the disclosure will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

The formulations of the application can be distributed as articles of manufacture comprising packaging material and a pharmaceutical agent which comprises the antibody capable of inhibiting complement and a pharmaceutically acceptable carrier as appropriate to the mode of administration. The packaging material may include a label which indicates that the formulation is for use in the treatment of hemolytic diseases such as PNH. Although antibodies are preferred, especially anti-C5 antibodies which have already been shown to be safe and effective at decreasing the accumulation of downstream complement components in persons, the use of other complement inhibitors is also contemplated by this disclosure. The pharmaceutical formulations and uses of the disclosure may be combined with any known complement inhibitors or hemolytic diseases treatments known in the art.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

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EXEMPLIFICATION

METHODS

Patient Selection

The TRIUMPH trial consisted of a 2-week screening period, an observation period of up to 3 months duration, and a 26-week treatment period.

During the screening period, patients were evaluated with respect to inclusion and exclusion criteria. Men and women, 18 years or older, diagnosed as having PNH with a type III erythrocyte population of ≥10%, and who had received at least 4 transfusions in the previous 12 months were eligible. Concomitant administration of erythropoietin, immunosuppressants, corticosteroids, coumadin, low molecular weight heparin, iron supplements, and folic acid were not reasons for exclusion, provided the doses were steady prior to the first visit and throughout the duration of the study. Because of the increased frequency of neisserial infections in individuals genetically deficient in terminal complement proteins, all patients were vaccinated against *Neisseria meningitides*. Patients were to avoid conception. The protocol was approved by an Investigational Review Board at each clinical site and written informed consent was obtained from all patients enrolled.

Patients transfused with a mean pre-transfusion hemoglobin level >10.5 g/dL over the previous 12 months, and those who showed evidence of having a suppressed immune response, complement deficiency, or active bacterial infection, including any history of meningococcal disease, were excluded from the study. Patients were also not eligible if they had previously received a bone marrow transplant or if they had participated in another trial or received another investigational drug within 30 days of the first visit. An individualized transfusion algorithm was calculated for each patient based on their prior 12-month transfusion history; the written algorithm documented the number of packed red blood cell (PRBC) units transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during observation and treatment periods.

Each patient considered eligible entered an observation period of up to 13 weeks in order to confirm their PBRC transfusion dependence. At least one transfusion --termed the "qualifying" transfusion-- during the 13-week observation period at a hemoglobin value at or below 9 g/dL with symptoms, or at or below 7 g/dL with or without symptoms, in accordance with the transfusion algorithm indicated for each patient, was a requirement to

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proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set point" for that individual for the purpose of the primary efficacy variable. A platelet count ≥100,000/mL and a LDH level ≥1.5 times the upper limit of the normal range were also required either at screening or during the observation period for eligibility.

Study Design

Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Measures of Clinical Efficacy

There were two co-primary endpoints in the study: (1) stabilization of hemoglobin levels, defined as a hemoglobin value maintained above the individual hemoglobin set point in the absence of transfusions for the entire 26-week treatment period, and (2) reduction in units of PRBCs transfused during the 26-week treatment phase of the study. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia and reached their individualized, pre-determined "set point". Pre-specified secondary endpoints included transfusion avoidance, hemolysis as measured by LDH area under the curve from baseline to 26 weeks, and QoL changes as measured from baseline to 26 weeks using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.[13] Pre-specified exploratory analyses included assessment of the EORTC QLQ-C30 instrument,[14] the change in LDH from baseline through week 26, and thrombosis. Other pre-specified measurements included pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. Time to first transfusion during the 26-week treatment phase and the proportion of PNH type III blood cells were also assessed.

Safety Assessments

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Treatment-emergent adverse events, clinical laboratory tests (e.g., serum chemical analyses and complete blood counts), electrocardiogram data, and vital signs were assessed. Adverse events were defined using the MedDRA preferred terms and tabulated as incidence rates per treatment group.

Statistical Analysis

For co-primary endpoints, analyses were performed according to the intention to treat using the data from all patients who were randomized and received study drug; stabilization of hemoglobin levels was analyzed using the Fisher's exact test and total PRBC units transfused were analyzed with the Wilcoxon's rank sum test. For comparison of treatment effect on transfusion avoidance, the Fisher's exact test was used on the incidence and the log rank test was used for time to first transfusion. For LDH area under the curve the Wilcoxon's rank sum test was used.

Quality of life measure of fatigue was assessed using the scoring guidelines for the FACIT-Fatigue instrument.[15] Assessment of quality of life measures based on the EORTC QLQ-C30 instrument was conducted in accordance with the appropriate scoring guidelines.[16] The changes of FACIT-Fatigue and EORTC QLQ-C30 scores from baseline through 26 weeks were analyzed using a mixed model, with baseline as covariate, treatment and time as fixed effects, and patient as a random effect. Changes in LDH levels and PNH type III erythrocytes from baseline through 26 weeks were analyzed using the same mixed model. Two-sided tests were used for all analyses. The adverse events and long-term safety checklist were tabulated separately and compared between treatments using the Fisher's exact test. A p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

Characteristics of Patients

A total of 115 PNH patients were screened. Six patients did not meet the inclusion/exclusion criteria during the screening period. Twenty-one other patients did not receive a qualifying transfusion and were not randomized into the treatment phase. One patient who did not meet the inclusion criteria was inadvertently randomized, but did not receive study medication. Thus 87 hemolytic PNH patients (35 men and 52 women) were enrolled and randomized to receive either eculizumab (N=43) or placebo (N=44), exceeding the original target of 75 randomized patients.

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Patient characteristics were similar in the eculizumab- and placebo-treated cohorts: median age, 41 (range 20-85) and 35 (range 18-78) years; median duration of PNH, 4.2 (range 0.8 to 29.7) and 9.2 (range 0.4 to 38.3) years; patients with history of aplastic anemia, 4 and 11; history of myelodysplastic syndrome, 1 and 0; and history of thrombosis, 9 (16 events) and 8 (11 events). Stable usage of concomitant medications at baseline in the eculizumab- and placebo-treated groups included the following: erythropoietin, 3 patients and 0 patients; cyclosporine, 1 and 1; anticoagulants (coumarins or heparins) 21 and 11; and steroids (glucocorticoids or androgenic steroids), 12 and 12, respectively.

Of the 87 patients randomized, 85 completed the trial. Two patients who did not complete the trial had been randomized to the eculizumab arm: one patient discontinued due to the inconvenience of travel to the study site and the second patient became pregnant. Ten patients in the placebo-treatment group discontinued infusions, in all cases due to perceived lack of efficacy, but they remained in the study for monitoring purposes.

Pharmacokinetics/Pharmacodynamics

In 42 of the 43 eculizumab-treated patients the levels of drug during the maintenance period (900 mg every 2 weeks±2 days) were sufficient to completely block serum hemolytic activity (mean trough value at week 26 of 101.8 μg/mL). A single patient did not sustain therapeutic trough levels of eculizumab and demonstrated a breakthrough in complement blockade during the last few days of each dosing interval. These breakthroughs were clinically manageable and quickly resolved following the next dose.

Hemolytic Efficacy Variables

The impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an immediate (one week) and sustained decrease in mean levels of LDH (Figure 1A). The median LDH area under the curve during the 26-week study period was reduced 85.8% in eculizumab- relative to placebo-treated patients ($P<0.001$). The mean LDH level decreased from 2199.7±157.7 IU/L at baseline to 327.3±67.6 IU/L by 26 weeks in eculizumab-treated patients while levels in placebo-treated patients remained consistently elevated with values of 2259.0±158.5 IU/L at baseline and 2418.9±140.3 IU/L at 26 weeks ($P<0.001$, for eculizumab versus placebo). A second biochemical measure of hemolysis, serum aspartate aminotransferase (AST), also showed a statistically significant improvement following eculizumab- versus placebo-treatment (data not shown). Haptoglobin levels were statistically significantly increased in eculizumab- as compared to placebo-treated patients

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but mean levels of haptoglobin were still below normal levels in eculizumab-treated patients (data not shown).

Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels (±standard error) from baseline (study week 0) to week 26 for both eculizumab- and placebo-treated patient populations. Screening occurred up to 3 months prior to study week 0. The upper limit of the normal range (103-223 IU/L) for LDH is indicated by a dashed line. LDH was reduced to a mean level just above the upper limit of normal at week 26 for eculizumab-treated patients; 15 of 41 patients who completed the study demonstrated LDH levels within the normal range. All placebo-treated patients remained at least 5 times above the upper limit of normal at week 26. The P value is based on a mixed model analysis from baseline through week 26. Figure 1B shows the mean proportion (±standard error) of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients. The screening visit occurred up to 3 months prior to study week 0. The P value is based on a mixed model analysis from baseline through week 26.

A corollary to the reduction in intravascular hemolysis during eculizumab treatment was an observed increase in the PNH type III erythrocyte population (Figure 1B). The mean proportions of type III erythrocytes increased from 28.1±2.0% at baseline to 56.9±3.6% by week 26 for eculizumab-treated patients while proportions in the placebo group remained constant with mean values of 35.7±2.8% before treatment to 35.5±2.8% at 26 weeks ($P<0.001$, for eculizumab versus placebo). By contrast, the proportions of PNH type III granulocytes and monocytes did not change significantly between the treatment groups during the treatment period and were greater than 90% at week 26.

CLINICAL EFFICACY

Co-primary endpoints

The co-primary efficacy endpoints in the TRIUMPH trial were stabilization of hemoglobin levels and reduction in PRBC units transfused. At the end of the treatment period, 48.8% of eculizumab-treated patients had maintained levels of hemoglobin above the pre-specified set-point (median set-point value of 7.7 g/dL for both treatment groups) in the absence of transfusions, whereas stabilization of hemoglobin did not occur in any of the patients in the placebo group ($P<0.001$; Table 1). By week 26, the median of PRBC units transfused per patient was 0 in the eculizumab group and 10.0 in the placebo cohort

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(P<0.001), while the mean of PRBC units transfused was 3.0 and 11.0 in the eculizumab and placebo cohorts, respectively. In the 6-month period prior to the study, the median of PRBC units transfused per patient was 9.0 in the eculizumab cohort and 8.5 in placebo patients while the mean of PRBC units transfused was 9.6±0.6 and 9.7±0.7, respectively. Mean hemoglobin levels were similar between the treatment groups at baseline (10.0±1.8 g/dL in eculizumab-treated patients and 9.7±1.8 g/dL in placebo-treated patients) and did not substantially change by week 26 (10.1±2.5 g/dL and 8.9±2.2 g/dL in eculizumab and placebo cohorts, respectively).

The median time to first transfusion was not reached during the study period in eculizumab-treated patients (it was greater than 26 weeks) while the placebo group reached the median time to first transfusion in only 4 weeks (P<0.001; Figure 2). Transfusion avoidance was achieved in 51.2% and 0% of the eculizumab and placebo cohorts, respectively (P<0.001). By the end of the 26-week treatment period, the total PRBC units transfused were 131 in eculizumab-treated patients versus 482 in the placebo group (Table 1). By contrast, in the 6-month period prior to the study, total PRBC units transfused in the eculizumab- and placebo-cohorts were 413 and 417, respectively.

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Table 1

Stabilization of Hemoglobin Levels and Reduction

in Transfusion Requirements during Eculizumab Treatment

	PRE-TREATMENT HISTORY*		TREATMENT PERIOD		
	Placebo	Eculizumab	Placebo	Eculizumab	P Value
†Stabilization of Hemoglobin Levels in the absence of transfusions (percent of patients)	NA	NA	0	48.8	<0.001‡
†Units Transfused per Patient					
Median	8.5	9.0	10	0	<0.001§
Mean±SE	9.7±0.7	9.6±0.6	11.0±0.83	3.0±0.67	
Total Units Transfused per Group	417	413	482	131	

*Twelve month historical transfusion data normalized to 6 months

†Co-primary endpoints

‡Base on 2-sided Fisher's exact test

§Based on Wilcoxon's rank sum test

NA, not applicable

Improvements in quality of life measures

Assessments of quality of life in PNH patients during eculizumab treatment were performed using two different instruments, FACIT-Fatigue and the EORTC QLQ-C30. Eculizumab-treated patients showed a mean increase (improvement) in the FACIT-Fatigue score of 6.4±1.2 points from baseline to 26-weeks while the mean score in placebo patients decreased by 4.0±1.7 points, a total difference between the treatment groups of 10.4 points (Figure 3). Mixed model analysis of covariance demonstrated a statistically significant difference between treatment groups (P<0.001).

For the EORTC instrument, improvements were observed with eculizumab-treatment in each subscale. Statistically significant improvements with eculizumab-compared with placebo-treated groups were observed in the following quality of life

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subscales (Table 2): global health status (P<0.001), physical functioning (P<0.001), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P<0.001), social functioning (P=0.003), fatigue (P<0.001), pain (P=0.002), dyspnea (P<0.001), appetite loss (P<0.001), and insomnia (P=0.014). The improvements with eculizumab treatment in the other scales, including nausea and vomiting, diarrhea, constipation, and financial difficulties, did not reach statistical significance.

Table 2

Effect of Eculizumab Treatment on

Quality of Life Assessed by the EORTC QLQ-C30 Instrument

	Mean Change from Baseline to Week 26*			
	Placebo	**Eculizumab**	**Absolute Difference**	**P Value†**
Global Health Status	-8.5	10.9	19.4	<0.001
Functional				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.6	=0.003
Cognitive	-6.1	7.9	14.0	=0.002
Physical	-3.5	9.4	13.0	<0.001
Emotional	-3.7	7.5	11.2	=0.008
Symptoms/Single Items				
Fatigue	10.0	-16.9	27.0	<0.001
Pain	5.3	-12.3	17.6	=0.002
Dyspnea	8.9	-7.9	16.9	<0.001
Appetite Loss	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	=0.014

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Financial Difficulties	0.0	-10.3	10.3	=0.186
Constipation	0.0	-6.3	6.3	=0.199
Nausea/vomiting	2.8	-0.4	3.2	=0.056
Diarrhea	5.7	4.8	0.9	=0.147

*A positive change indicates an improvement in global health status and functional scales and a negative change indicates an improvement in symptom and single item scales.

†Based on a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect and baseline as a covariate.

Relationship between FACIT-Fatigue quality of life and intravascular hemolysis

In order to determine if there was a treatment independent relationship between the FACIT-Fatigue quality of life instrument and intravascular hemolysis, an analysis was performed whereby the mean LDH level (through the 26 week study period) for each TRIUMPH patient was analyzed as a function of the patient's respective mean change in FACIT-Fatigue score from baseline (through the 26 week study period) (see Table 3). For this analysis, mean levels of LDH were divided into 4 groups that included: normal levels, 1-2 times the upper limit of normal (ULN), 2-10 times the upper limit of normal, and greater than 10 times the upper limit of normal. The analysis demonstrated that patients who maintained normal LDH levels throughout the study experienced significant improvements in fatigue when compared to patients who had incrementally higher levels of LDH throughout the study ($p=0.0048$). These data establish a clear link between increasing intravascular hemolysis as measured by LDH levels and decreased quality of life as measured by the FACIT-Fatigue quality of life instrument.

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Table 3

Relationship between FACIT-Fatigue and Intravascular Hemolysis

		Change of FACIT from Baseline		
Treatment Group	LDH Category	< 4	>= 4	P Value
Combined	Normal	4 (30.77%)	9 (69.23%)	.0048
	1 - 2 X ULN	16 (61.54%)	10 (38.46%)	
	2 - 10 X ULN	18 (72.00%)	7 (28.00%)	
	> 10 X ULN	16 (80.00%)	4 (20.00%)	

Safety

There were no deaths in the study. Serious adverse events (SAEs) were reported for 13 patients, of which 4 occurred in the eculizumab-treated cohort and 9 were in the placebo-treated cohort (see Table 4). All patients recovered without sequelae.

The most common AEs reported for eculizumab-treated patients were headache, nasopharyngitis, back pain, and upper respiratory tract infection. Headache and back pain occurred more commonly in the eculizumab-treatment group compared with the placebo group. However, the increase in headaches was limited to the first 2 weeks of therapy and was mild to moderate. There were no statistically significant differences in incidents rates between treatment groups for any AEs reported.

One episode of thrombosis (Budd-Chiari) occurred in a placebo-treated patient. There were no thromboses in eculizumab-treated patients.

Only one patient showed a detectable level of anti-eculizumab antibodies in the eculizumab-treated cohort; this response was weak (did not titrate), occurred at only one time point and did not result in a disruption of complement blockade.

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Table 4

Adverse Event Reporting

SERIOUS ADVERSE EVENTS*	**Placebo Patients n (percent)**	**Eculizumab Patients n (percent)**
Total	9 (20.5)	4 (9.3)
Eculizumab treatment emergent		
Exacerbation of PNH	3 (6.8)	1 (2.3)
Renal colic	0	1 (2.3)
Lumbar sacral disc prolapse	0	1 (2.3)
Alpha streptococcal bacteremia	0	1 (2.3)
Central line infection and UTI	1 (2.3)	0 (0)
Upper respiratory tract infection	1 (2.3)	0 (0)
Probable viral infection	1 (2.3)	0 (0)
Neutropenia	1 (2.3)	0 (0)
Cellulitis / folliculitis / neutropenia	1 (2.3)	0 (0)
Anemia and pyrexia	1 (2.3)	0 (0)
MOST FREQUENT ADVERSE EVENTS*†		
Headache§	12 (27.3)	19‡ (44.2)
Nasopharyngitis	8 (18.2)	10 (23.3)
Upper respiratory tract infection	10 (22.7)	6 (14)
Back pain	4 (9.1)	8 (18.6)
Nausea	5 (11.4)	7 (16.3)
Cough	4 (9.1)	5 (11.6)
Diarrhea	5 (11.4)	4 (9.3)
Arthralgia	5 (11.4)	3 (7.0)
Abdominal pain	5 (11.4)	2 (4.7)
Dizziness	5 (11.4)	2 (4.7)
Vomiting	5 (11.4)	2 (4.7)
Fatigue	1 (2.3)	5 (11.6)

Viral infection	5 (11.4)	1 (2.3)

*By preferred terms

†Occurring in 10% or more of patients

‡Sixteen of 19 patients experienced headache within 48 hours of infusion

§Following the first 2 weeks of dosing, 20.9% of eculizumab- and 22.7% of placebo-treated patients experienced headache

DISCUSSION

Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44% reduction in the rate of transfusion (data now shown).

Lactate dehydrogenase, a biochemical marker of hemolysis in PNH,[9] was immediately and consistently decreased in all eculizumab-treated patients, while patients in the placebo cohort continued to hemolyze with levels of LDH exceeding 5 times the upper limit of the normal range in all patients at the study end. Levels of LDH were reduced into the normal range in approximately one-third of eculizumab-treated patients, while the remainder stabilized at a level just above the upper limit of normal suggesting residual low level hemolysis in some patients. Levels of haptoglobin, a more sensitive marker of the presence of cell free hemoglobin in the circulation, were undetectable in most patients. Low level hemolysis in a subset of eculizumab-treated patients is possibly due to an inherent decrease in survival of these cells or C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.[17]

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Before eculizumab treatment, hemoglobin levels in study patients were artificially maintained by frequent transfusion. Therefore, stabilization of hemoglobin levels with a concomitant cessation of or reduction in transfusions represents a net increase in endogenous hemoglobin levels. Our data suggest that resolution of hemolysis with eculizumab results in a new steady state hemoglobin level determined by a balance between the extent of the underlying bone marrow dysfunction, the number of PNH erythrocytes that are preserved by eculizumab therapy and the new level (if any) of transfusion requirement.

Patients with PNH generally experience markedly impaired quality of life characterized by fatigue, anemia, thrombosis, and pulmonary hypertension as well as smooth muscle dystonia including abdominal pain, dysphagia, and erectile dysfunction.[9,10,18] These symptoms have been attributed to both excessive intravascular hemolysis and downstream scavenging of nitric oxide by cell free hemoglobin in plasma. The reduction of intravascular hemolysis in eculizumab-treated patients in the current study was associated with significant improvements in the fatigue component of quality of life relative to placebo-treated patients as assessed via the FACIT-Fatigue instrument. Further, eculizumab therapy was associated with a median increase of 6.4 points over baseline values established before treatment. It has previously been demonstrated that an increase of 3 or more points from baseline represents a clinically important difference in this quality of life instrument.[19] Patients who received eculizumab also experienced a significant improvement in most domains of the EORTC QLQ-30 relative to the placebo-treated cohort including global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and insomnia. Improvement in the fatigue component of the EORTC QLQ-30 provides support for the improvement demonstrated in the FACIT-Fatigue instrument during eculizumab therapy. Importantly, these improvements in quality of life in the eculizumab-treated patients occurred despite similar levels of erythrocyte hemoglobin in the two treatment groups, further supporting the contribution of hemolysis per se, as opposed to anemia, in mediating the poor quality of life in PNH patients. Clinical assessment of additional life quality-related symptoms of PNH, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[20]

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Eculizumab was safe and well-tolerated. There were no deaths in the study and only a single thrombotic event which occurred in a placebo patient in a site (the hepatic veins) which is typical of the thrombosis in PNH. The relative brief duration of this study was not sufficient to address the relevant issue of a possible protection from thrombosis by terminal complement inhibition with eculizumab.

Adverse events were generally mild with headache occurring at increased frequency in the eculizumab-treated patients; however, this increased frequency did not persist following the first two doses of therapy. There were 4 SAEs in the eculizumab treatment group and 9 SAEs in the placebo group. There was no evidence of increased infection risk in eculizumab-treated patients during the study period. One eculizumab-treated patient showed a low level of anti-eculizumab antibodies at one time point during the study which did not persist and did not result in a disruption of complement blockade. There were no AEs associated with eculizumab withdrawal in the 2 eculizumab-treated patients who did not complete the trial. Additional safety assessments, as well as efficacy measures, are being examined in an ongoing multi-center, open-label Phase III safety trial of eculizumab (SHEPHERD) in approximately 95 patients with PNH.

Results from the current randomized, double-blind, placebo-controlled, global study show that terminal complement inhibition with eculizumab appears to be a safe and effective therapy for patients with the rare disorder PNH. Treatment with eculizumab reduced intravascular hemolysis, and stabilized hemoglobin levels despite a reduction of transfusions, to the point where most PNH patients were rendered transfusion independent. Substantial and clinically meaningful improvements in fatigue and other key quality of life parameters were also demonstrated. All of the 85 patients who completed the study elected to receive eculizumab in an open-label extension study and all currently remain on drug. The results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency.

The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

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All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

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SEQUENCES

SEQ ID NO: 1 – Eculizumab V_H

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSA

SEQ ID NO: 2 – Eculizumab Heavy chain

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPG
SGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYF
DVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNS
GALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
RKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLP
SSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ
PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK

SEQ ID NO: 3 – Eculizumab V_L

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRT

SEQ ID NO: 4 – Eculizumab Light chain

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASENIYGAL
NWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

SEQ ID NO: 5 – Eculizumab CDRH1

NYWIQ

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SEQ ID NO: 6 – Eculizumab CDRH2
EILPGSGSTEYTENFKD

SEQ ID NO: 7 – Eculizumab CDRH3
YFFGSSPNWYFDV

SEQ ID NO: 8 – Eculizumab CDRL1
GASENIYGALN

SEQ ID NO: 9 – Eculizumab CDRL2
GATNLAD

SEQ ID NO: 10 – Eculizumab CDRL3
QNVLNTPLT

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WHAT IS CLAIMED IS:

1. A method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

2. The method of claim 1 wherein said quality of life is measured by a FACIT-Fatigue score.

3. The method of claim 2 wherein the FACIT-Fatigue score increases by at least 3 points.

4. The method of claim 2 wherein the FACIT-Fatigue score increases by $\geq$ 4 points.

5. The method of claim 1 wherein said quality of life is measured by an EORTC QLQ-C30 score.

6. The method of claim 5 wherein said EORTC QLQ-C30 score improves by $\geq$ 10% of the pretreatment score.

7. The method of claim 5 wherein said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia.

8. The method of claim 7 wherein said aspect of quality of life is fatigue.

9. The method of claim 1 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

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10. The method of claim 1 wherein said compound is a steroid that suppresses complement.

11. The method of claim 1 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

12. The method of claim 11 wherein said compound is an antibody or an active antibody fragment.

13. The method of claim 12 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

14. The method of claim 12 wherein said antibody or active antibody fragment blocks C5 cleavage.

15. The method of claim 12 wherein said antibody or active antibody fragment inhibits the formation of C5b-9.

16. The method of claim 12 wherein said antibody is eculizumab.

17. The method of claim 12 wherein said antibody or active antibody fragment is administered for at least 6 months.

18. The method of claim 1 wherein said patient has aplastic anemia or myelodysplastic syndrome.

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19. The method of claim 1 wherein said patient is anemic

20. The method of claim 19 wherein said patient remains anemic following treatment.

21. The method of claim 19 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

22. The method of claim 19 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

23. The method of claim 19 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

24. A method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis.

25. The method of claim 24 wherein said method results in a greater than 30% reduction in LDH in said patient.

26. The method of claim 24 wherein said quality of life is measured by a FACIT-Fatigue score.

27. The method of claim 26 wherein the FACIT-Fatigue score increases by at least 3 points.

28. The method of claim 26 wherein the FACIT-Fatigue score increases by ≥ 4 points.

29. The method of claim 24 wherein said quality of life is measured by an EORTC QLQ-C30 score.

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30. The method of claim 29 wherein said EORTC QLQ-C30 score improves by ≥ 10% of the pretreatment score.

31. The method of claim 29 wherein said aspect of the quality of life is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia.

32. The method of claim 31 wherein said aspect of quality of life is fatigue.

33. The method of claim 24 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

34. The method of claim 24 wherein said compound is a steroid that suppresses complement.

35. The method of claim 24 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

36. The method of claim 35 wherein said compound is an antibody or an active antibody fragment.

37. The method of claim 36 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

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38. The method of claim 36 wherein said antibody or active antibody fragment blocks C5 cleavage.

39. The method of claim 36 wherein said antibody or active antibody fragment is administered for at least 6 months.

40. The method of claim 24 wherein said compound inhibits complement or inhibits the formation of C5b-9.

41. The method of claim 40 wherein said compound is an antibody or active antibody fragment.

42. The method of claim 41 wherein said antibody is eculizumab.

43. The method of claim 24 wherein said patient has aplastic anemia or myelodysplastic syndrome.

44. A method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic.

45. The method of claim 44 wherein said method results in a greater than 30% reduction in LDH in said patient.

46. The method of claim 44 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

47. The method of claim 44 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

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48. The method of claim 44 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

49. The method of claim 44 wherein said patient suffers from paroxysmal nocturnal hemoglobinuria.

50. The method of claim 44 wherein said quality of life is measured by a FACIT-Fatigue score.

51. The method of claim 50 wherein the FACIT-Fatigue score increases by at least 3 points.

52. The method of claim 50 wherein the FACIT-Fatigue score increases by $\geq$ 4 points.

53. The method of claim 44 wherein said quality of life is measured by an EORTC QLQ-C30 score.

54. The method of claim 53 wherein said EORTC QLQ-C30 score improves by $\geq$ 10% of the pretreatment score.

55. The method of claim 53 wherein said aspect of the quality of life is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia.

56. The method of claim 55 wherein said aspect of quality of life is fatigue.

57. The method of claim 44 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

58. The method of claim 44 wherein said compound is a steroid that suppresses complement.

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59. The method of claim 44 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

60. The method of claim 59 wherein said compound is an antibody or an active antibody fragment.

61. The method of claim 60 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

62. The method of claim 60 wherein said antibody or active antibody fragment blocks C5 cleavage.

63. The method of claim 60 wherein said antibody or active antibody fragment is administered for at least 6 months.

64. The method of claim 44 wherein said compound inhibits complement or inhibits the formation of C5b-9.

65. The method of claim 64 wherein said compound is an antibody or an active antibody fragment.

66. The method of claim 65 wherein said antibody is eculizumab.

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67. The method of claim 44 wherein said patient has aplastic anemia or myelodysplastic syndrome.

68. A method of prolonging the health-adjusted life expectancy of a patient comprising administering to said patient in need thereof a compound which inhibits formation of C5b-9.

69. The method of claim 68 wherein said patient is anemic.

70. The method of claim 69 wherein said patient remains anemic following treatment.

71. The method of claim 68 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

72. The method of claim 68 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

73. The method of claim 68 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

74. The method of claim 68 wherein said patient suffers from paroxysmal nocturnal hemoglobinuria.

75. The method of claim 68 wherein said health-adjusted life expectancy is measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

76. The method of claim 75 wherein the health-adjusted life expectancy in a subject is prolonged by at least one day.

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77. The method of claim 75 wherein the health-adjusted life expectancy in a subject is prolonged by at least week.

78. The method of claim 75 wherein the health-adjusted life expectancy in a subject is prolonged by at least one month.

79. The method of claim 75 wherein the health-adjusted life expectancy in a subject is prolonged by at least one year.

80. The method of claim 68 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

81. The method of claim 68 wherein said compound is a steroid that suppresses complement.

82. The method of claim 68 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

83. The method of claim 82 wherein said compound is an antibody or an active antibody fragment.

84. The method of claim 83 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

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85. The method of claim 83 wherein said antibody or active antibody fragment blocks C5 cleavage.

86. The method of claim 83 wherein said antibody or active antibody fragment is administered for at least 6 months.

87. The method of claim 68 wherein said compound inhibits complement or inhibits the formation of C5b-9.

88. The method of claim 87 wherein said compound is an antibody or an active antibody fragment.

89. The method of claim 88 wherein said antibody is eculizumab.

90. The method of claim 68 wherein said patient has aplastic anemia or myelodysplastic syndrome.

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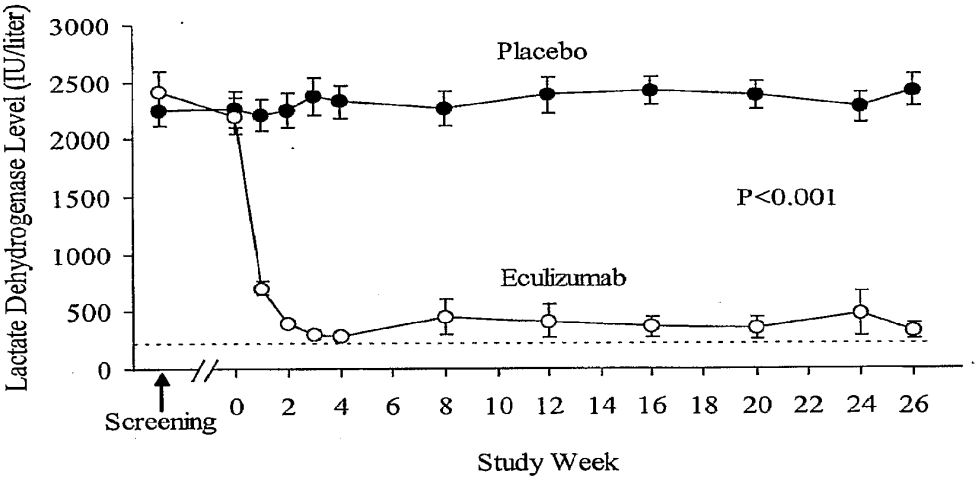
Lactate Dehydrogenase Level (IU/liter)
3000
2500
2000
1500
1000
500
0
Placebo
P<0.001
Eculizumab
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1A

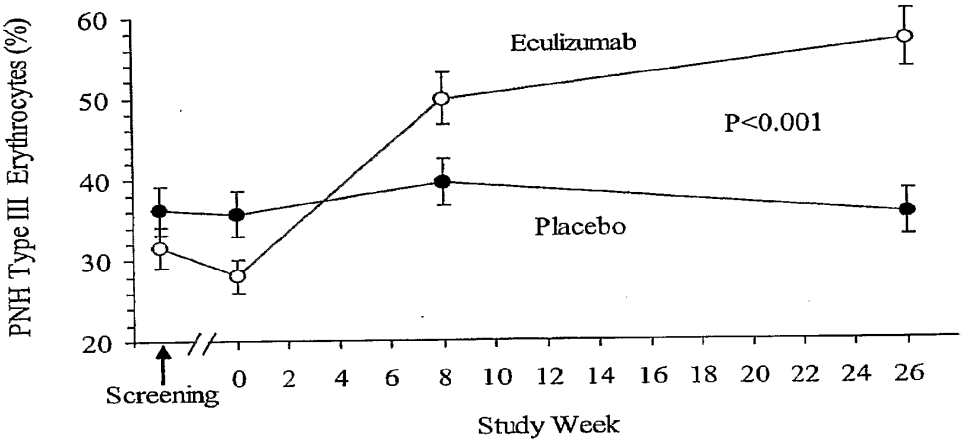
PNH Type III Erythrocytes (%)
60
50
40
30
20
Eculizumab
P<0.001
Placebo
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1B

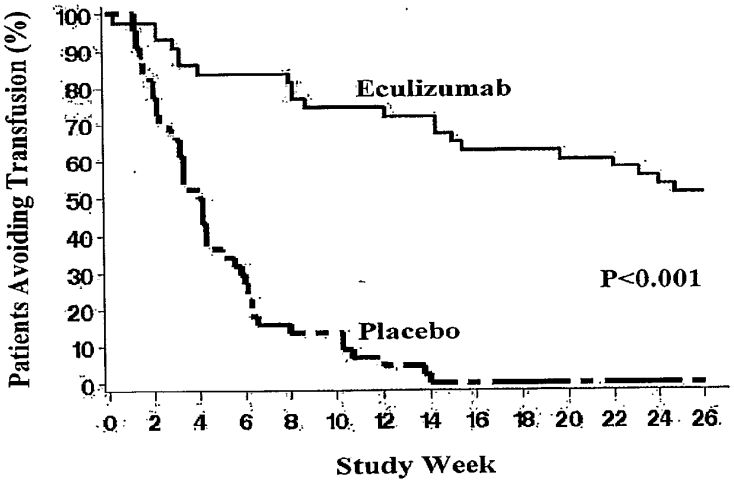
Patients Avoiding Transfusion (%)
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Eculizumab
P<0.001
Placebo

FIGURE 2

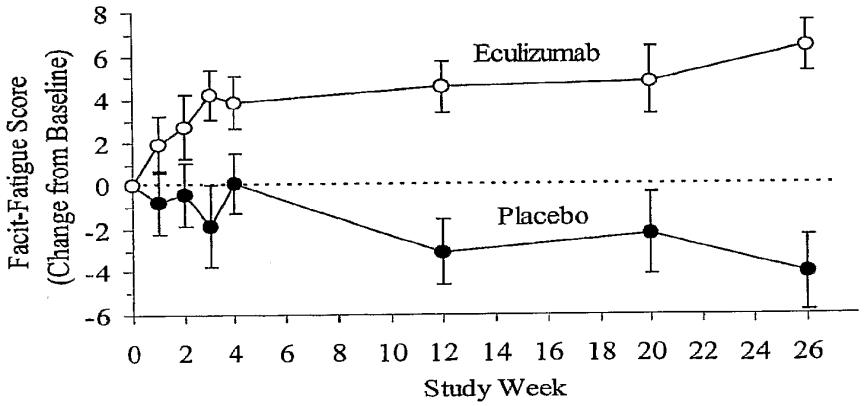
Facit-Fatigue Score
(Change from Baseline)
8
6
4
2
0
-2
-4
-6
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Eculizumab
Placebo

FIGURE 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/006606

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/7105 A61K38/00 A61K39/395 A61P7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/191298 A1 (BELL LEONARD [US] ET AL) 1 September 2005 (2005-09-01) the whole document	1-90
A	US 2005/221382 A1 (ROTHER RUSSELL P [US]) 6 October 2005 (2005-10-06) page 5, left-hand column, paragraph 40	1-90

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2007	27/07/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Collura, Alessandra

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/006606

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-90
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-90 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/006606

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005191298 A1	01-09-2005	AU 2005209854 A1	18-08-2005
		CA 2554632 A1	18-08-2005
		CN 1938047 A	28-03-2007
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US 2005221382 A1	06-10-2005	NONE	

(19) Europäisches Patentamt
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Office européen des brevets

(11) EP 2 359 834 B1

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(51) Int Cl.:
A61K 31/7105 *(2006.01)* ***A61K 38/00*** *(2006.01)*
A61K 39/395 *(2006.01)* ***A61P 7/06*** *(2006.01)*

(54) **Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement**

Hemmer des Komplements zur Behandlung der paroxysmalen nächtlichen Haemoglobinurie

Traitement des patients souffrant de l'hémoglobinurie paroxystique nocturne par un inhibiteur complémentaire

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR

(30) Priority: **15.03.2006 US 783070 P**

(43) Date of publication of application:
24.08.2011 Bulletin 2011/34

(60) Divisional application:
16172335.8

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
07753249.7 / 2 001 490

(73) Proprietor: **ALEXION PHARMACEUTICALS, INC.**
Cheshire, CT 06410 (US)

(72) Inventors:
- **Bell, Leonard**
  Woodbridge, CT 06525 (US)
- **Rother, Russell P.**
  Oklahoma City, Oklahoma 73151 (US)

(74) Representative: **Vossius & Partner**
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München (DE)

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US-A1- 2005 191 298 **US-A1- 2005 221 382**

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- **HILLMEN P ET AL: "EFFECT OF ECULIZUMAB ON HEMOLYSIS AND TRANSFUSION REQUIREMENTS IN PATIENTS WITH PAROXYSMAL NOCTRURNAL HEMAGLOBINURIA", NEW ENGLAND JOURNAL OF MEDICINE, MASSACHUSETTS MEDICAL SOCIETY, BOSTON, MA, US, vol. 350, no. 6, 5 February 2004 (2004-02-05), pages 552-559, XP009057948, ISSN: 1533-4406, DOI: DOI:10.1056/NEJMOA031688**
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- **HILL ANITA: "Eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria", CLINICAL ADVANCES IN HEMATOLOGY & ONCOLOGY, MILLENNIUM MEDICAL PUB., NEW YORK, NY, US, vol. 3, no. 11, 1 November 2005 (2005-11-01), pages 849-850, XP001538426, ISSN: 1543-0790**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

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(Cont. next page)

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Description

BACKGROUND

[0001] Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disease that results from clonal expansion of hematopoietic stem cells with somatic mutations in the X-linked gene called PIG-A.[1,2] Mutations in PIG-A lead to an early block in the synthesis of glycosylphosphatidylinositol (GPI)-anchors, which are required to tether many proteins to the cell surface. Consequently, PNH blood cells have a partial (type II) or complete (type III) deficiency of GPI-anchored proteins.

[0002] Intravascular hemolysis is a prominent feature of PNH and a direct result of the absence of the GPI-anchored complement regulatory protein CD59.[3,4] Under normal circumstances, CD59 blocks the formation of the terminal complement complex (also called the membrane attack complex) on the cell surface, thereby preventing erythrocyte lysis and platelet activation.[5-8] Excessive or persistent intravascular hemolysis in PNH patients not only results in anemia (normal ranges of hemoglobin are 14-18 g/dL for men and 12-16 g/dL for women, and persons with lower levels are considered to be anemic), but also hemoglobinuria and clinical sequelae related to the release of the erythrocyte contents into the circulation: fatigue, thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9,10,21,22] Indeed, impaired quality of life in PNH is disproportionate to the degree of anemia. Many PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels. There have been no therapies that effectively reduce intravascular hemolysis and improve the associated clinical morbidities in PNH.

[0003] Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5.[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

SUMMARY

[0004] The present invention is characterised by the claim.

[0005] The present pivotal, phase III study, Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH), evaluated the effect of eculizumab on the stabilization of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of 87 transfusion-dependent PNH patients. Measures of intravascular hemolysis and quality of life were also assessed. This is the first placebo controlled study of a PNH patient population to control hemolysis and to differentiate between the effects due to hemolysis and the effects due to anemia.

[0006] It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.

[0007] Described is a method to improve at least one aspect
of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

[0008] Described is a method to improve at least one aspect
of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis. Said method may result 2 in a greater than 30% reduction in LDH in said patient.

[0009] Described is a method to improve at least one aspect
of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic. Said method may result in a greater than 30% reduction in LDH in said patient.

[0010] Described is a method of prolonging the health-adjusted life expectancy of a patient comprising administering

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to said patient in need thereof a compound which inhibits formation of C5b-9. Said patient may be anemic. Said patient may remain anemic following
treatment. Said patient may have a hemoglobin level less than i) 14 g/dL
if a man or ii) 12 g/dL if a woman. Said patient may have a hemoglobin
level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. Said patient may have a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman. Said patient suffers from paroxysmal nocturnal hemoglobinuria.

[0011] The application provides a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof as characterised in the claim. The antibody that binds C5 or an active antibody fragment thereof is eculizumab. The pharmaceutical formulations of the application may be administered to a subject having PNH.

[0012] Described are kits comprising a pharmaceutical composition of the application. The kit may further comprise at least
one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. The kit may comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

[0013] Said quality of life may be measured by a FACIT-Fatigue score.

[0014] The FACIT-Fatigue score may increase by at least 3 points. The FACIT-Fatigue score may increase by ≥ 4 points.

[0015] Said quality of life may be measured by an EORTC QLQ-C30 score. Said EORTC QLQ-C30 score may improve by ≥ 10% of the pretreatment score. Said aspect of the quality of life as measured by an EORTC QLQ-C30 score may be selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia. Said aspect of quality of life may be fatigue.

[0016] Said antibody binds C5 and is eculizumab. Said antibody may be administered for at least 6 months. Said patient may have aplastic anemia or myelodysplastic syndrome.

[0017] Said antibody that binds C5 is administered in a single unit dosage form. The single unit dosage form is a 300 mg unit dosage form. The single unit dosage form is a sterile solution. The single unit dosage form is a preservative free formulation. The 300 mg single-use dosage form comprises 30 ml of a 10 mg/ml sterile, preservative free solution.

[0018] In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 1 and the light chain variable region consists of SEQ ID NO: 3. The pharmaceutical composition comprises eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ TD NO: 4.

[0019] Said patient may be anemic. Said patient may remain anemic following treatment. Said patient may have a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. Said patient may have a hemoglobin level less than i) 13 g/dL if a man or ii)) 11 g/dL if a woman. Said patient may have a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

[0020] Said health-adjusted life expectancy may be measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

[0021] The health-adjusted life expectancy in a subject may be prolonged by at least one day. The health-adjusted life expectancy in a subject may be prolonged by at least one week. The health-adjusted life expectancy in a subject may be prolonged by at least one month. The health-adjusted life expectancy in a subject may be prolonged by at least one year.

[0022] The pharmaceutical composition is in a single unit dosage form. The single unit dosage form is a 300 mg unit dosage form. The pharmaceutical composition is a sterile solution.

[0023] Figure 2 shows the effect of eculizumab treatment on transfusion requirements in PNH patients. This is a Kaplan-Meier plot of time to first transfusion for eculizumab- and placebo-treated patients from baseline through week 26. The P value is from the log rank analysis.

[0024] Figure 3 shows the effect of eculizumab on fatigue assessed by the FACIT-Fatigue Instrument. Quality of Life scores were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. Values for change from baseline to 26 weeks represent least-square means. A positive change indicates an improvement and a negative change indicates deterioration in the FACIT-Fatigue measures of quality of life.

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DETAILED DESCRIPTION

I. Definitions

[0025] The term "derived from" means "obtained from" or "produced by" or "descending from".

[0026] The term "genetically altered antibodies" means antibodies wherein the amino acid sequence has been varied from that of a native antibody. Because of the relevance of recombinant DNA techniques to this application, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. The possible variations are many and range from the changing of just one or a few amino acids to the complete redesign of, for example, the variable or constant region. Changes in the constant region will, in general, be made in order to improve or alter characteristics, such as complement fixation, interaction with membranes and other effector functions. Changes in the variable region will be made in order to improve the antigen binding characteristics.

[0027] The term "an antigen-binding fragment of an antibody" refers to any portion of an antibody that retains the binding utility to the antigen. An exemplary antigen-binding fragment of an antibody is the heavy chain and/or light chain CDR, or the heavy and/or light chain variable region.

[0028] The term "homologous," in the context of two nucleic acids or polypeptides refers to two or more sequences or subsequences that have at least about 85%, at least 90%, at least 95%, or higher nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using the following sequence comparison method and/or by visual inspection. In certain embodiments, the "homolog" exists over a region of the sequences that is about 50 residues in length, at least about 100 residues, at least about 150 residues, or over the full length of the two sequences to be compared.

[0029] Methods of determining percent identity are known in the art. "Percent (%) sequence identity" with respect to a specified subject sequence, or a specified portion thereof, may be defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul et al., J. Mol. Biol. 215:403-410 (1997); http://blast.wustl.edu/blast/README.htm-1) with search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A "% identity value" is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported.

II. Overview

[0030] The present disclosure relates to a pharmaceutical composition as characterised in the claim. It is for treating paroxysmal nocturnal hemoglobinuria ("PNH"), more specifically to improving certain aspects of quality of life which are impaired in PNH patients. Specifically, the pharmaceutical composition for treating PNH which is described herein, involve using eculizumab which binds to or otherwise blocks the generation and/or activity of C5. The present invention has been found to provide surprising results. For instance, hemolysis rapidly ceases upon administration of the compound which binds to or otherwise blocks the generation and/or activity of said complement component, with hemoglobinuria being significantly reduced after treatment. Also, hemolytic patients can be rendered less dependent on transfusions or transfusion-independent for extended periods (twelve months or more), well beyond the 120 day life cycle of red blood cells. In addition, type III red blood cell count can be increased dramatically in the midst of other mechanisms of red blood cell lysis (non-complement mediated and/or earlier complement component mediated e.g., Cb3). Another example of a surprising result is that symptoms resolved, indicating that NO serum levels were increased enough even in the presence of other mechanisms of red blood cell lysis. These and other results reported herein are unexpected and could not be predicted from prior treatments of hemolytic diseases.

III The Complement System

[0031] The complement system, useful complement inhibitors, and use of these inhibitors to treat PNH and other patients are more fully described in PCT Patent Application PCT/US2005/003225 filed February 3, 2005 and published as International Publication Number WO 2005/074607 A2 on August 18, 2005.

[0032] The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to

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the production of products with opsonic, immunoregulatory, and lytic functions.

[0033] The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

[0034] The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

[0035] C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

[0036] C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

[0037] C5 is a 190 kDa beta globulin found in normal serum at approximately 75 ng/mL (0.4 μM). C5 is glycosylated, with about 1.5-3 percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

[0038] The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

[0039] C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

[0040] C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment (Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

[0041] C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b-8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

[0042] As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

[0043] The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction.

IV Measures of Quality ofLife

[0044] Various measurements exist to assess quality of life and the effect of medical interventions on quality of life for example the Mini-Mental State Examination (MMSE), the Short Test of Mental Status, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the FACIT questionnaires and subscales

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including fatigue and anemia, the Likert Scale, and Borg Scale (Tombaugh, et al., J. Am. Geriatr. Soc. 40:922, 1992; Cummings, JAMA. 269(18):2420, 1993; Crum, et al., JAMA. 269(18):2386, 1993; Folstein, et al., J. Psychiat. Res. 12:189,1975; Kokmen, et al., Mayo Clin. Proc. 62:281, 1987; Tang-Wai, et al., Arch. Neurol. 60:1777, 2003; Tamburini, Ann. Oncol. 12(Suppl. 3):S7, 2001; Webster et al., Health and Quality of Life Outcomes. 1:79, 2003, www.hqlo.com/content/l/l/79; Grant, et al., Chest. 116:1208, 1999; and www.qolid.org). Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

[0045] Improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 may be measured by the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. Improvement in quality of life may be measured by: a) full scales; b) stand-alone subscales; and c) symptom indices.

[0046] Improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 may be measured by a
European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. In certain embodiments, the EORTC questionnaire is the QLQ-C30.

[0047] Improvement in quality of life may be measured by the health-adjusted life expectancy (HALE) index as described in Wilkins, R. and Adams, OB., Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein MC and Stason WB, N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

[0048] Improvement in quality of life may be measured by the following instruments: Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, and Years of healthy life. These measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

[0049] The disclosed methods may improve the quality of life of a patient for at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years, or the duration of treatment.

[0050] The symptoms used to measure quality of life may be scaled for intensity. The symptoms may be scaled for frequency. The symptoms may be scaled for intensity and frequency.

[0051] Described is a method for prolonging the health-adjusted life expectancy of a subject comprising administering to the subject a compound which inhibits complement or inhibits formation of C5b-9. The above measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality-adjusted life expectancy due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

[0052] The disclosed methods may prolong the health-adjusted life
expectancy in a subject by at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years as measured by the health-adjusted life expectancy (HALE) index as described in Wilkins et al. Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein et al., N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

V Inhibitors of the Complement Cascade

[0053] The concentration and/or physiologic activity of C5a and C5b in a body fluid can be measured by methods well known in the art. For C5a such methods include chemotaxis assays, RIAs, or ELISAs (see, for example, Ward and Zvaifler, J Clin Invest. 1971 Mar;50(3):606-16; Wurzner, et al., Complement Inflamm. 8:328-340, 1991). For C5b, hemolytic assays or assays for soluble C5b-9 as discussed herein can be used. Other assays known in the art can also be used.

[0054] The described method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. The antibody is disclosed in U.S. Patent 6,355,245 and is named eculizumab. A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)).

[0055] It is well known that the binding to a molecule (or a pathogen) of antibodies with an Fc region assists in the

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processing and clearance of the molecule (or pathogen). The Fc portions of antibodies are recognized by specialized receptors expressed by immune effector cells. The Fc portions of IgG1 and IgG3 antibodies are recognized by Fc receptors present on the surface of phagocytic cells such as macrophages and neutrophils, which can thereby bind and engulf the molecules or pathogens coated with antibodies of these isotypes (C. A. Janeway et al., Immunobiology 5th edition, page 147, Garland Publishing (New York, 2001)).

VI Methods of Treatment

[0056] Methods described in the application are used to treat paroxysmal nocturnal hemoglobinuria associated symptoms. Treatments of the application may be used in combination with known treatments for paroxysmal nocturnal hemoglobinuria. Treatments of the application may be co-administered with other treatments that treat symptoms of paroxysmal nocturnal hemoglobinuri a.

VII Pharmaceutical Formulations and Uses

[0057] The pharmaceutical composition is in a single unit dosage form, namely a 300 mg unit dosage form. The pharmaceutical composition is a sterile solution. The pharmaceutical composition is a preservative free formulation. The pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. The antibody may be administered according to the following protocol:

> 600 mg via 25 to 45 minute IV infusion every 7 ± 2 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 ± 2 days later, then 900 mg every 14 ± 2 days thereafter. Antibody is administered via IV infusion over 25 to 45 minutes.

[0058] Administration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection. Other routes of administration may be used if desired but an intravenous route will be the most preferable. The formulations may contain pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like. Eculizumab may be administered via

[0059] A typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints with the dosage levels adjusted as needed to achieve the desired clinical outcome. Treatment may be administered in multiple dosages over at least a week. Treatment may be administered in multiple dosages over at least a month. Treatment may be administered in multiple dosages over at least a year. Treatment may be administered in multiple dosages over the remainder of the patient's life.

[0060] The frequency of administration may also be adjusted according to various parameters. These include the clinical response, and the levels of the antibody in a body fluid, such as, blood, plasma, serum, or synovial fluid. To guide adjustment of the frequency of administration, levels of the therapeutic of the disclosure in the body fluid may be monitored during the course of treatment.

[0061] The frequency of administration may be adjusted according to an assay measuring cell-lysing ability of complement present in one or more of the patient's body fluids. The cell-lysing ability can be measured as percent hemolysis in hemolytic assays of the types described herein. A 10% or 25% or 50% reduction in the cell-lysing ability of complement present in a body fluid after treatment with the antibody capable of inhibiting complement used in the practice of the application means that the percent hemolysis after treatment is 90, 75, or 50 percent, respectively, of the percent hemolysis before treatment.

[0062] For the treatment of PNH by systemic administration of eculizumab (as opposed to local administration), administration of a large initial dose is specific, i.e., a single initial dose sufficient to yield a substantial reduction, and more preferably an at least about 50% reduction, in the hemolytic activity of the patient's serum. Such a large initial dose is preferably followed by regularly repeated administration of tapered doses as needed to maintain substantial reductions of serum hemolytic titer. The initial dose may be given by both local and systemic routes, followed by repeated systemic administration of tapered doses as described above.

[0063] Formulations particularly useful for antibody-based therapeutic agents are also described in U.S. Patent App. Publication Nos. 20030202972, 20040091490 and 20050158316. The liquid formulations of the application may be substantially free of surfactant and/or inorganic salts. The liquid formulations may have a pH ranging from about 5.0 to about 7.0. The liquid formulations may comprise histidine at a concentration ranging from about 1 mM to about 100 mM. The liquid formulations may comprise histidine at a concentration ranging from 1 mM to 100 mM. It is also contemplated that the liquid formulations may further comprise one or more excipients such as a saccharide, an amino acid (e.g., arginine, lysine, and methionine) and a polyol. Additional descriptions and methods of preparing and analyzing liquid formulations can be found, for example, in PCT publications WO 03/106644, WO 04/066957, and WO 04/091658.

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[0064] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the application.

[0065] In certain embodiments, formulations of the subject antibodies are pyrogen-free formulations which are substantially free of endotoxins and/or related pyrogenic substances. Endotoxins include toxins that are confined inside microorganisms and are released when the microorganisms are broken down or die. Pyrogenic substances also include fever-inducing, thermostable substances (glycoproteins) from the outer membrane of bacteria and other microorganisms. Both of these substances can cause fever, hypotension and shock if administered to humans. Due to the potential harmful effects, it is advantageous to remove even low amounts of endotoxins from intravenously administered pharmaceutical drug solutions. The Food & Drug Administration ("FDA") has set an upper limit of 5 endotoxin units (EU) per dose per kilogram body weight in a single one hour period for intravenous drug applications (The United States Pharmacopeial Convention, Pharmacopeial Forum 26 (1):223 (2000)). When therapeutic proteins are administered in amounts of several hundred or thousand milligrams per kilogram body weight, as can be the case with monoclonal antibodies, it is advantageous to remove even trace amounts of endotoxin.

[0066] Doses of therapeutics of the disclosure will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

[0067] The formulations of the application can be distributed as articles of manufacture comprising packaging material and a pharmaceutical agent which comprises the antibody capable of inhibiting complement and a pharmaceutically acceptable carrier as appropriate to the mode of administration. The packaging material may include a label which indicates that the formulation is for use in the treatment of PNH.

[0068] The pharmaceutical formulations and uses of the disclosure may be combined with any known complement inhibitors or hemolytic diseases treatments known in the art.

[0069] The application describes kits comprising a pharmaceutical composition of the application. The kit may further comprise at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. The kit may comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

EXEMPLIFICATION

METHODS

Patient Selection

[0070] The TRIUMPH trial consisted of a 2-week screening period, an observation period of up to 3 months duration, and a 26-week treatment period.

[0071] During the screening period, patients were evaluated with respect to inclusion and exclusion criteria. Men and women, 18 years or older, diagnosed as having PNH with a type III erythrocyte population of ≥10%, and who had received at least 4 transfusions in the previous 12 months were eligible. Concomitant administration of erythropoietin, immunosuppressants, corticosteroids, coumadin, low molecular weight heparin, iron supplements, and folic acid were not reasons for exclusion, provided the doses were steady prior to the first visit and throughout the duration of the study. Because of the increased frequency of neisserial infections in individuals genetically deficient in terminal complement proteins, all patients were vaccinated against *Neisseria meningitides.* Patients were to avoid conception. The protocol was approved by an Investigational Review Board at each clinical site and written informed consent was obtained from all patients enrolled.

[0072] Patients transfused with a mean pre-transfusion hemoglobin level >10.5 g/dL over the previous 12 months, and those who showed evidence of having a suppressed immune response, complement deficiency, or active bacterial infection, including any history of meningococcal disease, were excluded from the study. Patients were also not eligible if they had previously received a bone marrow transplant or if they had participated in another trial or received another investigational drug within 30 days of the first visit. An individualized transfusion algorithm was calculated for each patient based on their prior 12-month transfusion history; the written algorithm documented the number of packed red blood cell (PRBC) units transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during observation and treatment periods.

[0073] Each patient considered eligible entered an observation period of up to 13 weeks in order to confirm their PBRC transfusion dependence. At least one transfusion --termed the "qualifying" transfusion-- during the 13-week observation period at a hemoglobin value at or below 9 g/dL with symptoms, or at or below 7 g/dL with or without symptoms, in

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accordance with the transfusion algorithm indicated for each patient, was a requirement to proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set point" for that individual for the purpose of the primary efficacy variable. A platelet count ≥100,000/mL and a LDH level ≥1.5 times the upper limit of the normal range were also required either at screening or during the observation period for eligibility.

Study Design

[0074] Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Measures of Clinical Efficacy

[0075] There were two co-primary endpoints in the study: (1) stabilization of hemoglobin levels, defined as a hemoglobin value maintained above the individual hemoglobin set point in the absence of transfusions for the entire 26-week treatment period, and (2) reduction in units of PRBCs transfused during the 26-week treatment phase of the study. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia and reached their individualized, predetermined "set point". Pre-specified secondary endpoints included transfusion avoidance, hemolysis as measured by LDH area under the curve from baseline to 26 weeks, and QoL changes as measured from baseline to 26 weeks using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. [13] Pre-specified exploratory analyses included assessment of the EORTC QLQ-C30 instrument, [14] the change in LDH from baseline through week 26, and thrombosis. Other pre-specified measurements included pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. Time to first transfusion during the 26-week treatment phase and the proportion of PNH type III blood cells were also assessed.

Safety Assessments

[0076] Treatment-emergent adverse events, clinical laboratory tests (e.g., serum chemical analyses and complete blood counts), electrocardiogram data, and vital signs were assessed. Adverse events were defined using the MedDRA preferred terms and tabulated as incidence rates per treatment group.

Statistical Analysis

[0077] For co-primary endpoints, analyses were performed according to the intention to treat using the data from all patients who were randomized and received study drug; stabilization of hemoglobin levels was analyzed using the Fisher's exact test and total PRBC units transfused were analyzed with the Wilcoxon's rank sum test. For comparison of treatment effect on transfusion avoidance, the Fisher's exact test was used on the incidence and the log rank test was used for time to first transfusion. For LDH area under the curve the Wilcoxon's rank sum test was used.

[0078] Quality of life measure of fatigue was assessed using the scoring guidelines for the FACIT-Fatigue instrument.[15] Assessment of quality of life measures based on the EORTC QLQ-C30 instrument was conducted in accordance with the appropriate scoring guidelines The changes of FACIT-Fatigue and EORTC QLQ-C30 scores from baseline through 26 weeks were analyzed using a mixed model, with baseline as covariate, treatment and time as fixed effects, and patient as a random effect. Changes in LDH levels and PNH type III erythrocytes from baseline through 26 weeks were analyzed using the same mixed model. Two-sided tests were used for all analyses. The adverse events and long-term safety checklist were tabulated separately and compared between treatments using the Fisher's exact test. A p-value ≤0.05 was considered to be statistically significant.

RESULTS

Characteristics of Patients

[0079] A total of 115 PNH patients were screened. Six patients did not meet the inclusion/exclusion criteria during the screening period. Twenty-one other patients did not receive a qualifying transfusion and were not randomized into the

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treatment phase. One patient who did not meet the inclusion criteria was inadvertently randomized, but did not receive study medication. Thus 87 hemolytic PNH patients (35 men and 52 women) were enrolled and randomized to receive either eculizumab (N=43) or placebo (N=44), exceeding the original target of 75 randomized patients.

[0080] Patient characteristics were similar in the eculizumab- and placebo-treated cohorts: median age, 41 (range 20-85) and 35 (range 18-78) years; median duration of PNH, 4.2 (range 0.8 to 29.7) and 9.2 (range 0.4 to 38.3) years; patients with history of aplastic anemia, 4 and 11; history of myelodysplastic syndrome, 1 and 0; and history of thrombosis, 9 (16 events) and 8 (11 events). Stable usage of concomitant medications at baseline in the eculizumab- and placebo-treated groups included the following: erythropoietin, 3 patients and 0 patients; cyclosporine, 1 and 1; anticoagulants (coumarins or heparins) 21 and 11; and steroids (glucocorticoids or androgenic steroids), 12 and 12, respectively.

[0081] Of the 87 patients randomized, 85 completed the trial. Two patients who did not complete the trial had been randomized to the eculizumab arm: one patient discontinued due to the inconvenience of travel to the study site and the second patient became pregnant. Ten patients in the placebo-treatment group discontinued infusions, in all cases due to perceived lack of efficacy, but they remained in the study for monitoring purposes.

Pharmacokinetics/Pharmacodynamics

[0082] In 42 of the 43 eculizumab-treated patients the levels of drug during the maintenance period (900 mg every 2 weeks±2 days) were sufficient to completely block serum hemolytic activity (mean trough value at week 26 of 101.8 μg/mL). A single patient did not sustain therapeutic trough levels of eculizumab and demonstrated a breakthrough in complement blockade during the last few days of each dosing interval. These breakthroughs were clinically manageable and quickly resolved following the next dose.

Hemolytic Efficacy Variables

[0083] The impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an immediate (one week) and sustained decrease in mean levels of LDH (Figure 1A). The median LDH area under the curve during the 26-week study period was reduced 85.8% in eculizumab-relative to placebo-treated patients (P<0.001). The mean LDH level decreased from 2199.7±157.7 IU/L at baseline to 327.3±67.6 IU/L by 26 weeks in eculizumab-treated patients while levels in placebo-treated patients remained consistently elevated with values of 2259.0±158.5 IU/L at baseline and 2418.9±140.3 IU/L at 26 weeks (P<0.001, for eculizumab versus placebo). A second biochemical measure of hemolysis, serum aspartate aminotransferase (AST), also showed a statistically significant improvement following eculizumab- versus placebo-treatment (data not shown). Haptoglobin levels were statistically significantly increased in eculizumab- as compared to placebo-treated patients but mean levels of haptoglobin were still below normal levels in eculizumab-treated patients (data not shown).

[0084] Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels (±standard error) from baseline (study week 0) to week 26 for both eculizumab- and placebo-treated patient populations. Screening occurred up to 3 months prior to study week 0. The upper limit of the normal range (103-223 IU/L) for LDH is indicated by a dashed line. LDH was reduced to a mean level just above the upper limit of normal at week 26 for eculizumab-treated patients; 15 of 41 patients who completed the study demonstrated LDH levels within the normal range. All placebo-treated patients remained at least 5 times above the upper limit of normal at week 26. The P value is based on a mixed model analysis from baseline through week 26. Figure 1B shows the mean proportion (±standard error) of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients. The screening visit occurred up to 3 months prior to study week 0. The P value is based on a mixed model analysis from baseline through week 26.

[0085] A corollary to the reduction in intravascular hemolysis during eculizumab treatment was an observed increase in the PNH type III erythrocyte population (Figure 1B). The mean proportions of type III erythrocytes increased from 28.1±2.0% at baseline to 56.9±3.6% by week 26 for eculizumab-treated patients while proportions in the placebo group remained constant with mean values of 35.7±2.8% before treatment to 35.5±2.8% at 26 weeks (P<0.001, for eculizumab versus placebo). By contrast, the proportions of PNH type III granulocytes and monocytes did not change significantly between the treatment groups during the treatment period and were greater than 90% at week 26.

CLINICAL EFFICACY

Co-primary endpoints

[0086] The co-primary efficacy endpoints in the TRIUMPH trial were stabilization of hemoglobin levels and reduction in PRBC units transfused. At the end of the treatment period, 48.8% of eculizumab-treated patients had maintained levels of hemoglobin above the pre-specified set-point (median set-point value of 7.7 g/dL for both treatment groups) in

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the absence of transfusions, whereas stabilization of hemoglobin did not occur in any of the patients in the placebo group (P<0.001; Table 1). By week 26, the median of PRBC units transfused per patient was 0 in the eculizumab group and 10.0 in the placebo cohort (P<0.001), while the mean of PRBC units transfused was 3.0 and 11.0 in the eculizumab and placebo cohorts, respectively. In the 6-month period prior to the study, the median of PRBC units transfused per patient was 9.0 in the eculizumab cohort and 8.5 in placebo patients while the mean of PRBC units transfused was 9.6±0.6 and 9.7±0.7, respectively. Mean hemoglobin levels were similar between the treatment groups at baseline (10.0±1.8 g/dL in eculizumab-treated patients and 9.7±1.8 g/dL in placebo-treated patients) and did not substantially change by week 26 (10.1±2.5 g/dL and 8.9±2.2 g/dL in eculizumab and placebo cohorts, respectively).

[0087] The median time to first transfusion was not reached during the study period in eculizumab-treated patients (it was greater than 26 weeks) while the placebo group reached the median time to first transfusion in only 4 weeks (P<0.001; Figure 2). Transfusion avoidance was achieved in 51.2% and 0% of the eculizumab and placebo cohorts, respectively (P<0.001). By the end of the 26-week treatment period, the total PRBC units transfused were 131 in eculizumab-treated patients versus 482 in the placebo group (Table 1). By contrast, in the 6-month period prior to the study, total PRBC units transfused in the eculizumab- and placebo-cohorts were 413 and 417, respectively.

Table 1

Stabilization of Hemoglobin Levels and Reduction in Transfusion Requirements during Eculizumab Treatment					
	PRE-TREATMENT HISTORY*		TREATMENT PERIOD		
	Placebo	Eculizumab	Placebo	Eculizumab	P Value
†Stabilization of Hemoglobin Levels in the absence of transfusions (percent of patients)	NA	NA	0	48.8	<0.001‡
†Units Transfused per Patient					
Median	8.5	9.0	10	0	<0.001§
Mean±SE	9.7±0.7	9.6±0.6	11.0±0.83	3.0±0.67	
Total Units Transfused per Group	417	413	482	131	
*Twelve month historical transfusion data normalized to 6 months †Co-primary endpoints ‡Base on 2-sided Fisher's exact test §Based on Wilcoxon's rank sum test NA, not applicable					

Improvements in quality of life measures

[0088] Assessments of quality of life in PNH patients during eculizumab treatment were performed using two different instruments; FACIT-Fatigue and the EORTC QLQ-C30. Eculizumab-treated patients showed a mean increase (improvement) in the FACIT-Fatigue score of 6.4±1.2 points from baseline to 26-weeks while the mean score in placebo patients decreased by 4.0±1.7 points, a total difference between the treatment groups of 10.4 points (Figure 3). Mixed model analysis of covariance demonstrated a statistically significant difference between treatment groups (P<0.001).

[0089] For the EORTC instrument, improvements were observed with eculizumab-treatment in each subscale. Statistically significant improvements with eculizumab-compared with placebo-treated groups were observed in the following quality of life subscales (Table 2): global health status (P<0.001), physical functioning (P<0.001), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P<0.001), social functioning (P=0.003), fatigue (P<0.001), pain (P=0.002), dyspnea (P<0.001), appetite loss (P<0.001), and insomnia (P=0.014). The improvements with eculizumab treatment in the other scales, including nausea and vomiting, diarrhea, constipation, and financial difficulties, did not reach statistical significance.

Table 2

Effect of Eculizumab Treatment on Quality of Life Assessed by the EORTC QLQ-C30 Instrument				
	Mean Change from Baseline to Week 26*			
	Placebo	**Eculizumab**	**Absolute Difference**	**P Value†**
Global Health Status	-8.5	10.9	19.4	<0.001

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(continued)

Effect of Eculizumab Treatment on Quality of Life Assessed by the EORTC QLQ-C30 Instrument Mean Change from Baseline to Week 26*				
	Placebo	Eculizumab	Absolute Difference	P Value†
Functional				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.6	=0.003
Cognitive	-6.1	7.9	14.0	=0.002
Physical	-3.5	9.4	13.0	<0.001
Emotional	-3.7	7.5	11.2	=0.008
Symptoms/Single Items				
Fatigue	10.0	-16.9	27.0	<0.001
Pain	5.3	-12.3	17.6	=0.002
Dyspnea	8.9	-7.9	16.9	<0.001
Appetite Loss	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	=0.014
Financial Difficulties	0.0	-10.3	10.3	=0.186
Constipation	0.0	-6.3	6.3	=0.199
Nausea/vomiting	2.8	-0.4	3.2	=0.056
Diarrhea	5.7	4.8	0.9	=0.147

*A positive change indicates an improvement in global health status and functional scales and a negative change indicates an improvement in symptom and single item scales.
†Based on a mixed analysis-of covariance model with visit as a fixed effect, patient as a random effect and baseline as a covariate.

Relationship between FACIT-Fatigue quality of life and intravascular hemolysis

[0090] In order to determine if there was a treatment independent relationship between the FACIT-Fatigue quality of life instrument and intravascular hemolysis, an analysis was performed whereby the mean LDH level (through the 26 week study period) for each TRIUMPH patient was analyzed as a function of the patient's respective mean change in FACIT-Fatigue score from baseline (through the 26 week study period) (see Table 3). For this analysis, mean levels of LDH were divided into 4 groups that included: normal levels, 1-2 times the upper limit of normal (ULN), 2-10 times the upper limit of normal, and greater than 10 times the upper limit of normal. The analysis demonstrated that patients who maintained normal LDH levels throughout the study experienced significant improvements in fatigue when compared to patients who had incrementally higher levels of LDH throughout the study (p=0.0048). These data establish a clear link between increasing intravascular hemolysis as measured by LDH levels and decreased quality of life as measured by the FACIT-Fatigue quality of life instrument.

Table 3

Relationship between FACIT-Fatigue and Intravascular Hemolysis				
		Change of FACIT from Baseline		
Treatment Group	LDH Category	<4	>= 4	P Value
Combined	Normal	4 (30.77%)	9 (69.23%)	.0048
1 - 2 X ULN	1 - 2 X ULN	16(61.54%)	10 (38.46%)	
	2-10XULN	18(72.00%)	7 (28.00%)	
	> 10 X ULN	16(80.00%)	4 (20.00%)	

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Safety

[0091] There were no deaths in the study. Serious adverse events (SAEs) were reported for 13 patients, of which 4 occurred in the eculizumab-treated cohort and 9 were in the placebo-treated cohort (see Table 4). All patients recovered without sequelae.

[0092] The most common AEs reported for eculizumab-treated patients were headache, nasopharyngitis, back pain, and upper respiratory tract infection. Headache and back pain occurred more commonly in the eculizumab-treatment group compared with the placebo group. However, the increase in headaches was limited to the first 2 weeks of therapy and was mild to moderate. There were no statistically significant differences in incidents rates between treatment groups for any AEs reported.

[0093] One episode of thrombosis (Budd-Chiari) occurred in a placebo-treated patient. There were no thromboses in eculizumab-treated patients.

[0094] Only one patient showed a detectable level of anti-eculizumab antibodies in the eculizumab-treated cohort; this response was weak (did not titrate), occurred at only one time point and did not result in a disruption of complement blockade.

Table 4
Adverse Event Reporting

SERIOUS ADVERSE EVENTS*	**Placebo Patients n (percent)**	**Eculizumab Patients n (percent)**
Total	9 (20.5)	4 (9.3)
Eculizumab treatment emergent		
Exacerbation of PNH	3 (6.8)	1 (2.3)
Renal colic	0	1 (2.3)
Lumbar sacral disc prolapse	0	1 (2.3)
Alpha streptococcal bacteremia	0	1 (2.3)
Central line infection and UTI	1 (2.3)	0(0)
Upper respiratory tract infection	1 (2.3)	0(0)
Probable viral infection	1 (2.3)	0(0)
Neutropenia	1 (2.3)	0(0)
Cellulitis / folliculitis / neutropenia	1 (2.3)	0(0)
Anemia and pyrexia	1 (2.3)	0(0)
MOST FREQUENT ADVERSE EVENTS*†		
Headache§	12 (27.3)	19‡ (44.2)
Nasopharyngitis	8 (18.2)	10 (23.3)
Upper respiratory tract infection	10 (22.7)	6 (14)
Back pain	4 (9.1)	8 (18.6)
Nausea	5 (11.4)	7 (16.3)
Cough	4 (9.1)	5 (11.6)
Diarrhea	5 (11.4)	4 (9.3)
Arthralgia	5 (11.4)	3 (7.0)
Abdominal pain	5 (11.4)	2 (4.7)
Dizziness	5 (11.4)	2 (4.7)
Vomiting	5 (11.4)	2 (4.7)
Fatigue	1 (2.3)	5 (11.6)
Viral infection	5(11.4)	1 (2.3)

*By preferred terms
†Occurring in 10% or more of patients
‡Sixteen of 19 patients experienced headache within 48 hours of infusion
§Following the first 2 weeks of dosing, 20.9% of eculizumab- and 22.7% of placebo-treated patients experienced headache

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DISCUSSION

[0095] Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44% reduction in the rate of transfusion (data now shown).

[0096] Lactate dehydrogenase, a biochemical marker of hemolysis in PNH,[9] was immediately and consistently decreased in all eculizumab-treated patients, while patients in the placebo cohort continued to hemolyze with levels of LDH exceeding 5 times the upper limit of the normal range in all patients at the study end. Levels of LDH were reduced into the normal range in approximately one-third of eculizumab-treated patients, while the remainder stabilized at a level just above the upper limit of normal suggesting residual low level hemolysis in some patients. Levels of haptoglobin, a more sensitive marker of the presence of cell free hemoglobin in the circulation, were undetectable in most patients. Low level hemolysis in a subset of eculizumab-treated patients is possibly due to an inherent decrease in survival of these cells or C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.[17]

[0097] Before eculizumab treatment, hemoglobin levels in study patients were artificially maintained by frequent transfusion. Therefore, stabilization of hemoglobin levels with a concomitant cessation of or reduction in transfusions represents a net increase in endogenous hemoglobin levels. Our data suggest that resolution of hemolysis with eculizumab results in a new steady state hemoglobin level determined by a balance between the extent of the underlying bone marrow dysfunction, the number of PNH erythrocytes that are preserved by eculizumab therapy and the new level (if any) of transfusion requirement.

[0098] Patients with PNH generally experience markedly impaired quality of life characterized by fatigue, anemia, thrombosis, and pulmonary hypertension as well as smooth muscle dystonia including abdominal pain, dysphagia, and erectile dysfunction.[9,10,18] These symptoms have been attributed to both excessive intravascular hemolysis and downstream scavenging of nitric oxide by cell free hemoglobin in plasma. The reduction of intravascular hemolysis in eculizumab-treated patients in the current study was associated with significant improvements in the fatigue component of quality of life relative to placebo-treated patients as assessed via the FACIT-Fatigue instrument. Further, eculizumab therapy was associated with a median increase of 6.4 points over baseline values established before treatment. It has previously been demonstrated that an increase of 3 or more points from baseline represents a clinically important difference in this quality of life instrument.[19] Patients who received eculizumab also experienced a significant improvement in most domains of the EORTC QLQ-30 relative to the placebo-treated cohort including global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and insomnia. Improvement in the fatigue component of the EORTC QLQ-30 provides support for the improvement demonstrated in the FACIT-Fatigue instrument during eculizumab therapy. Importantly, these improvements in quality of life in the eculizumab-treated patients occurred despite similar levels of erythrocyte hemoglobin in the two treatment groups, further supporting the contribution of hemolysis per se, as opposed to anemia, in mediating the poor quality of life in PNH patients. Clinical assessment of additional life quality-related symptoms of PNH, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[20]

[0099] Eculizumab was safe and well-tolerated. There were no deaths in the study and only a single thrombotic event which occurred in a placebo patient in a site (the hepatic veins) which is typical of the thrombosis in PNH. The relative brief duration of this study was not sufficient to address the relevant issue of a possible protection from thrombosis by terminal complement inhibition with eculizumab.

[0100] Adverse events were generally mild with headache occurring at increased frequency in the eculizumab-treated patients; however, this increased frequency did not persist following the first two doses of therapy. There were 4 SAEs in the eculizumab treatment group and 9 SAEs in the placebo group. There was no evidence of increased infection risk in eculizumab-treated patients during the study period. One eculizumab-treated patient showed a low level of anti-eculizumab antibodies at one time point during the study which did not persist and did not result in a disruption of complement blockade. There were no AEs associated with eculizumab withdrawal in the 2 eculizumab-treated patients who did not complete the trial. Additional safety assessments, as well as efficacy measures, are being examined in an ongoing multi-center, open-label Phase III safety trial of eculizumab (SHEPHERD) in approximately 95 patients with PNH.

[0101] Results from the current randomized, double-blind, placebo-controlled, global study show that terminal complement inhibition with eculizumab appears to be a safe and effective therapy for patients with the rare disorder PNH. Treatment with eculizumab reduced intravascular hemolysis, and stabilized hemoglobin levels despite a reduction of transfusions, to the point where most PNH patients were rendered transfusion independent. Substantial and clinically

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meaningful improvements in fatigue and other key quality of life parameters were also demonstrated. All of the 85 patients who completed the study elected to receive eculizumab in an open-label extension study and all currently remain on drug. The results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency.

[0102] The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

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Ref Type: Abstract

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SEQUENCES

[0103]

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[0104]

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Claims

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

Patentansprüche

1. Pharmazeutische Zusammensetzung zur Verwendung in der Behandlung eines Patienten, der an paroxysmaler nächtlicher Hämoglobinurie (PNH) leidet, wobei die Zusammensetzung eine 300-mg-Eculizumab-Einmal-Darreichungsform ist, umfassend 30 ml einer 10 mg Eculizumab pro ml enthaltenden sterilen, konservierungsmittelfreien Lösung.

Revendications

1. Composition pharmaceutique pour une utilisation dans le traitement d'un patient atteint d'une hémoglobinurie paroxystique nocturne (HPN), dans laquelle la composition est une forme galénique à usage unique de 300 mg d'eculizumab comprenant 30 ml d'une solution à 10 mg d'eculizumab/ml, stérile et sans conservateur.

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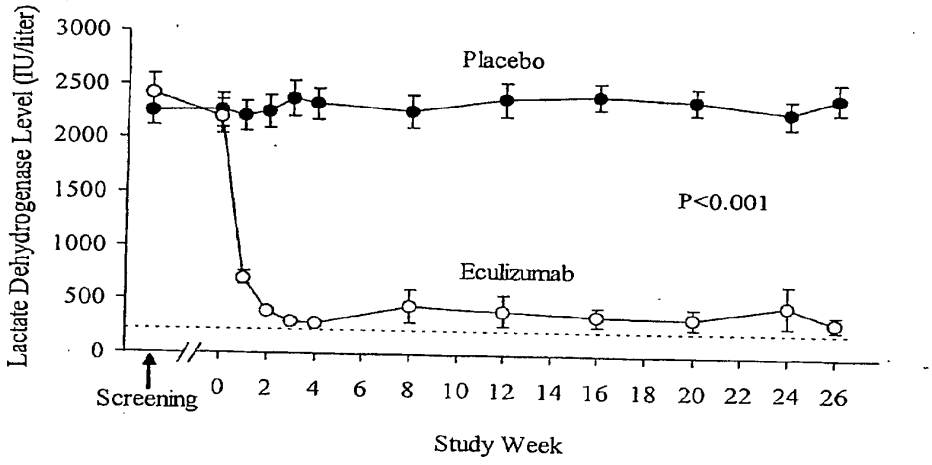

FIGURE 1A

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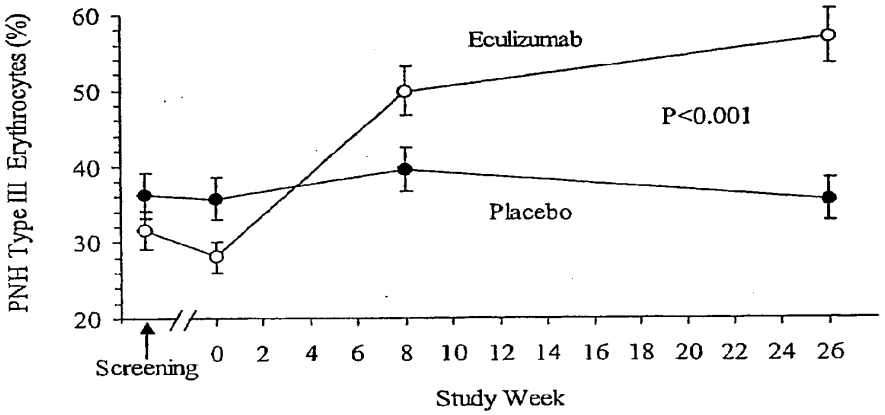

FIGURE 1B

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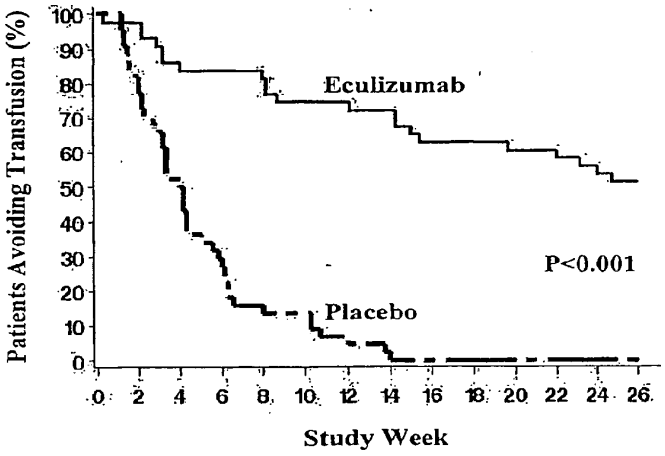

FIGURE 2

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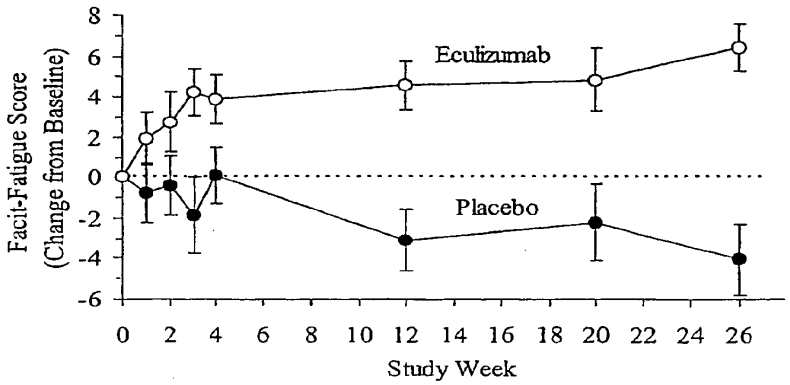

FIGURE 3

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REFERENCES CITED IN THE DESCRIPTION

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(71) Applicant: ALEXION PHARMACEUTICALS, INC. [US/US]; Suite 360, 25 Science Park, New Haven, CT 06511 (US).

(72) Inventors: MUELLER, John, P.; 4 Butterwick Lane, Old Lyme, CT 06371 (US). EVANS, Mark, J.; 528 Wood Hill Road, Cheshire, CT 06410 (US). MUELLER, Eileen, Elliott; 4 Butterwick Lane, Old Lyme, CT 06371 (US). ROLLINS, Scott; 12 Nutmeg Circle, Monroe, CT 06468 (US). ROTHER, Russell, P.; 67 Fernwood Lane, Cheshire, CT 06410 (US). MATIS, Louis, A.; 75 Flintlock Road, Southport, CT 06490 (US).

(74) Agent: FIDEL, Seth, A.; Alexion Pharmaceuticals, Inc., Suite 360, 25 Science Park, New Haven, CT 06511 (US).

(54) Title: PORCINE CELL INTERACTION PROTEINS

(57) Abstract

Antibodies to porcine P-selecting protein, porcine VCAM protein and porcine CD86 protein are useful for diagnosing human rejection of porcine xenotransplants and for improving xenotransplantation of porcine, cells, tissues and organs into human recipients.

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PORCINE CELL INTERACTION PROTEINS

FIELD OF THE INVENTION

This invention relates to xenotransplantation, and to the monitoring and modulation of the immune response to the xenotransplant. More specifically, the invention relates to the development of reagents and methods that will improve the ability to rapidly and specifically diagnose rejection of porcine xenotransplants by human patients. The invention also relates to compositions, including nucleic acid molecules, proteins (including antibodies), porcine cells, porcine tissues, and porcine organs, that will improve the outcome of the xenotransplantation of porcine cells, tissues, and organs into human recipients. To this end the invention provides a porcine P-selectin protein, a porcine VCAM protein, and a porcine CD86 protein, as well as the amino acid sequences of these proteins, the sequences of the cDNAs encoding these proteins, antibodies reactive with these proteins (but not with their human homologues), and methods for the use of these molecules.

BACKGROUND OF THE INVENTION

Xenotransplant Rejection: There is an ongoing shortage of human organs for transplant. This shortage has resulted in a long felt need for organs, and has resulted in attempts to develop xenotransplantation technology.

The primary non-primate candidate donor species for clinical xenotransplantation (e.g., the transplantation of non-human organs into human recipients) has been the pig. Swine provide an abundant supply of organs that are similar in size, anatomy, and physiology to their human counterparts (Auchincloss, 1988; Najarian, 1992; and Somervile and d'Apice, 1993). Transplantation of porcine pancreatic islets and of a pig liver into human patients has been reported, (Makowka et al., 1993; Satake et al., 1993; Tibell et al., 1993), but the outcomes of these transplants need to be improved. One improvement that is needed is better control (e.g., inhibition) of transplant rejection.

The rejection of transplanted organs may involve both an extremely rapid hyperacute rejection (HAR) phase and a slower cellular rejection phase. HAR of discordant (i.e., non-primate)

xenotransplants is initiated by preformed "natural" antibodies that bind to donor organ endothelium and activate complement attack by the recipient immune system (Dalmasso et al., 1992; and Tuso et al., 1993).

Activation of complement leads to the generation of fluid phase (C3a, C5a) and membrane bound (C3b and C5b-9, i.e., C5b, C6, C7, C8, and C9) proteins with chemotactic, procoagulant, proinflammatory, adhesive, and cytolytic properties (Muler-Eberhard, 1988). Immunohistological analysis of hyperacutely rejected xenotransplants reveals antibody deposition, complement fixation, and vascular thrombosis as well as neutrophil infiltration (Auchincloss, 1988; Mejia-Laguna et al., 1972; Najarian, 1992; Somervile and d'Apice, 1993; and Zehr et al., 1994).

While HAR is a major impediment to the xenotransplantation of vascularized organs, some discordantly xenotransplanted tissues (e.g., porcine pancreatic islets) do not appear to be rejected by this mechanism. Methods for the control of the HAR are also available. These include interference with the antibody antigen reactions responsible for initiating the HAR response, either by removing the antibodies from the circulation or by interfering with the expression of the antigens (see copending U.S. patent application Serial No. 08/214,580, entitled "Xenotransplantation Therapies" and filed by Mauro S. Sandrin and Ian F.C. McKenzie on March 15, 1994). Inhibition of complement attack on the xenotransplant may be accomplished by several means, including the use of complement inhibitors such as the 18kDa C5b-9 inhibitory protein and monoclonal antibodies against human C5b-9 proteins as taught in U.S. Patent No. 5,135,916, issued August 4, 1992.

In order to better understand the porcine xenograft rejection phenomenon, studies have been undertaken to investigate interactions between human white blood cells and porcine cells, particularly porcine aortic endothelial cells (PAEC). The role of neutrophils in the actual destruction of xenografts has not been well characterized, and the precise mechanism of complement independent neutrophil activation and adherence to xenograft endothelium are beginning to be understood.

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Previous studies have shown that human complement component C3b (C3bi) deposited on PAEC mediates the binding of human neutrophils to the PAEC through interactions with the heterodimeric neutrophil cell surface receptor CD11b/CD18 (Vercellotti et al., 1991). Furthermore, blocking HAR by inhibition or depletion of complement results in decreased neutrophil infiltration and increased xenograft survival, providing additional evidence for the role of complement in mediating human neutrophil binding to porcine endothelium.

However, a significant neutrophil infiltrate into PAEC monolayers has been observed even in the absence of complement activation (Leventhal et al., 1993; and Pruitt et al., 1991). The development of such infiltrates is believed to play an important role in xenograft rejection, albeit not necessarily in hyperacute xenograft rejection. Means and methods allowing the control or elimination of such interactions are thus needed in order to make the transplantation of porcine cells, tissues, or organs into human recipients more practicable.

Cell interaction molecules: Numerous cell surface molecules serve to mediated cell-cell interactions such as cell adhesion and cell activation. These molecules include cell adhesion molecules such as P-selectin and VCAM, as well as "costimulatory" molecules, such as CD86 (B7-2) that are involved in the activation of certain cells of the immune system, e.g., T cells.

P-selectin: P-selectin (also known as CD62P, platelet activation-dependent granule external membrane protein - PADGEM, and granule membrane protein of molecular weight 140kDa - GMP-140) is a cytokine inducible cell adhesion molecule that is a glycoprotein found on alpha-granules of platelets and storage granules of endothelial cells, known as Weibel-Palade bodies (Bevilacqua and Nelson, 1993; Bonfanti et al., 1989; Collins et al., 1993) from whence it is released to the cell surface upon cell activation.

Structurally, P-selectin belongs to a family of adhesion molecules termed "selectins" that also includes E-selectin and L-selectin (see reviews in Lasky, 1992 and Bevilacqua and Nelson, 1993). These molecules are characterized by common structural features such as an amino-terminal lectin-like domain, an epidermal growth factor (EGF) domain, a discrete number of

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complement repeat modules (approximately 60 amino acids each) similar to those found in certain complement binding proteins, a transmembrane domain, and a cytoplasmic tail (Dunlop et al., 1992).

P-selectin mediates the adhesion of various leukocytes (including neutrophils, monocytes, eosinophils, natural killer cells, and a subset of T cells) to activated platelets bound in the region of tissue injury, and to activated endothelium (Bevilacqua, et al., 1989; Carlos, et al., 1991; Graber, et al., 1990; Hakkert, et al., 1991; and Picker, et al., 1991; Shimuzu, et al., 1991). The importance of adhesive interactions with neutrophils is demonstrated by the observation that patients with an inherited defect in neutrophil adhesion exhibit neutrophilia and life-threatening bacterial infections of the classic leukocyte adhesion deficiency (LAD) syndrome (Carlos and Harlan, 1994; Lasky, 1992).

The expression of P-selectin is induced on human platelets and endothelial cells in response to thrombin generation, histamine generation, and the cytokines IL-1 and TNFa through transcriptional upregulation similar to that of E-selectin (Bevilacqua and Nelson, 1993; Carlos and Harlan, 1994). Phorbol esters, calcium ionophores, and complement proteins also activate P-selectin expression on endothelial cells (Collins et al., 1993; Hattori et al., 1989; Ishiwata et al., 1994).

Recent attempts to characterize the human leukocyte receptor for P-selectin have identified several different P-selectin ligands (Carlos and Harlan, 1994). These ligands contain sialic acid (sialyl Lewis x, or SLe^X) or other fucose-containing carbohydrate structures as a component mediating interaction with the P-selectin protein. Although SLe^X containing molecules seem to be higher affinity ligands, the number of these ligands and their precise specificity remains uncertain (Bevilacqua and Nelson, 1993; Carlos and Harlan, 1994).

Clinically, increased P-selectin expression on endothelium is associated with a variety of acute and chronic leukocyte-mediated inflammatory reactions. In addition to inflammation associated with graft rejection, leukocyte-mediated inflammatory reactions associated with increased P-selectin expression on endothelium include delayed type hypersensitivity, immune

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complex-mediated lung injury, ischemic reperfusion injury, psoriasis, contact dermatitis, and arthritis, in addition to microcirculatory disorders such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) (Bevilacqua and Nelson, 1993; Carlos and Harlan, 1994; Ishiwata et al., 1994; Katayama et al., 1993; Mulligan et al., 1992).

During inflammatory reactions, P-selectin has been characterized as an adhesion molecule to mediate leukocyte "rolling" on the vessel wall where neutrophils emigrate from circulation to sites of injured tissue or graft tissue (Hattori et al., 1989). According to recent studies, increased C5b-9 complement protein stimulates platelets to secrete adhesion proteins for deposition of platelets at sites of inflammation (Collins et al., 1993; Hattori et al., 1989). Moreover, membrane deposition of C5b-9 proteins causes the release of very high molecular weight von Willebrand Factor multimers, which are accompanied by endothelial surface expression of an intracellular granule membrane protein, P-selectin. Thus, platelet activation regulates human responses to recognition of foreign tissue such that cytokine-induced expression of P-selectin by donor organ endothelium contributes to the binding and subsequent transmigration of inflammatory cells into the graft tissue and thereby plays an important role in acute cellular allograft rejection.

SOLUBLE P-SELECTIN

In normal humans, soluble P-selectin (sP-selectin) is known to exist in plasma at a concentration level of from 0.10 to 0.30 mg/ml (Carlos and Harlan, 1994; Dunlop et al., 1992; Ishiwata et al., 1994). The demonstration of sP-selectin in the blood would therefore be taken as evidence of either endothelial activation or platelet activation in diseases such as thrombotic and inflammatory diseases (Gearing and Newman, 1993; Dunlop et al., 1992). Gearing and Newman, 1993, review the levels of sP-selectin found in healthy and sick patients in various previous studies.

Elevated levels of sP-selectin have been found in patients with thrombotic thrombocytopenic purpura by a three-fold increase and hemolytic uremic syndrome by a two-fold increase (Gearing and Newman, 1993; Ushiyama et al., 1993). Similarly, sP-selectin was

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detected in patients with circulatory disorders and adult respiratory distress syndrome (ARDS) with an increase of about 1 mg/ml.

Ushiyama et al., 1993 have cloned cDNAs encoding two recombinant forms of soluble P-selectin (sP-selectin). These soluble forms were characterized as having either a truncation after the 9th repeat or were lacking a transmembrane domain, encoded by exon 14, through alternative RNA splicing. Unlike the tetrameric P-selectin protein from platelet membranes, these soluble forms of P-selectin are monomeric. It is unknown where these monomers originate. However, studies suggest that soluble forms of P-selectin may have been produced by proteolytic cleavage of the protein or by shedding of the microvesicles containing the protein (Dunlop et al., 1992; Ushiyama et al., 1993). Other studies also suggest that sP-selectin were secreted as soluble forms from megakaryotes and vascular endothelial cells (Disdier et al., 1992; Ishiwata et al., 1994).

VCAM and CD86 are also cell adhesion molecules that are involved in the aggregation of various leukocytes at sites of inflammation. These molecules are also important mediators of inflammation, and are believed to be involved in xenograft rejection, albeit not necessarily in hyperacute xenograft rejection.

VCAM

Vascular cell adhesion molecule (VCAM) is an inducible transmembrane glycoprotein member of the immunoglobulin gene superfamily, expressed predominantly on endothelial cells (9-11). The interaction of VCAM with leukocytes is mediated by very late antigen-4 (VLA-4, a4b1), a b1 integrin molecule found on all leukocytes except neutrophils (12). VCAM expression is low or absent on resting endothelial cells in culture but can be induced by cytokines such as TNFa or IL-1 (9, 13-15). Thus, VCAM expression promotes a4 integrin-bearing leukocyte adhesion primarily to inflamed vascular endothelial cells (9, 15).

VCAM participates with intercellular adhesion molecule (ICAM) and endothelial-leukocyte adhesion molecule (ELAM) in the cellular recruitment, migration, and localization of inflammatory lymphocytes, monocytes, eosinophils and basophils to sites of tissue inflammation (8, 12, 14, 16). Recent in vitro and in vivo

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studies performed under flow conditions have revealed that multiple receptor-ligand pairs can act sequentially and in an overlapping manner to effect leukocyte initial attachment, rolling, stable arrest and migration (17, 18). However, in an in vitro model that mimics microcirculatory flow conditions, a4b1-VCAM interactions were recently shown to be the predominant mechanism mediating the arrest of rolling T cells (17). The binding of VCAM to VLA-4 has been implicated in a variety of inflammatory and immune conditions involving leukocyte-endothelial cell adhesion, including both cardiac and renal allograft transplant rejection (18-23).

A role for VLA-4/VCAM interactions during the immune response to organ transfer has been shown by experiments in which treatment of experimental animals with mAbs to VCAM has delayed murine cardiac allograft rejection (20, 23). Anti-VLA-4 and anti-VCAM mAbs also have been shown to block migration of lymphocytes, monocytes and eosinophils into tissue, and to exhibit anti-inflammatory effects in animal models of experimental allergic encephalomyelitis (19-24).

SUMMARY OF THE INVENTION

In view of the foregoing state of the art, it is an object of this invention to prevent and/or treat xenograft rejection of porcine organs, tissues, or cells through modulation of P-selectin, VCAM, and/or CD86 mediated cell cell interactions, and to provide a means for diagnostic monitoring of xenotransplant rejection by specific measurement of the amount of porcine P-selectin and/or VCAM in the blood of the porcine xenotransplant recipient. It is a further object of the invention to provide antibody molecules that neither activate ("fix") complement, nor bind to the Fc receptor, particularly the FcRI receptor.

To achieve these and other goals, the invention provides:

1) Isolated porcine P-selectin and VCAM proteins.

2) Porcine P-selectin, VCAM, and CD86 genes, in the form of, for example, cDNA and genomic DNA molecules comprising porcine coding sequences.

3) A method for producing porcine P-selectin, VCAM, and CD86 by growing a recombinant host cell containing the gene of the invention (i.e., a nucleic acid molecule coding for porcine P-

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selectin, VCAM, and/or CD86). The host cell is grown so that it expresses the porcine protein encoded by the gene of the invention and the expressed porcine protein is then isolated.

4) Anti porcine P-selectin antibodies that bind to porcine P-selectin, but not to human P-selectin; anti porcine VCAM antibodies that bind to porcine VCAM, but not to human VCAM; and anti porcine CD86 antibodies that bind to porcine CD86, but not to human CD86.

5) Therapeutic agents and methods for their use for the prevention and/or treatment of porcine xenograft rejection. These agents contain the porcine proteins of paragraph 1, immediately above, and/or the anti-porcine antibodies of paragraph 4, immediately above.

6) Agents for the diagnosis of porcine xenograft rejection based upon the anti-porcine P-selectin and anti-porcine VCAM antibodies of paragraph 4, immediately above.

7) Methods for disrupting the porcine genes of paragraph 1 in porcine cells, and the cell interaction molecule negative porcine cells generated via such methods.

8) Recombinant (chimeric and/or humanized) antibody molecules that react with porcine cell interaction proteins, but not with the analogous human cell interaction proteins.

9) Recombinant (chimeric and/or humanized) antibody molecules comprising the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4, such antibodies being referred to hereinafter as "HuG2/G4 mAb".

The accompanying drawings, which are incorporated in and constitute part of the specification, illustrate the preferred embodiments of the invention, and together with the description, serve to explain the principles of the invention. It is to be understood, of course, that both the drawings and the description are explanatory only and are not restrictive of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1. Adhesion of Ramos cells to TNFa-activated PAEC or COS-7 cells expressing pVCAM. Labeled Ramos cells were incubated for 30 min at 37°C with PAEC monolayers treated with 25 ng/ml recombinant human TNFa or with COS-7 monolayers transfected with APEX-1 (mock transfected) or pAPEX-1/pVCAM 72 h previously (no mAb). Specific adhesion of Ramos was analyzed by measuring dye

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release of SDS cell lysates in a fluoremeter. Binding is expressed as the average Fluorescence units from three replicate wells with bars representing the standard error of the mean. The average background fluorescence from wells containing PAEC or COS-7 cells alone was ~130 units and was subtracted from the data. Inhibition of Ramos cell attachment to pVCAM expressing cells was carried out using an anti-human VLA-4 mAb (HP2/1; 10 ug/ml) or an isotype matched control mAb. The data presented are representative of three separate experiments.

FIGURE 2. spVCAM-His_6 fusion gene and protein. (A) Schematic of the putative structures of the full length pVCAM and truncated pVCAM. Six histidine residues and a stop codon and were inserted at the putative domain 7/transmembrane boundary. (B) Purification of spVCAM. spVCAM-His_6 protein was purified by adsorption and elution from Ni^{++} charged NTA resin as described in Materials and Methods, separated by SDS-PAGE under nonreducing conditions and stained with Coomassie Blue. The electrophoretic mobility of molecular mass standards is shown in kDa. Apparent differences in kDa are consistent with differential glycosylation of pVCAM-derived fragments, since potential N-glycosylation sites occur in domains 1, 2 and 3 (one site in each) and domain 6 (two sites) of pVCAM.

FIGURE 3. Adhesion of calcein-labeled Ramos cells to immobilized spVCAM. spVCAM was immobilized to plastic and assessed for the ability to support Ramos cell adhesion. (A) Concentration dependence of binding of Ramos cells to immobilized spVCAM. Adhesion of Ramos cells to the indicated concentrations of spVCAM is shown. spVCAM was immobilized to microtiter wells and 3×10^4 labeled Ramos cells in 0.1 ml RPMI/1640 medium containing 10% FBS were added to each well. Binding was quantitated after 30 min at 37°C. Background binding of Ramos cells to a negative control protein (BSA) was subtracted from the data. (B) Effect of mAb reactive with VLA-4 on binding of Ramos cells to immobilized spVCAM. Thirty thousand labeled Ramos cells were treated with anti-VLA-4 (HP2/1; 10 ug/ml) for 15 min at 37°C and added to microtiter wells precoated with a saturating concentration of

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spVCAM (1 mg/well) or to BSA-coated control wells. Data are expressed as the average of triplicate wells. Experimental variation was less than 10%. Results presented are representative of three independent experiments.

FIGURE 4. Binding of Ramos cells to spVCAM in the continuous presence of mAbs to pVCAM. The indicated concentrations of anti-pVCAM mAb were added to microtiter wells precoated with spVCAM (1.0 mg/well) and incubated for 30 min at 37°C. Thirty thousand labeled Ramos cells in 0.1 ml RPMI/1640 medium containing 10% FBS were added to each microtiter well and binding examined after 30 min at 37°C. Binding is expressed as Fluorescence units. Representative data are shown from two experiments. Each value is a mean of triplicate wells.

FIGURE 5. Cell surface expression of VCAM on TNFa-activated HUVECs and PAEC. Cells were stained with anti-hVCAM (51-10C9) or anti pVCAM mAbs (2A2, 3F4, 5D11) followed by FITC goat-anti-mouse immunoglobulin and analyzed for VCAM expression by immunofluorecence and flow cytometry using a FACScan (Becton Dickinson Immunocytometry Systems). Data are displayed as histograms. The x-axis represents fluorescence and the y-axis represents the relative cell number. Background staining by secondary FITC-labeled antibody (SECONDARY) is indicated.

FIGURE 6. Epitope mapping of 2A2, 3F4 and 5D11 mAbs. Each anti-pVCAM mAb was assayed for the ability to bind to spVCAM captured on microtiter plates coated with either 2A2 or 3F4 F(ab')2 fragments. Detection of bound mAb was performed using peroxidase-conjugated goat anti-mouse IgG Fc. The background absorbance obtained in the absence of anti-pVCAM mAb was subtracted from all values. Results shown are the average of duplicate determinations.

FIGURE 7. Monoclonal antibody inhibition of Ramos and human peripheral T cell adhesion to TNFa-stimulated PAEC. Labeled Ramos or T cells were added to TNFa-stimulated PAEC monolayers in the presence or absence of the indicated mAb. Cell binding was quantitated in a 30 min adhesion assay. Each value is a mean of

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triplicate wells with bars representing the standard error of the mean. Representative data are shown from three experiments using different blood donors. Each antibody was added at a final concentration of 10 ug/ml at the initiation of the assay.

FIGURE 8. Inhibition of Ramos cell binding to porcine aortic endothelial cells (PAEC). Cell adhesion assays were performed as described except the paec were stimulated with 1 μg/ml LPS for 16 hours prior to the assay. The binding reactions contained the indicated concentrations of either (A) 2A2 mAb, 2A2 $F(ab')_2$, or 2A2 Fab, or (B) 3F4 mAb, 3F4 $F(ab')_2$, or 3F4 Fab. Binding in the presence of inhibitor is defined as percent of binding found in the absence of inhibitor. The results demonstrate that only the bivalent inhibitors (2A2 mAb, 2A2 $F(ab')_2$, 3F4 mAb, 3F4 $F(ab')_2$) inhibited binding at concentrations of 3 to 10 μg/ml. Significantly higher concentrations of the monovalent 2A2 Fab or 3F4 Fab were required for inhibition of binding.

FIGURE 9. Sequences of the murine 2A2 and 3F4 variable regions.

FIGURE 10. Flow cytometry analysis of chimeric antibodies. (A) Murine antibodies 2A2 and 3F4 or purified chimeric antibodies (ch2A2 HuG4 and ch3F4 HuG4) were assayed for binding to 293-EBNA cells (293) or 293-EBNA cells expressing pVCAM (293/pVCAM). Cells were incubated with either no primary antibody (2°) or 10 μg/ml of the murine or chimeric antibodies. Bound antibody was detected using either FITC-conjugated goat anti-mouse IgG antibody or FITC-conjugated goat anti-human IgG antibody. (B) Murine 2A2 or 3F4 antibodies or the recombinant ch2A2 HuG4 and ch3F4 HuG4 were assayed for binding to PAEC stimulated with 1μg/ml LPS for approximately 16 hours. Results demonstrate identical staining using either the parental murine antibodies or the chimeric antibodies in both cases, indicating the appropriate variable regions had been cloned.

FIGURE 11. Inhibition of Ramos binding to PAEC. Binding experiments containing the indicated concentrations of antibody were performed as described in Figure 1. Results demonstrate the recombinant the 2A2 HuG4 and ch3F4 HuG4 inhibit binding as

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potently as the murine 3F4 mAb. Neither a humanized antibody directed against human C5 (h5G1.1 CO12 HuG4 mAb) nor a murine antibody specific for human VCAM (anti-hVCAM) blocked binding of Ramos to PAEC.

FIGURE 12. Inhibition of Jurkat binding to PAEC. Binding experiments containing the indicated concentrations of antibody were performed as described in Figure 1 using calcein labeled Jurkat cells. Results demonstrate the recombinant the ch2A2 HuG4 and ch3F4 HuG4 inhibit binding as potently as the murine 3F4 mAb.

FIGURE 13. Inhibition of T-cell binding to PAEC. Binding experiments containing the indicated concentrations of inhibitor were performed as described in Figure 1 using calcein labeled purified human T-cells. Results demonstrate the recombinant the 2A2 HuG4 and ch3F4 HuG4 inhibit binding as potently as the murine 3F4 mAb.

FIGURE 14. Inhibition of U937 binding to PAEC. Binding experiments containing the indicated concentrations of antibody were performed as described in Figure 1 using calcein labeled U937 cells. Results demonstrate the recombinant ch3F4 HuG4 mAb does not inhibit binding, whereas the recombinant ch3F4 $F(ab')_2$ inhibits binding. This suggested that although the ch3F4 HuG4 mAb may have bound to the PAEC, U937 cells then adhered to the PAEC through interaction of the U937 cell FcRI receptor with the bound ch3F4 HuG4 mAb. To eliminate this interaction, chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4 were constructed (HuG2/G4 mAb). Flow cytometry demonstrated the resulting antibody does not bind to U937 cells. The ch3F4 HuG2/G4 mAb inhibited U937 binding to PAEC as potent as the ch3F4 HuG4 $F(ab')_2$.

FIGURE 15. Flow cytometry of HuG4 mAb and HuG2/G4 mAb binding to U937 cells. U937 cells were incubated with 10 µg/ml ch3F4 HuG4 mAb, ch3F4 HuG2/G4 mAb, ch2A2 HuG4 mAb, ch2A2 HuG2/G4 mAb, h5G1.1 CO12 HuG4 mAb, h5G1.1 CO12 HuG2/G4 mAb, or buffer. Bound antibody was detected using FITC-labeled goat anti-human IgG.

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Results demonstrate that the HuG4 mAb bound to U937 cells whereas the HuG2/G4 mAb did not.

FIGURE 16. Assays of human neutrophil binding to PAEC.

FIGURE 17. Amino acid sequence of porcine P-selectin.

FIGURE 18. Soluble porcine P-selectin cell ELISAs.

FIGURE 19. FACS profiles of COS expression of porcine P-selectin.

FIGURE 20. Neutrophil binding to porcine P-selectin.

FIGURE 21. FACS analysis of porcine P-selectin expression by PAEC.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The isolated nucleic acid molecules of the invention comprise sequences that are unique to the porcine genome. As used herein, the term "unique to the porcine genome" refers to sequences found in porcine-derived nucleic acid molecules that do not appear in published form as of the filing date of this application, e.g., they are not found in the cDNAs encoding the VCAM, P-selectin, or CD86 proteins of humans, cows, mice, or dogs.

The isolated nucleic acid molecules of the invention comprise sense sequences of contiguous nucleotides of the porcine sequences disclosed herein, for example in the figures. These sense sequences are unique to the porcine genome, and can be used as PCR primers or hybridization probes for the identification and/or isolation of the homologous porcine genes from genomic DNA. Antisense sequences of contiguous nucleotides complementary to such sense sequences are also required in order to practice PCR, and may also be used as hybridization probes. In order to be used for such purposes, the sequences of contiguous nucleotides must span a sufficient length. The minimum oligonucleotide length required for specific hybridization (i.e., hybridization under conditions requiring an essentially perfect match of complementary nucleotides wherein the sequence of the

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probe can be expected to occur only once in the genome of the organism being probed) of both hybridization probes and PCR primers is well known in the art, and is discussed in, for example, Sambrook, et al, 1989, on pages 11.7-11.8. In practice, this span is at least 14 nucleotides, and, preferably, at least 18 nucleotides. Because at least 2 PCR primers are generally required to carry out a PCR reaction, the specificity of the PCR reaction is greater than that of each of the oligonucleotide primers used to drive the reaction.

Another isolated nucleic acid molecule of the invention is a cloned porcine genomic DNA molecule comprising a sequence of nucleotides unique to the porcine genome. This cloned molecule is characterized by hybridizing specifically to an isolated nucleic acid molecule as described in the preceding paragraph. Specific hybridization is used to clone this genomic DNA molecule. This cloning can be accomplished by several methods well known in the art such as by PCR using porcine genomic DNA templates, or by conventional screening of phage libraries of porcine genomic DNA, e.g., by plaque lift filter hybridization.

Certain of the isolated nucleic acid molecules of the invention are also useful as means to direct and/or modulate the expression of porcine cell interaction molecules in porcine cells, e.g., by altering the expression of any of the porcine P-selectin, VCAM, or CD86 genes. Such modulation may be accomplished by several means well known in the art. Modulation, specifically inhibition, of the expression of any particular gene may be accomplished by the use of antisense nucleic acid molecules or DNA constructions specially engineered to allow gene inactivation as described below for antisense RNAs, antisense oligonucleotides, and gene knockout constructions. For example, for the inhibition of the porcine VCAM, the antisense nucleic acid molecules or DNA constructions will comprise nucleic acid sequences of the VCAM nucleic acid molecules of the invention.

Antisense RNAs can be used to specifically inhibit gene expression (see, for example, Eguchi, et al., 1991). Such nucleic acid molecules can be expressed by recombinant transcription units engineered for expression in porcine cells. Such transcription units can be introduced as transgenes into porcine

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cells, and, when introduced into porcine embryos or embryonic stem cells can be used to generate transgenic pigs.

Antisense nucleic acid molecules in the form of oligonucleotides (including oligonuclotide analogs) and derivatives thereof can also be used to specifically inhibit gene expression, as described, for example, in Cohen, 1989. As described therein, antisense oligonucleotides can be designed and used to inhibit expression of specific genes (Cohen, 1989, pp. 1-6, 53-77).

Such antisense oligonucleotides can be in the form of oligonucleotide analogs, for example, phosphorothioate analogs (Cohen, 1989, pp. 97-117), non-ionic analogs (Cohen, 1989, pp. 79-95), and a-oligodeoxynucleotide analogs (Cohen, 1989, pp. 119-136). Derivatives of oligonucleotides that can be used to inhibit gene expression include oligonucleotides covalently linked to intercalating agents or to nucleic acid-cleaving agents (Cohen, 1989, pp. 137-172), and oligonucleotides linked to reactive groups (Cohen, 1989, pp. 173-196). Oligonucleotides and derivatives designed to recognize double-helical DNA by triple-helix formation (Cohen, 1989, pp. 197-210) may also be used to specifically inhibit gene expression.

All of the oligonucleotides and derivatives described above are used by adding them to the fluids bathing the cells in which specific inhibition of gene expression in accordance with the present invention is desired.

Another method by which the expression of specific genes can be inhibited is by genetic manipulations referred to in the art as "gene disruption" or "gene knockout." Gene knockout is a method of genetic manipulation via homologous recombination that has long been carried out in microorganisms, but has only been practiced in mammalian cells within the past decade. These techniques allow for the use of specially designed DNA molecules (gene knockout constructions) to achieve targeted inactivation (knockout) of a particular gene upon introduction of the construction into a cell. The practice of mammalian gene knockout, including the design of gene knockout constructions and the detection and selection of successfully altered mammalian cells, is discussed in numerous publications, including Thomas, et al., 1986; Thomas, et al., 1987; Jasin and Berg, 1988;

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Mansour, et al., 1988; Brinster, et al., 1989; Capecchi, 1989; Frohman and Martin, 1989; Hasty, et al., 1991; Jeannotte, et al., 1991; and Mortensen, et al., 1992.

Gene knockouts and gene replacements can be achieved in mammalian zygotes through microinjection techniques well known in the art (Brinster, et al., 1989). The introduction of the DNA constructions used to effect gene knockouts into cultured cells is a more common route to the production of knockout cells, tissues, and organs. In those cases where knockout tissues or organs are desired, cultured embryonic stem cells provide a means to introduce the DNA constructions into cells in culture and to generate transgenic animals derived from such engineered cells. Such animals can also be obtained from knockout transgenic zygotes obtained by microinjection as described above.

Thus, in accordance with certain aspects of the invention, the nucleic acid molecules of the present invention are used to generate engineered transgenic animals using techniques known in the art. These techniques include, but are not limited to, microinjection, e.g., of nuclei or pronuclei, electroporation of ova or zygotes, nuclear transplantation, and/or the stable transfection or transduction of embryonic stem cells.

The most well known method for making transgenic animals is that used to produce transgenic mice by superovulation of a donor female, surgical removal of the egg, injection of the transgene transcription unit into the pronuclei of the embryo, and introduction of the transgenic embryo into the reproductive tract of a pseudopregnant host mother, usually of the same species. See Brinster, et al., 1985, Hogan, et al., 1986, Robertson 1987, Pedersen, et al., 1990.

The use of this method to make transgenic livestock is also widely practiced by those of skill in the art. As an example, transgenic swine are routinely produced by the microinjection of nucleic acid molecules into pig embryos. See, for example, PCT Publication No. WO92/11757. In brief, this procedure may, for example, be performed as follows. First, the nucleic acid molecules are gel isolated and extensively purified, for example, through an ELUTIP column (Schleicher & Schuell, Keene, NH), dialyzed against pyrogen free injection buffer (10mM Tris, pH7.4

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+ 0.1mM EDTA in pyrogen free water), and used for embryo injection.

Embryos are recovered from the oviduct of a hormonally synchronized, ovulation induced sow, preferably at the pronuclear stage. They are placed into a 1.5 ml microfuge tube containing approximately 0.5 ml of embryo transfer media (phosphate buffered saline with 10% fetal calf serum). These are centrifuged for 12 minutes at 16,000 x g in a microcentrifuge. Embryos are removed from the microfuge tube with a drawn and polished Pasteur pipette and placed into a 35 mm petri dish for examination. If the cytoplasm is still opaque with lipid such that the pronuclei are not clearly visible, the embryos are centrifuged again for an additional 15 minutes.

Embryos to be microinjected are placed into a drop of media (approximately 100 µl) in the center of the lid of a 100 mm petri dish. Silicone oil is used to cover this drop and to fill the lid to prevent the medium from evaporating. The petri dish lid containing the embryos is set onto an inverted microscope equipped with both a heated stage (37.5-38°C) and Hoffman modulation contrast optics (200X final magnification). A finely drawn and polished micropipette is used to stabilize the embryos while about 1-2 picoliters of injection buffer containing approximately 200-500 copies of the purified transgene transcription unit is delivered into the nucleus, preferably the male pronucleus, with another finely drawn and polished micropipette. Embryos surviving the microinjection process as judged by morphological observation are loaded into a polypropylene tube (2 mm ID) for transfer into the recipient pseudopregnant sow.

Offspring are tested for the presence of the transgene by isolating genomic DNA, e.g., from tissue removed from the tail of each piglet, and subjecting about 5 micrograms of this genomic DNA to nucleic acid hybridization analysis with a transgene specific probe.

Another commonly used technique for generating transgenic animals involves the genetic manipulation of embryonic stem cells (ES cells) as described in PCT Patent Publication No. WO 93/02188 and Robertson, 1987. In accordance with this technique, ES cells are grown as described in, for example, Robertson, 1987,

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and in U.S. Patent No. 5,166,065 to Williams et al. Genetic material is introduced into the embryonic stem cells by, for example, electroporation according, for example, to the method of McMahon, et al., 1990, or by transduction with a retroviral vector according, for example, to the method of Robertson, et al., 1986, or by any of the various techniques described by Lovell-Badge, 1987.

Chimeric animals are generated as described, for example, in Bradley, 1987. Briefly, genetically modified ES cells are introduced into blastocysts and the modified blastocysts are then implanted in pseudo-pregnant female animals. Chimeras are selected from the offspring, for example by the observation of mosaic coat coloration resulting from differences in the strain used to prepare the ES cells and the strain used to prepare the blastocysts, and are bred to produce non-chimeric transgenic animals.

Other methods for the production of transgenic animals are disclosed in U.S. Patent No. 5,032,407 to Wagner et al., and PCT Publication No. WO90/08832.

The practice of gene knockout in embryonic stem cells, and the generation of engineered animals from such cells, is discussed in numerous publications, including Thomas, et al., 1987; Robertson, 1987; Mansour, et al., 1988; Capecchi, 1989; Frohman and Martin, 1989; Hasty, et al., 1991; Jeannotte, et al., 1991; Mortensen, et al., 1992; Thomas, et al., 1992; and PCT Patent Publication No. WO 93/02188.

Among other applications, transgenic pigs prepared in accordance with the invention are useful as model systems for testing the xenotransplantation of their engineered cells, tissues, or organs and as sources of engineered cells, tissues, or organs for xenotransplantation. The lack of expression of porcine porcine cell interaction proteins on the endothelial cells of the transgenic pigs will provide enhanced protection from rejection following xenotransplantation of those cells, or of tissues and organs containing those cells, into recipient animals, e.g., humans. In addition to their use in producing tissues, and organs for transplantation, the nucleic acid molecules of the invention can also be used to directly engineer

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cultured porcine endothelial cells for subsequent use in transplantation.

The nucleic acid molecules of the invention can also be used to express porcine cell interaction proteins for subsequent purification and use. Recombinant DNA methods for the production of recombinant proteins are well known in the art, as are methods for the purification of such proteins (see, for example, Ausubel, et al., 1992; Goeddel, 1990; Harris and Angal, 1989; and Deutscher, 1990).

Preferred uses of such proteins include the use of porcine cell interaction proteins as immunogens for the purpose of raising anti porcine cell interaction protein antibodies, or as an antigen for use in immunoassays to detect soluble porcine cell interaction proteins as markers of inflammation in primate recipients of porcine xenografts. See, for example, below under "ELISA screen for anti-porcine VCAM antibodies".

The present invention provides recombinant expression vectors which include synthetic or cDNA-derived DNA fragments encoding porcine cell interaction proteins. The nucleotide sequences coding for porcine cell interaction proteins can be inserted into an appropriate expression vector, i.e., a vector that contains the necessary elements for the transcription and translation of the inserted protein-coding sequence. The necessary transcriptional and translational signals can also be supplied by the native gene and/or its flanking regions. A variety of host vector systems may be utilized to express the protein-coding sequence. These include, but are not limited to, mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, retroviruses, etc.); mammalian cell systems transfected with plasmids; insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast expression vectors, or bacteria transformed with bacteriophage DNA, plasmid DNA, or cosmid DNA (see, for example, Goeddel, 1990).

Useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well-known cloning vector pBR322 (American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852,

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United States of America; ATCC Accession No. 37017). These pBR322 "backbone sections," or functionally equivalent sequences, are combined with an appropriate promoter and the structural gene to be expressed. Promoters commonly used in recombinant microbial expression vectors include, but are not limited to, the lactose promoter system (Chang, et al., 1978), the tryptophan (trp) promoter (Goeddel, et al., 1980) and the tac promoter, or a fusion between the tac and trp promoters referred to as the trc promoter (Maniatis, 1982). Preferred bacterial expression vectors include, but are not limited to, vector pSE420 (Invitrogen Corporation, San Diego, California). This vector harbors the trc promoter, the lacO operon, an anti-terminator sequence, the g10 ribosome binding sequence, a translation terminator sequence, the lacIq repressor, the ColE1 origin of replication, and the ampicillin resistance gene.

Recombinant porcine cell interaction proteins may also be expressed in fungal hosts, preferably yeast of the Saccharomyces genus such as S. cerevisiae. Fungi of other genera such as Aspergillus, Pichia or Kluyveromyces may also be employed. Fungal vectors will generally contain an origin of replication from the 2 μm yeast plasmid or another autonomously replicating sequence (ARS), a promoter, DNA encoding a porcine cell interaction molecule, sequences directing polyadenylation and transcription termination, and a selectable marker gene. Preferably, fungal vectors will include an origin of replication and selectable markers permitting transformation of both E. coli and fungi.

Suitable promoter systems in fungi include the promoters for metallothionein, 3-phosphoglycerate kinase, or other glycolytic enzymes such as enolase, hexokinase, pyruvate kinase, glucokinase, the glucose-repressible alcohol dehydrogenase promoter (ADH2), the constitutive promoter from the alcohol dehydrogenase gene, ADH1, and others. See, for example, Schena, et al. 1991. Secretion signals, such as those directing the secretion of yeast a-factor or yeast invertase, can be incorporated into the fungal vector to promote secretion of a soluble porcine cell interaction proteins into the fungal growth medium. See Moir, et al., 1991.

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Preferred fungal expression vectors can be assembled using DNA sequences from pBR322 for selection and replication in bacteria, and fungal DNA sequences, including the ADH1 promoter and the alcohol dehydrogenase ADH1 termination sequence, as found in vector pAAH5 (Ammerer, 1983). The ADH1 promoter is effective in yeast in that ADH1 mRNA is estimated to be 1 - 2% of total poly(A) RNA.

Various mammalian or insect cell culture systems can be employed to express recombinant porcine cell interaction proteins. Suitable baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow, et al., 1988. Examples of suitable mammalian host cell lines include the COS cell of monkey kidney origin, mouse L cells, murine C127 mammary epithelial cells, mouse Balb/3T3 cells, Chinese hamster ovary cells (CHO), human 293 EBNA and HeLa cells, myeloma, and baby hamster kidney (BHK) cells. Mammalian expression vectors may comprise non-transcribed elements such as origin of replication, a suitable promoter and enhancer linked to the porcine cell interaction protein gene to be expressed, and other 5' or 3' flanking sequences such as ribosome binding sites, a polyadenylation sequence, splice donor and acceptor sites, and transcriptional termination sequences.

The transcriptional and translational control sequences in mammalian expression vector systems to be used in transforming vertebrate cells may be provided by viral sources. For example, commonly used promoters and enhancers are derived from Polyoma virus, Adenovirus, Simian Virus 40 (SV40), and human cytomegalovirus, including the cytomegalovirus immediate-early gene 1 promoter and enhancer (CMV).

Particularly preferred eukaryotic vectors for the expression of porcine cell interaction proteins are pAPEX-1 and pAPEX-3, as described below. A particularly preferred host cell for the expression of inserts in the pAPEX-3 vector is the human 293 EBNA cell line (Invitrogen, San Diego, CA).

Another preferred eukaryotic vector for the expression of porcine cell interaction proteins is pcDNAI/Amp (Invitrogen Corporation, San Diego, California). The pcDNAI/Amp expression vector contains the human cytomegalovirus immediate-early gene I promoter and enhancer elements, the Simian Virus 40 (SV40)

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consensus intron donor and acceptor splice sequences, and the SV40 consensus polyadenylation signal. This vector also contains an SV40 origin of replication that allows for episomal amplification in cells (e.g., COS cells, MOP8 cells, etc.) transformed with SV40 large T antigen, and an ampicillin resistance gene for propagation and selection in bacterial hosts.

Purified porcine cell interaction proteins are prepared by culturing suitable host/vector systems to express the recombinant translation products of the nucleic acid molecules of the present invention, which are then purified from the culture media or cell extracts of the host system, e.g., the bacteria, insect cells, fungal, or mammalian cells. Fermentation of fungi or mammalian cells that express soluble porcine cell interaction proteins containing a histidine tag sequence (comprising a string of at least 5 histidine residues in a row) as a secreted product greatly simplifies purification. Such a histidine tag sequence enables binding under specific conditions to metals such as nickel, and thereby to nickel columns for purification.

In general terms, the purification of recombinant porcine cell interaction proteins is performed using a suitable set of concentration, fractionation, and chromatography steps well known in the art (see, for example, Deutscher, 1990; and Harris and Angal, 1989). For recombinant porcine cell interaction proteins requiring correct disulfide bond formation for full biological activity, denaturation of the purified protein followed by chemical-mediated refolding under reducing conditions can be done to promote proper disulfide interactions.

Porcine cell interaction proteins purified from bodily fluids of transgenic animals engineered to produce the porcine cell interaction proteins of the invention are also within the scope of the invention, as are porcine cell interaction proteins that are produced in part or entirely by chemical synthesis.

Porcine cell interaction proteins synthesized in recombinant culture and subsequently purified may be characterized by the presence of contaminating components. These components may include proteins or other molecules in amounts and of a character which depend on the production and purification processes. These components will ordinarily be of viral, prokaryotic, eukaryotic, or synthetic origin, and preferably are present in innocuous

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contaminant quantities, on the order of less than about 1% by weight. Recombinant cell culture, however, enables the production of porcine cell interaction proteins relatively free of other proteins that may normally be associated with the proteins as found in nature.

As discussed above, certain aspects of the present invention relates to the use of anti porcine cell interaction protein antibodies or soluble cell interaction proteins (collectively referred to hereinafter as "therapeutic porcine cell interaction agents") in treating patients suffering from xenotransplant rejection. The therapeutic porcine cell interaction agents are used in an amount effective to achieve blood concentrations equivalent to <u>in vitro</u> concentrations that substantially reduce (e.g., reduce by at least about 50%) the binding of human test cells expressing the human cell interaction protein binding ligand, such as PBLs, neutrophils, and HL-60 cells, to cells expressing porcine cell interaction proteins, such as TNFa treated porcine endothelial cells. Reduction of the binding of human test cells to cells expressing porcine cell interaction proteins can be measured by methods well known in the art such as, for example, by the assay described below under the heading "assays for neutrophil / HL-60 binding to PAEC".

To achieve the desired reductions in binding, the therapeutic porcine cell interaction agents can be administered in a variety of unit dosage forms. The dose will vary according to the particular agent. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab' or $F(ab')_2$ fragments will also require differing dosages than the equivalent intact immunoglobulins, as they are of considerably smaller mass than intact immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood.

The dose will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician. Dosage levels of the therapeutic porcine cell interaction agents for human subjects are generally between about 1 mg per kg and about 100 mg per kg per patient per treatment, and preferably between

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about 5 mg per kg and about 50 mg per kg per patient per treatment. In terms of plasma concentrations, the therapeutic porcine cell interaction agent concentrations are preferably in the range from about 25 µg/ml to about 500 µg/ml. See, also, Kung et al., 1993.

Subject to the judgment of the physician, a typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints such as xenotransplant biopsies, or measures of organ function, such as, for example, for xenotransplanted kidneys, BUN levels, proteinuria levels, etc., with the dosage levels adjusted as needed to achieve the desired clinical outcome.

The therapeutic porcine cell interaction agents of the present invention can be used in therapeutic compositions to treat episodes of xenograft rejection. Such treatment will result in the reduction of the severity of the rejection episode. For such application, purified therapeutic porcine cell interaction agents can be administered to a patient, e.g., a human, in a variety of ways. Thus, therapeutic porcine cell interaction agents can be given by bolus injection, continuous infusion, sustained release from implants, or other suitable techniques.

Formulations suitable for injection are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA, 17th ed. (1985). Such formulations must be sterile and non-pyrogenic, and generally will include purified therapeutic porcine cell interaction agents in conjunction with a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The formulations may contain pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like.

In one preferred embodiment, the therapeutic porcine cell interaction agent is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose, albumin) as diluents. The amount and frequency of administration will

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depend, of course, on such factors as the nature and severity of the rejection episode being treated, the desired response, the condition of the patient, and so forth.

The formulations of the invention can be distributed as articles of manufacture comprising packaging material and the therapeutic porcine cell interaction agents. The packaging material will include a label which indicates that the formulation is for use in the treatment of porcine xenotransplant rejection.

Hybridomas producing the monoclonal antibodies of the invention, i.e., monoclonal antibodies reactive with porcine cell interaction proteins, but not with human cell interaction proteins, can be obtained using purified porcine cell interaction proteins as immunogens followed by screening. Such screening is carried out to identify hybridomas producing antibodies with the desired properties, and can be carried out using appropriate immunoassays. Examples of appropriate immunoassays are the ELISA described below and in copending U.S. patent application serial No.: 08/252,493, filed June 1, 1994, which is incorporated herein by reference. A simple modification of this ELISA (i.e., substituting soluble human cell interaction proteins for soluble porcine cell interaction proteins) can be used to identify those of the hybridomas producing antibodies that bind to porcine cell interaction proteins in which the antibodies do not bind to human cell interaction proteins.

General methods for the immunization of animals (in this case with isolated porcine cell interaction proteins), isolation of antibody producing cells, fusion of such cells with immortal cells (e.g., myeloma cells) to generate hybridomas secreting monoclonal antibodies, screening of hybridoma supernatants for reactivity and/or lack of reactivity of secreted monoclonal antibodies with particular antigens (in this case reactivity with a porcine cell interaction protein but not with the corresponding human cell interaction protein), the preparation of quantities of such antibodies in hybridoma supernatants or ascites fluids, and for the purification and storage of such monoclonal antibodies, can be found in numerous publications. These include: Coligan, et al., eds. Current Protocols In Immunology, John Wiley & Sons, New York, 1992; Harlow and Lane, Antibodies, A Laboratory Manual,

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Cold Spring Harbor Laboratory, New York, 1988; Liddell and Cryer, A Practical Guide To Monoclonal Antibodies. John Wiley & Sons, Chichester, West Sussex, England, 1991; Montz, et al., 1990; Wurzner, et al., 1991; and Mollnes, et al., 1988.

The present invention also includes porcine cell interaction proteins and anti porcine cell interaction protein antibodies with or without associated native patterns of glycosylation. For example, expressing proteins recombinantly in bacteria such as E. coli provides non-glycosylated molecules, while expressing porcine cell interaction proteins or anti porcine cell interaction protein antibodies in mammalian cells can provide glycosylated molecules.

As used herein, the term "antibodies" refers to immunoglobulins produced in vivo, as well as those produced in vitro by a hybridoma, and antigen binding fragments (e.g., Fab' preparations) of such immunoglobulins, as well as to recombinantly expressed antigen binding proteins, including immunoglobulins, chimeric immunoglobulins, "humanized" immunoglobulins, antigen binding fragments of such immunoglobulins, single chain antibodies, and other recombinant proteins containing antigen binding domains derived from immunoglobulins. Publications describing methods for the preparation of such antibodies, in addition to those listed immediately above, include: Reichmann, et al., 1988; Winter and Milstein, 1991; Clackson, et al., 1991; Morrison, 1992; Haber, 1992; and Rodrigues, et al., 1993.

Diagnostic use of the anti porcine cell interaction protein antibodies of the invention can be carried out by assaying the patient's blood for levels of one or more porcine cell interaction proteins. Assays for porcine cell interaction protein levels may be by RIA, ELISA, or other suitable immunoassay using the anti porcine cell interaction protein antibodies of the invention. General methods for performing such assays are set forth in Coligan, et al., 1992. Blood porcine cell interaction protein levels must be monitored at regular intervals, e.g., daily or weekly, and changes in such levels recorded. Any distinct increase in porcine cell interaction protein levels in the patient's blood is an indication that the

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porcine tissue is becoming inflamed, and may indicate the onset of a rejection episode.

An alternative test for rejection, (or a test providing confirmation of the occurrence of rejection as indicated by measurement of soluble cell interaction protein levels) may be obtained by monitoring porcine organ function or by biopsy and histopathological examination of the porcine organ. Such examination will be carried out in order to detect the typical manifestations of transplant rejection, e.g., cellular infiltrates, inflammation, and necrosis. In accordance with the invention, the histopathological examination of xenotransplanted organ biopsy tissues will also include the use of certain of the antibodies of the invention to detect the levels of expression of one or more porcine cell interaction proteins on the surfaces of the cells of the biopsied tissues of the xenotransplanted organ. High levels of such expression (compared to levels on non-transplanted control tissue samples) are indicative of xenotransplant rejection.

Although specific embodiments of the invention are described and illustrated herein, it is to be understood that modifications can be made without departing from the invention's spirit and scope.

For example, the nucleotide sequences of the porcine cell interaction protein-encoding nucleic acid molecules of the invention may be modified by creating nucleic acid mutations which do not significantly change the encoded amino acid sequences. Such mutations include third nucleotide changes in degenerate codons (and other "silent" mutations that do not change the encoded amino acid sequence).

Other such mutations within the scope of the invention and considered as equivalents of the specific embodiments set forth herein include those which result in a highly conservative amino acid substitution for an encoded amino acid while leaving the leucocyte binding (or other cell binding) characteristics of the porcine cell interaction proteins essentially unchanged. Such silent or highly conservative mutations are included within the scope of the invention.

Also included are:

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1) Nucleotide and amino acid sequences comprising changes that are found as naturally occurring allelic variants of the porcine cell interaction protein genes;

2) Sequences which have been truncated so as to only encode the mature porcine cell interaction protein polypeptides, i.e., a porcine cell interaction polypeptide without the amino terminal leader sequence that directs the protein to its typical transmembrane orientation in the cell;

3) Sequences in which the cell interaction protein amino terminal leader sequences have been altered, e.g., substituted with a different leader;

4) Sequences in which a peptide "tag" sequence has been inserted or added on to enable the ready identification and/or purification of recombinant proteins. Such tags include the FLAG epitope (which enables specific binding to anti-FLAG antibodies) and a histidine tag sequence, as described above;

5) Sequences that have been altered to produce a soluble porcine cell interaction protein by, for example, truncation.

Without intending to limit it in any manner, the present invention will be more fully described by the following examples. Materials and methods used in various of the examples are as follows.

MATERIALS AND METHODS

Materials: A monoclonal antibody to human LFA-1 (clone 25.3) was obtained from AMAC Inc, Westbrook ME. Human TNFa and IL-1 were obtained from Collaborative Biomedical Products, Bedford MA. Dulbecco's modified Eagles medium (DMEM) and RPMI-1640 medium were purchased from JRH Biosciences, Lenexa KS. Fetal bovine serum (FBS) was purchased from Harlan, Indianapolis IN. Sterile Hank's balanced salt solution (HBSS) and phosphate buffered saline (PBS) were purchased from Bio Whittaker, Walkersville MD. Calcein AM was obtained from Molecular Probes, Eugene OR. Neuraminidase was purchased from Boehringer Mannheim, Indianapolis IN. All other reagents were of analytical grade or better and purchased from Sigma Chemical Co., Saint Louis MO, unless otherwise specified.

Cell culture: Ramos, Jurkat, and U-937 cells were obtained from the American Type Culture Collection. Ramos and Jurkat were maintained in RPMI 1640 supplemented with 10% heat-inactivated

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FCS and 2 mM glutamine. U937 cells were maintained in RPMI 1640 supplemented with 15% FCS.

Porcine aortic endothelial cells (PAEC) were obtained at passage 1 (Cell Systems, Kirkland WA) and maintained in DMEM containing 10% FBS, penicillin 100 U/ml, and streptomycin 100 µg/ml (pen/strep, JRH Biosciences, Lenexa KS), hereinafter referred to as D10 medium. PAEC were at passage 2-4 in all assays. For cell binding assays, PAEC were removed from culture flasks with trypsin EDTA and replated onto 96 well culture dishes at a density of 1 x 10^4 cells/well. The human promyelocytic leukemia cell line HL-60 was obtained from the American Type Culture Collection (ATCC), Rockville, MD and maintained in D10.

Assays for Neutrophil / HL-60 binding to PAEC: Confluent monolayers of PAEC in 96 well plates were incubated (4 hr, 37°C) in 200 µl/well DMEM alone, DMEM containing 25 ng/ml human TNFa, or DMEM containing 10 ng/ml human IL-1. During this incubation, human neutrophils were isolated from 60 ml of human blood obtained from a healthy donor using the manufacturer's protocol (Polymorphoprep, Oslo, Norway), or HL-60 cells were spun down from culture medium.

The isolated neutrophils or HL-60 cells were washed 2x with HBSS, resuspended in HBSS containing 1% BSA (HBSS/BSA) at a final concentration of 3 x 10^6 cells/ml, incubated (30 min, 37°C) in the cytoplasmic indicator dye calcein AM (10 µM), washed 2x with HBSS and resuspended to 3 x 10^6 cells/ml in HBSS/BSA. Prior to addition to PAEC monolayers, the purified human neutrophils or HL-60 cells were incubated (30 min, 37°C) in either, HBSS/BSA, HBSS/BSA containing 0.25 U/ml neuraminidase, or HBSS/BSA containing 10 µg/ml anti-LFA-1 mAb.

Following this incubation, the neutrophils or HL-60 cells were washed 2x with HBSS/BSA and resuspended to 3 x 10^6 cells/ml. PAEC monolayers were then washed 3x with HBSS/BSA and calcein-loaded human neutrophils or HL-60 cells were added at 3 x 10^5 cells/well. The plates were centrifuged briefly (250 x g, 1 minute), incubated in the dark for 5 min at 37°C and then centrifuged upside down at 250 x g for 3 minutes. The media and unbound neutrophils or HL-60 cells were removed from the plate

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and the bound cells were lysed by the addition of 1% SDS (100 µl/well) in HBSS. Neutrophil or HL-60 cell binding was determined by measuring the release of calcein from bound neutrophils or HL-60 cells into the lysis buffer using a Cytofluor 2350 (Millipore, Bedford MA -- excitation wavelength=485nm, emission wavelength=530nm). Background fluorescence was determined from wells containing PAEC that did not receive labeled neutrophils or HL-60 cells.

ELISA screen for anti-porcine cell interaction protein antibodies: To test antibodies for reactivity with porcine cell interaction proteins, an ELISA is carried out using the following protocol:

A 50 µL aliquot of a solution of a solublized (or soluble form of) a porcine cell interaction molecule is suspended in sodium carbonate/bicarbonate buffer, pH 9.5 and incubated overnight at 4°C in each test well of a 96 well plate (Nunc-Immuno F96 Polysorp, A/S Nunc, Roskilde, Denmark) in order to bind the protein to the plastic plate. The wells are then subjected to a wash step. (Each wash step consisted of three washes with TBST.) Next, test wells were blocked with 200 µL of blocking solution, 1% BSA in TBS (BSA/TBS), for 1 hour at 37°C (or, in some cases, 4°C overnight). After an additional wash step, a 50 µL aliquot of test antibody solution (e.g., hybridoma supernatant) is incubated in each test well for 1 hour at 37°C with a subsequent wash step.

As a secondary (detection) antibody, 50 µL of a 1:2000 dilution of horseradish peroxidase (HRP) conjugated goat anti-mouse IgG in BSA/TBS is incubated in each test well for 1 hour at 37°C, followed by a wash step. Following the manufacturer's procedures, 10 mg of O-phenylenediamine (Sigma Chemical Company, St. Louis, MO, Catalog No. P-8287) is dissolved in 25 mLs of phosphate-citrate buffer (Sigma Chemical Company, St. Louis, MO, Catalog No. P-4922), and 50 µL of this substrate solution is added to each well to allow detection of peroxidase activity. Finally, to stop the peroxidase detection reaction, a 50 µL aliquot of 3N hydrochloric acid is added to each well. The presence of antibodies reactive with a porcine cell interaction protein in the test antibody solutions is read out by a spectrophotometric OD determination at 490 nm.

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The solution of porcine cell adhesion protein in sodium carbonate/bicarbonate buffer that serves as a source of the protein bound to the plastic plate is used at 2-fold serial dilutions across the plate starting at 50 µg of protein per mL, i.e., at 50, 25, 12.5, 6.25, 3.125, 1.5625, and 0.78125 µg/mL. These dilutions are used to determine the minimum amount of porcine cell interaction protein that will give maximum sensitivity in this assay.

Cloning of Porcine VCAM. Total RNA was prepared from TNFa-stimulated PAEC (25) and used to generate a porcine cDNA probe by reverse transcriptase-PCR using the following primers: 5' AAAAAAGCGGAGACAGGAGACA 3' and 5' TTCTGTGCTTCTACAAGACT 3'. The primer selection was based on sequence similarity between human, murine and rat VCAM. The resulting 299 bp PCR product was subcloned by TA-cloning into plasmid pCRII creating plasmid pCRIIpVCAM48 (Invitrogen, San Diego, CA). Plasmid pCRIIpVCAM48 was random primed and used to screen a TNFa-stimulated PAEC cDNA Uni-ZAP XR 1 library (25). A full-length, five Ig domain pVCAM cDNA was identified and entirely sequenced on both strands using a series of internal primers. The sequence for our porcine VCAM was identical to that reported by Tsang et al. (26) except for seven nucleotide differences between the two sequences at positions 185 (T>G), 655 (C>T), 815 (A>G), 1060 (C>T), 1120 (G>A), 1234 (A>C) and 1311 (C>T) which result in 4 amino acid changes at residues 30 (F>V), 240 (M>V), 379 (E>D), and 405 (T>I). This sequence has been submitted to the GenBank database under accession number L43124.

Cells. COS-7 and Ramos cells were obtained from the American Type Culture Collection. Ramos cells were maintained in RPMI 1640 supplemented with 10% heat-inactivated FBS and 2 mM glutamine. COS-7-7 and human 293-EBNA cells were grown as previously described (27). PAEC AND HUVECs were obtained (Cell Systems, Kirkland WA) at passage 1 and maintained as described (6) and used for adhesion assays or RNA isolation at passages 2-4. Human resting T cells were purified as previously described (6).

Construction of pVCAM and spVCAM Expression Vectors. The complete pVCAM coding region was cloned into the mammalian

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expression vectors pAPEX-1 and pAPEX-3 (27). Plasmid pAPEX-1-pVCAM was transfected into COS-7 cells as described previously (27). A truncated version of pVCAM was constructed by deleting the transmembrane and cytoplasmic domains as follows. Briefly, the mammalian expression vector pAPEX-3/pVCAM was cleaved with *Nhe*I and *Sph*I and ligated to a 181 bp PCR fragment which supplied a six histidine tag and a stop codon using the following primers: 5'-CCCGAATTCGCATATACCATCCACAGG-3' and 5'-CGCGGA TCCTGCATGCATTAATGGTGATGGTGATGGTGTTCAGAAGAAAAATAGTCC-3'. This plasmid, pAPEX-3/spVCAM, encodes the signal sequence and extracellular domains of pVCAM.

Cell Adhesion Assays. Confluent monolayers of PAEC were used untreated or stimulated with 25 ng/ml of TNFa for 16-24 h. Ramos cells or human peripheral blood T cells were washed twice with RPMI containing 1.0% FBS (RPMI/1) and labeled with 10 mM Calcein-AM (Molecular Probes, Eugene OR) as previously described (6). Labeled cells (3 x 10^5 cells/ml) were washed twice with RPMI/1 and added (100 ml/well) to cell monolayers. The plates were gently centrifuged (50 x g, 1 min) and incubated in the dark for 30 min at 37°C in 5% CO_2. The plates were inverted and centrifuged at 250 x g for 3 min. Nonadherent cells were removed from the plate by gently washing five times with RPMI/1 and after a brief centrifugation, adherent cells were lysed by addition of 0.1 ml 1 % SDS to each well. Adherence was quantified by measuring the release of the fluorescent dye from bound cells using a Cytofluor 2350 fluorescent plate reader (Millipore, Bedford, MA) using an excitation wavelength of 485 nm and an emission wavelength of 530 nm. Background fluorescence was determined from wells containing COS-7 cells or PAEC that did not receive labeled cells. Test and control samples were performed in triplicate in each experiment. For the inhibition studies, labeled Ramos or human peripheral T cells were preincubated for 15 min at 37°C with mAb HP2/1 (anti-VLA-4) at 10 ug/ml prior to the adhesion assay. Blocking by anti-pVCAM mAbs was assessed in the continuous presence of the indicated concentrations of mAb.

Purification of spVCAM. The APEX-3/spVCAM expression vector was transfected into human 293-EBNA embryonic kidney cells (Invitrogen, San Diego, CA) as previously described (27). spVCAM was purified from concentrated serum-free conditioned medium from

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293-EBNA cells expressing spVCAM by metal affinity chromatography using a nickel charged nitrilotriacetic acid (NTA) resin (Qiagen, Chatsworth, CA). Briefly, 200 ml of concentrated medium was adjusted to 20 mM Tris-Cl, pH 7.9, 500 mM NaCl, 5mM imidazole and incubated overnight with 5 ml Ni^{++}-NTA resin at 4°C with gentle agitation. The resin was washed with an additional 30 ml of binding buffer followed by 40 ml of wash buffer (20 mM Tris-Cl, pH 7.9, 500 mM NaCl, 60 mM imidazole). Finally, spVCAM was eluted with 9 ml elution buffer (20 mM Tris-Cl, pH 7.9, 500 mM NaCl, 1 M imidazole), concentrated with a Centriprep-30 (Amicon, Beverly MA), dialyzed extensively against PBS, sterile filtered and stored at 4°C. Protein concentration was determined by the Lowry method. Affinity purified spVCAM was subjected to SDS-PAGE, transferred to polyvinylidene difluoride membranes (Problot, Applied Biosystems) and sequenced directly using an Applied Biosystems 470A gas phase protein sequencer.

spVCAM Adhesion Assay. The ability of the truncated soluble form of pVCAM to support adhesion was assessed after immobilization on plastic. Briefly, recombinant spVCAM or BSA was precoated onto separate microtest wells (NUNC-Immuno Plate, Maxisorp) at the indicated concentrations in 100 ml binding buffer (15 mM sodium bicarbonate/35 mM sodium carbonate, pH 9.2) at 4°C overnight. The wells were blocked with RPMI 1640 containing 10 mg/ml BSA for 1 h at ambient temperature and washed once with RPMI containing 10% fetal bovine serum. Labeled Ramos cells (3 x 10^5 cells/well) were added to the wells, the plates centrifuged (50 x g, 1 min) and incubated at 37°C for 30 min. The nonadherent cells were removed by centrifugation of the sealed microtiter plate in the inverted position at 200 x *g* for 3 min and the bound cells lysed with 1.0 % SDS. The amount of released fluorochrome from lysed cells was determined as described above. For spVCAM binding inhibition studies, Ramos cells were preincubated with anti-human VLA-4 mAb (HP2/1) at 10 mg/ml for 15 min at 37°C or spVCAM coated wells were treated with varying concentrations of anti-pVCAM mAbs for 1 h at 37°C prior to the adhesion assays.

Antibodies. Blocking anti-a4-integrin (CD49d) mAb HP2/1 was purchased from Amac, Inc. (Westbrook, ME). Mouse anti-porcine

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VCAM (anti-pVCAM) mAbs were prepared by intraperitoneal immunization of Balb/c mice with 100 mg of recombinant spVCAM in complete Freund's adjuvant. Following two boost injections with 100 mg of spVCAM in incomplete Freund's adjuvant, SP2/0 myeloma cells were fused using polyethylene glycol with spleen cells from the immunized animals. Hybridoma supernatants were screened 10-14 days later by ELISA for binding to spVCAM. Blocking anti-pVCAM mAbs were screened in a 30 min adhesion assay for the ability to inhibit the binding of Ramos cells to immobilized spVCAM and in a second adhesion assay for the ability to inhibit the binding of labeled Ramos cells to TNFa-stimulated PAEC (see below). Three anti-pVCAM mAbs (2A2, 3F4, 5D11) were selected for characterization. The mAbs were purified from ascites fluid on protein G-SEPHAROSE columns (Pharmacia, Piscataway, NJ) and are of the IgG1 isotype.

FACS analysis. Activated PAEC and HUVECs were analyzed for cell surface expression of VCAM using mouse anti-pVCAM mAb 2A2, 3F4, 5D11, or a commercially available mouse anti-hVCAM mAb (51-10C9; Pharmingen, San Diego, CA). Cells were treated with human TNFa (25 ng/ml) for approximately 24 h, harvested from culture flasks using mild trypsination and washed twice with PBS containing 2% FBS (PBS/2). Five hundred thousand cells were incubated with 5.0 mg/ml 3F4, 2A2, 5D11 or 51-10C9 for 1 h on ice. The cells were washed twice with PBS/2 and incubated for 30 min on ice with FITC-conjugated goat anti-mouse IgG (Zymed Laboratories, San Francisco, CA). The cells were washed in PBS/2 and analyzed by FACS using a Becton Dickerson FACSort (Becton Dickenson Immunocytometry Systems, San Jose, CA).

Epitope mapping by pairwise interaction analysis. F(ab')2 fragments were prepared by digestion of purified 2A2 and 3F4 mAb with ficin in the presence of 1 mM cysteine as described by the manufacturer (Pierce, Rockford, IL). Undigested mAb and Fc fragments were removed by subsequent protein A-sepharose chromatography. PolySorp microtiter plates (Nunc, Naperville, IL) were coated overnight at 4°C with 50 ml/well of 2 mg/ml 2A2 or 3F4 F(ab')2 in 0.1 M Na_2CO_3 pH 9.6. The plates were then washed three times with PBS containing 0.5% (v/v) Tween 20 and blocked with blocking buffer (PBS supplemented with 1% (w/v) BSA and 0.5% Tween 20) at 37°C for 1 h. The plates were washed and incubated

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with 50 ml/well blocking buffer containing 2 mg/ml spVCAM at 37°C for 1 h. After additional washing, the plates were incubated at 37°C for 1 h with 50 ml/well blocking buffer or blocking buffer containing 1 mg/ml 2A2, 3F4, or 5D11 mAb. After washing the plates were incubated with 50 ml/well blocking buffer containing peroxidase-conjugated goat anti-mouse IgG Fc (Sigma, St. Louis, MO) at a 1:2000 dilution. After three final washes, the plate was developed with 50 ml/well substrate buffer (0.05 M phosphate-citrate buffer, pH 5.0/0.3 mg/ml sodium perborate/0.4 mg/ml o-phenylenediamine dihydrochloride). Reactions were stopped by the addition of 50 ml/well 1 M sulfuric acid. Quantitation was performed using a Bio-Rad model 3550 plate reader set at 490 nm.

Statistical analysis. Differences between the results of experimental treatments were evaluated by means of the Student's *t*-test.

RESULTS

COS-7 Cells Transiently Transfected with pVCAM cDNA Bind Human Ramos Cells in a VLA-4 Dependent Manner. To test the ability of pVCAM to support adhesion, we assayed the binding of Ramos cells to TNFa-stimulated PAEC and pVCAM-transfected COS cells. Labeled Ramos cells bound to TNFa-induced PAEC and pVCAM-transfected COS-7 cells (Fig. 1). In contrast, Ramos cells did not adhere to mock-transfected COS-7 cells.

To evaluate the predicted role of human a4b1 integrins (VLA-4) in pVCAM dependent cell-cell adhesion, an anti-human VLA-4 mAb was tested for its ability to inhibit adhesion of Ramos cells to pVCAM-transfected COS-7 cells and PAEC stimulated with TNFa. As shown in Fig. 1, the anti-VLA-4 mAb HP2/1 completely blocked the attachment of Ramos to both TNFa-activated PAEC and pVCAM-transfected COS-7 cells. Cell-cell adhesion was not blocked by an isotype-matched control antibody. Thus, pVCAM is a functional adhesion molecule and supports binding of TNFa-stimulated PAEC and pVCAM-transfected COS-7 cells to human lymphoid cells in a VLA-4-dependent manner.

VLA-4$^+$ Ramos Cells Specifically Adhere to Immobilized spVCAM. The spVCAM-$(His)_6$ used in this study was created by fusing a cDNA fragment encoding the extracellular domain of pVCAM (residues 1-497) to a sequence encoding a C terminal hexahistidine tag and a

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stop codon at the leucine which is the first amino acid of the putative transmembrane domain (Fig. 2A). The resulting spVCAM was secreted into the culture medium of stably transfected 293-EBNA cells and purified by metal affinity chromatography to >90 % purity (Fig. 2B). spVCAM was subjected to 6 cycles of N-terminal sequencing. The sequence (VSQNVK) included four additional amino acids from that determined for the amino terminus of human VCAM (28), the putative termini for rat and mouse VCAM (29) and the pVCAM sequence recently reported by Tsang et al. (26). The secretion of spVCAM as a soluble protein, and its N-terminal sequence, confirms the assignment of the pVCAM signal sequence, transmembrane and cytoplasmic regions.

We examined the concentration dependence of the immobilized pVCAM on binding to labeled Ramos cells (Fig. 3A). A fixed number of labeled cells were incubated in wells precoated with the indicated concentrations of spVCAM. Ramos cells bound to immobilized spVCAM in a dose-dependent manner with saturation obtained at approximately 0.1 mg/well (Fig. 3A). Pretreatment of labeled Ramos cells with anti-VLA-4 mAb HP2/1 caused complete inhibition of spVCAM mediated binding (Fig. 3B). In control experiments, Ramos cells failed to bind to immobilized BSA (Fig. 3B). These results demonstrate that soluble spVCAM mediates binding of human VLA-4^+ target cells.

Anti-pVCAM mAbs. Having established the interaction of human VLA-4 with pVCAM, we investigated the potential of inhibiting this interaction with blocking mAbs to pVCAM. Hybridomas were derived from the spleen cells of Balb/c mice immunized with spVCAM and used to make hybridomas. Numerous mAbs were produced that recognized pVCAM by ELISA and FACS analysis (data not shown). Several mAbs were tested in a rapid screening assay involving the adherence of Ramos cells to immobilized spVCAM. Two mAbs, 2A2 and 3F4, significantly inhibited Ramos cell binding in a dose-dependent manner (Fig. 4). Anti-pVCAM mAb 3F4 completely blocked Ramos cell binding to spVCAM at a concentration of 3 mg/ml, where as mAb 2A2 maximally inhibited binding to pVCAM at a higher concentration (30 mg/ml) (Fig. 4). The weaker inhibition observed with the anti-pVCAM mAb 2A2 may reflect its reactivity with a distinct epitope on the pVCAM molecule (see below). In

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contrast, a third anti-pVCAM mAb, 5D11, showed virtually no inhibitory effect, even at high concentrations (Fig. 4).

To characterize the specificity of these mAbs to pVCAM, FACS analysis was performed on cytokine-stimulated HUVEC and PAEC. The anti-pVCAM mAbs 2A2 and 3F4 all reacted with TNFa-stimulated PAEC but did not react with TNFa-stimulated HUVEC cells (Fig. 5). Of the nonblocking mAbs, 5D11, was also shown to be specific for PAEC (Fig. 5). In contrast, the anti-human VCAM-1 mAb, 51-10C9, reacted with stimulated HUVEC but did not cross react with cell surface pVCAM present on stimulated PAEC, indicating that mAbs 2A2, 3F4 and 5D11 recognize porcine-specific epitopes. Flow cytometric analysis also revealed that pVCAM was highly expressed on LPS activated PAEC, whereas recombinant human IL-1 did not induce VCAM expression on PAEC (data not shown).

Epitope mapping of the anti-pVCAM mAbs was performed by pairwise interaction analysis. This approach tested the ability of mAb pairs to bind simultaneously to spVCAM. As shown in Fig. 6, mAbs 2A2 and 3F4 did not interfere with the binding of the remaining mAbs to spVCAM. Therefore, the mAb epitopes are nonoverlapping and represent distinct antigenic regions on the pVCAM molecule.

Inhibition of Ramos and Human T Cell Binding to Cytokine-Activated PAEC by Anti-pVCAM mAbs. We next tested the ability of mAbs 2A2 and 3F4 to block Ramos and human T cell binding to stimulated PAEC. The mAbs 3F4 and 2A2 inhibited Ramos cell binding to activated PAEC by >90% (Fig. 7). In analogous fashion, adhesion of human T cells to stimulated PAEC was blocked (~65%) by the same mAbs ($p<0.01$, Fig. 7). The anti-pVCAM mAbs 2A2 and 3F4 inhibited binding of human T cells to TNFa-stimulated PAEC to the same degree as the anti-VLA-4 mAb (Fig. 7). The degree of anti-pVCAM mAb-mediated inhibition of T cell interaction with PAEC was less than for Ramos binding to PAEC, suggesting that adhesion interactions other than VLA-4/VCAM are likely to play a role in human T cell/PAEC adhesion. Nevertheless, the data demonstrate a major role for pVCAM in mediating PAEC adhesion to human lymphocytes.

Recombinant Expression of anti-VCAM Antibodies

Standard molecular biology techniques were used (Sambrook et al., 1989). Cloning of the variable regions from the hybridomas 2A2

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and 3F4 was performed using a set of commercially available primers (Mouse Ig-Primer Set, Novagen, Madison, WI) as described previously (Evans et al, In press). Chimeric antibodies were produced by cloning the 2A2 and 3F4 variable regions into the expression plasmid pAPEX-3P (Evans et al., 1995) modified to contain the human gamma4 constant region in place of the human gamma 1 C1 region. The resulting expression plasmids were transfected into 293-EBNA cells and selected for puromycin resistance as described previously (Evans et al., 1995). Upon reaching confluence, cells were refed serum-free HB PRO (Irvine Scientific, Santa Ana, CA) every 3 to 4 days. The conditioned medium was centrifuged at 4500 x g to remove cell debris, concentrated 10-fold, and dialyzed into 20 mM sodium phosphate, pH 7.0. Antibody was subsequently purified using a 1 ml HiTrap Protein A column (Pharmacia, Piscataway, NJ), dialyzed into PBS, passed through a 0.2 micron filter, and stored at 4°C. $F(ab')_2$ and Fab were produced by digestion of murine monoclonal antibody or chimeric antibody with Ficin (Pierce, Rockford, IL) or papain (Pierce), respectively, followed by protein-A chromatography to remove undigested antibody and Fc fragments.

The antibodies were tested for function as described above.

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1. ANTIBODY SEQUENCES

2A2 LIGHT CHAIN DNA SEQUENCE

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4461/1                                          4491/11
ATG GGC TTC AAG ATG GAG TCA CAT TTT CAG GTC TTT GTA TAC ATG TTG CTG TGG TTG TCT
M   G   F   K   M   E   S   H   F   Q   V   F   V   Y   M   L   L   W   L   S
4521/21                                         4551/31
GGT GTT AAT GGA GAC ATT GTG ATG ACC CAG TCT CAA AAA TTC ATG TCC ACA TCA TTA GGA
G   V   N   G   D   I   V   M   T   Q   S   Q   K   F   M   S   T   S   L   G
4581/41                                         4611/51
GAC AGG GTC AGC GTC ACC TGC AAG GCC AGT CAG AAT GTG GGT CCT AAT GTA GCC TGG TTT
D   R   V   S   V   T   C   K   A   S   Q   N   V   G   P   N   V   A   W   F
4641/61                                         4671/71
CAA CAG AAA CCA GGC CAG TCT CCT AAA ACA CTT ATT TAC TCG GCA TCC TTC CGC TAC AGT
Q   Q   K   P   G   Q   S   P   K   T   L   I   Y   S   A   S   F   R   Y   S
4701/81                                         4731/91
GGA GTC CCT GAT CGC TTC ACA GGC AGT GGA TCT GGG ACA GAT TTC ACT CTC ACC ATC ACC
G   V   P   D   R   F   T   G   S   G   S   G   T   D   F   T   L   T   I   T
4761/101                                        4791/111
AAT GTG CAG TCT GAA GAC TTG GCA GAG TAT TTC TGT CAT CAA TAT AAC TCC TAT CCT CTC
N   V   Q   S   E   D   L   A   E   Y   F   C   H   Q   Y   N   S   Y   P   L
4821/121                                        4851/131
ACG TTC GGG GGG GGG ACC AAG CTG AAA ATA AAA CGA ACT GTG GCT GCA CCA TCT GTC TTC
T   F   G   G   G   T   K   L   K   I   K   R   T   V   A   A   P   S   V   F
4881/141                                        4911/151
ATC TTC CCG CCA TCT GAT GAG CAG TTG AAA TCT GGA ACT GCC TCT GTT GTG TGC CTG CTG
I   F   P   P   S   D   E   Q   L   K   S   G   T   A   S   V   V   C   L   L
4941/161                                        4971/171
AAT AAC TTC TAT CCC AGA GAG GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC CTC CAA TCG
N   N   F   Y   P   R   E   A   K   V   Q   W   K   V   D   N   A   L   Q   S
5001/181                                        5031/191
GGT AAC TCC CAG GAG AGT GTC ACA GAG CAG GAC AGC AAG GAC AGC ACC TAC AGC CTC AGC
G   N   S   Q   E   S   V   T   E   Q   D   S   K   D   S   T   Y   S   L   S
5061/201                                        5091/211
AGC ACC CTG ACG CTG AGC AAA GCA GAC TAC GAG AAA CAC AAA GTC TAC GCC TGC GAA GTC
S   T   L   T   L   S   K   A   D   Y   E   K   H   K   V   Y   A   C   E   V
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5121/221                                                    5151/231
ACC CAT CAG GGC CTG AGC TCG CCC GTC ACA AAG AGC TTC AAC AGG GGA GAG TGT TAG
T   H   Q   G   L   S   S   P   V   T   K   S   F   N   R   G   E   C   *
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2A2 HEAVY CHAIN cDNA SEQUENCE

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1/1                                                                 31/11
ATG GGA TGG AGC TAT ATC ATG TTC TTC TTG GTA TCA ACA GCT ACA GTT GTC CAC TCC CAG
M   G   W   S   Y   I   M   F   F   L   V   S   T   A   T   V   V   H   S   Q
61/21                                                               91/31
GTA CAA CTG CAG CAG TCT GGG CCT CAG CTG GTT AGG CCT GGG ACT TCA GTG AAG ATA TCC
V   Q   L   Q   Q   S   G   P   Q   L   V   R   P   G   T   S   V   K   I   S
121/41                                                              151/51
TGC AAG GCT TCT GGT TAC TCA TTC ACC AGC TAT TGG ATG CAC TGG GTG AAG CAG AGG CCT
C   K   A   S   G   Y   S   F   T   S   Y   W   M   H   W   V   K   Q   R   P
181/61                                                              211/71
GGA CAA GAT CTT GAG TGG ATT GGC ATG ATT GAT CCA TCC GAT AGT GAA GTT AAA TTA AAT
G   Q   D   L   E   W   I   G   M   I   D   P   S   D   S   E   V   K   L   N
241/81                                                              271/91
CAG AGG TTA AAG GAC AAG GCC ATA TTG ACT GTT GAC AAA TCC TCC AAC ACA GCC TAC ATG
Q   R   L   K   D   K   A   I   L   T   V   D   K   S   S   N   T   A   Y   M
301/101                                                             331/111
CAA TTC AGC GGC CCG ACT TCT GAG GAC TCT GCG GTC TAT TAC TGT ACA AGA GGG GAG GTT
Q   F   S   G   P   T   S   E   D   S   A   V   Y   Y   C   T   R   G   E   V
361/121                                                             391/131
TCC TGG TTT GCT TAC TGG GGC CAG GGG ACT CTG GTC ACT GTC TCT GCA GCC TCC ACC AAG
S   W   F   A   Y   W   G   Q   G   T   L   V   T   V   S   A   A   S   T   K
421/141                                                             451/151
GGC CCA TCC GTC TTC CCC CTG GCG CCC TGC TCC AGG AGC ACC TCC GAG AGC ACA GCC GCC
G   P   S   V   F   P   L   A   P   C   S   R   S   T   S   E   S   T   A   A
481/161                                                             511/171
CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC
L   G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S   G
541/181                                                             571/191
GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC
A   L   T   S   G   V   H   T   F   P   A   V   L   Q   S   S   G   L   Y   S
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601/201                                                631/211
CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACG AAG ACC TAC ACC TGC AAC
L   S   S   V   V   T   V   P   S   S   S   L   G   T   K   T   Y   T   C   N
661/221                                                691/231
GTA GAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AGA GTT GAG TCC AAA TAT GGT CCC
V   D   H   K   P   S   N   T   K   V   D   K   R   V   E   S   K   Y   G   P
721/241                                                751/251
CCA TGC CCA TCA TGC CCA GCA CCT GAG TTC CTG GGG GGA CCA TCA GTC TTC CTG TTC CCC
P   C   P   S   C   P   A   P   E   F   L   G   G   P   S   V   F   L   F   P
781/261                                                811/271
CCA AAA CCC AAG GAC ACT CTC ATG ATC TCC CGG ACC CCT GAG GTC ACG TGC GTG GTG GTG
P   K   P   K   D   T   L   M   I   S   R   T   P   E   V   T   C   V   V   V
841/281                                                871/291
GAC GTG AGC CAG GAA GAC CCC GAG GTC CAG TTC AAC TGG TAC GTG GAT GGC GTG GAG GTG
D   V   S   Q   E   D   P   E   V   Q   F   N   W   Y   V   D   G   V   E   V
901/301                                                931/311
CAT AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TTC AAC AGC ACG TAC CGT GTG GTC AGC
H   N   A   K   T   K   P   R   E   E   Q   F   N   S   T   Y   R   V   V   S
961/321                                                991/331
GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAC GGC AAG GAG TAC AAG TGC AAG GTC TCC
V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K   V   S
1021/341                                               1051/351
AAC AAA GGC CTC CCG TCC TCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA
N   K   G   L   P   S   S   I   E   K   T   I   S   K   A   K   G   Q   P   R
1081/361                                               1111/371
GAG CCA CAG GTG TAC ACC CTG CCC CCA TCC CAG GAG GAG ATG ACC AAG AAC CAG GTC AGC
E   P   Q   V   Y   T   L   P   P   S   Q   E   E   M   T   K   N   Q   V   S
1141/381                                               1171/391
CTG ACC TGC CTG GTC AAA GGC TTC TAC CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC AAT
L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   E   S   N
1201/401                                               1231/411
GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC
G   Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   G   S   F
1261/421                                               1291/431
TTC CTC TAC AGC AGG CTA ACC GTG GAC AAG AGC AGG TGG CAG GAG GGG AAT GTC TTC TCA
F   L   Y   S   R   L   T   V   D   K   S   R   W   Q   E   G   N   V   F   S
1321/441                                               1351/451
TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACA CAG AAG AGC CTC TCC CTG TCT
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C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   S   L   S   L   S
1381/461
CTG GGT AAA TGA
L   G   K   *
```

2A2 (CHIMERIC) HUMAN G2/G4 cDNA

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1/1                                                                    31/11
ATG GGA TGG AGC TAT ATC ATG TTC TTC TTG GTA TCA ACA GCT ACA GTT GTC CAC TCC CAG
M   G   W   S   Y   I   M   F   F   L   V   S   T   A   T   V   V   H   S   Q
61/21                                                                  91/31
GTA CAA CTG CAG CAG TCT GGG CCT CAG CTG GTT AGG CCT GGG ACT TCA GTG AAG ATA TCC
V   Q   L   Q   Q   S   G   P   Q   L   V   R   P   G   T   S   V   K   I   S
121/41                                                                 151/51
TGC AAG GCT TCT GGT TAC TCA TTC ACC AGC TAT TGG ATG CAC TGG GTG AAG CAG AGG CCT
C   K   A   S   G   Y   S   F   T   S   Y   W   M   H   W   V   K   Q   R   P
181/61                                                                 211/71
GGA CAA GAT CTT GAG TGG ATT GGC ATG ATT GAT CCA TCC GAT AGT GAA GTT AAA TTA AAT
G   Q   D   L   E   W   I   G   M   I   D   P   S   D   S   E   V   K   L   N
241/81                                                                 271/91
CAG AGG TTA AAG GAC AAG GCC ATA TTG ACT GTT GAC AAA TCC TCC AAC ACA GCC TAC ATG
Q   R   L   K   D   K   A   I   L   T   V   D   K   S   S   N   T   A   Y   M
301/101                                                                331/111
CAA TTC AGC GGC CCG ACT TCT GAG GAC TCT GCG GTC TAT TAC TGT ACA AGA GGG GAG GTT
Q   F   S   G   P   T   S   E   D   S   A   V   Y   Y   C   T   R   G   E   V
361/121                                                                391/131
TCC TGG TTT GCT TAC TGG GGC CAG GGG ACT CTG GTC ACT GTC TCT GCA GCC TCC ACC AAG
S   W   F   A   Y   W   G   Q   G   T   L   V   T   V   S   A   A   S   T   K
421/141                                                                451/151
GGC CCA TCC GTC TTC CCC CTG GCG CCC TGC TCC AGG AGC ACC TCC GAG AGC ACA GCC GCC
G   P   S   V   F   P   L   A   P   C   S   R   S   T   S   E   S   T   A   A
481/161                                                                511/171
CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC
L   G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S   G
541/181                                                                571/191
GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC
A   L   T   S   G   V   H   T   F   P   A   V   L   Q   S   S   G   L   Y   S
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601/201                                    631/211
CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AAC TTC GGC ACC CAG ACC TAC ACC TGC AAC
L   S   S   V   V   T   V   P   S   S   N   F   G   T   Q   T   Y   T   C   N
661/221                                    691/231
GTA GAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG ACA GTT GAG CGC AAA TGT TGT GTC
V   D   H   K   P   S   N   T   K   V   D   K   T   V   E   R   K   C   C   V
721/241                                    751/251
GAG TGC CCA CCG TGC CCA GCA CCA CCT GTG GCA GGA CCG TCA GTC TTC CTC TTC CCC CCA
E   C   P   P   C   P   A   P   P   V   A   G   P   S   V   F   L   F   P   P
781/261                                    811/271
AAA CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC ACG TGC GTG GTG GTG GAC
K   P   K   D   T   L   M   I   S   R   T   P   E   V   T   C   V   V   V   D
841/281                                    871/291
GTG AGC CAG GAA GAC CCC GAG GTC CAG TTC AAC TGG TAC GTG GAT GGC GTG GAG GTG CAT
V   S   Q   E   D   P   E   V   Q   F   N   W   Y   V   D   G   V   E   V   H
901/301                                    931/311
AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TTC AAC AGC ACG TAC CGT GTG GTC AGC GTC
N   A   K   T   K   P   R   E   E   Q   F   N   S   T   Y   R   V   V   S   V
961/321                                    991/331
CTC ACC GTC CTG CAC CAG GAC TGG CTG AAC GGC AAG GAG TAC AAG TGC AAG GTC TCC AAC
L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K   V   S   N
1021/341                                   1051/351
AAA GGC CTC CCG TCC TCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA GAG
K   G   L   P   S   S   I   E   K   T   I   S   K   A   K   G   Q   P   R   E
1081/361                                   1111/371
CCA CAG GTG TAC ACC CTG CCC CCA TCC CAG GAG GAG ATG ACC AAG AAC CAG GTC AGC CTG
P   Q   V   Y   T   L   P   P   S   Q   E   E   M   T   K   N   Q   V   S   L
1141/381                                   1171/391
ACC TGC CTG GTC AAA GGC TTC TAC CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC AAT GGG
T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   E   S   N   G
1201/401                                   1231/411
CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC
Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   G   S   F   F
1261/421                                   1291/431
CTC TAC AGC AGG CTA ACC GTG GAC AAG AGC AGG TGG CAG GAG GGG AAT GTC TTC TCA TGC
L   Y   S   R   L   T   V   D   K   S   R   W   Q   E   G   N   V   F   S   C
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                                    1351/451
1321/441
TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACA CAG AAG AGC CTC TCC CTG TCT CTG
S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   S   L   S   L
1381/461
GGT AAA TGA
G   K   *
```

2A2 HUMAN G2/G4 EXPERSSION PLASMID INSERT SEQUENCE

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   1 gtgaccaatacaaaacaaaagcgcccctcgtaccagcgaagaagggcagagatgccgtagtcaggtttagttcgtccgg 80

  81 cggcgggggatctgtatggtgcactctcagtacaatctgctctgatgccgcatagttaagccagtatctgctccctgctt 160

 161 gtgtgttggaggtcgctgagtagtgcgcgagcaaaatttaagctacaacaaggcaaggcttgaccgacaattgcatgaag 240

 241 aatctgcttagggttaggcgttttgcgctgcttcgcgatgtacgggccagatatacgcgttgacattgattattgactag 320

 321 ttattaatagtaatcaattacggggtcattagttcatagcccatatatggagttccgcgttacataacttacggtaaatg 400

 401 gcccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaataggg 480

 481 actttccattgacgtcaatgggtggactatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaag 560

 561 tacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagtacatgaccttatgggactttccta 640

 641 cttggcagtacatctacgtattagtcatcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatag 720

 721 cggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacggga 800

 801 ctttccaaaatgtcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagca 880

 881 gagctcgtttagtgaaccgtcagAATTCTGTTGGGCTCGCGGTTGATTACAAACTCTTCGCGGTCTTTCCAGTACTCTTG 960

 961 GATCGGAAACCCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGATCGGAAAAC 1040

1041 CTCTCGACTGTTTGGGgtgagtactcccctctcaaaagcgggcatgacttctgcgctaagattgtcagtttccaaaaacgag 1120
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1121 gaggatttgatattcacctggcccgcggtgatgcctttgagggtggccgcgtccatctggtcagaaaagacaatcttttt 1200

1201 gttgtcaagcttgaggtgtggcaggcttgagatctggccatacacttgagtgacaatgacatccactttgcctttctctc 1280

1281 cacagGTGTCCACTCCCAGGTCCAACTGCAGGTCGAC ATG GGA TGG AGC TAT ATC ATG TTC TTC TTG    1347
   1                                      M   G   W   S   Y   I   M   F   F   L      10

1348 GTA TCA ACA GCT ACA GTT GTC CAC TCC CAG GTA CAA CTG CAG CAG TCT GGG CCT CAG CTG  1407
  11 V   S   T   A   T   V   V   H   S   Q   V   Q   L   Q   Q   S   G   P   Q   L    30

1408 GTT AGG CCT GGG ACT TCA GTG AAG ATA TCC TGC AAG GCT TCT GGT TAC TCA TTC ACC AGC  1467
  31 V   R   P   G   T   S   V   K   I   S   C   K   A   S   G   Y   S   F   T   S    50

1468 TAT TGG ATG CAC TGG GTG AAG CAG AGG CCT GGA CAA GAT CTT GAG TGG ATT GGC ATG ATT  1527
  51 Y   W   M   H   W   V   K   Q   R   P   G   Q   D   L   E   W   I   G   M   I    70

1528 GAT CCA TCC GAT AGT GAA GTT AAA TTA AAT CAG AGG TTA AAG GAC AAG GCC ATA TTG ACT  1587
  71 D   P   S   D   S   E   V   K   L   N   Q   R   L   K   D   K   A   I   L   T    90

1588 GTT GAC AAA TCC TCC AAC ACA GCC TAC ATG CAA TTC AGC GGC CCG ACT TCT GAG GAC TCT  1647
  91 V   D   K   S   S   N   T   A   Y   M   Q   F   S   G   P   T   S   E   D   S    110

1648 GCG GTC TAT TAC TGT ACA AGA GGG GAG GTT TCC TGG TTT GCT TAC TGG GGC CAG GGG ACT  1707
 111 A   V   Y   Y   C   T   R   G   E   V   S   W   F   A   Y   W   G   Q   G   T    130

1708 CTG GTC ACT GTC TCT GCA GCC TCC ACC AAG GGC CCA TCC GTC TTC CCC CTG GCG CCC TGC  1767
 131 L   V   T   V   S   A   A   S   T   K   G   P   S   V   F   P   L   A   P   C    150

1768 TCC AGG AGC ACC TCC GAG AGC ACA GCC GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC  1827
 151 S   R   S   T   S   E   S   T   A   A   L   G   C   L   V   K   D   Y   F   P    170

1828 GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG  1887
 171 E   P   V   T   V   S   W   N   S   G   A   L   T   S   G   V   H   T   F   P    190

1888 GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC  1947
 191 A   V   L   Q   S   S   G   L   Y   S   L   S   S   V   V   T   V   P   S   S    210
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1948 AAC TTC GGC ACC CAG ACC TAC ACC TGC AAC GTA GAT CAC AAG CCC AGC AAC ACC AAG GTG  2007
 211 N   F   G   T   Q   T   Y   T   C   N   V   D   H   K   P   S   N   T   K   V    230

2008 GAC AAG ACA GTT G gtgagaggccagctcagggagggagggtgtctgctggaagccaggctcagcccctcctgcctg 2082
 231 D   K   T   V   E                                                               235

2083 gacgcaccccggctgtgcagccccagcccaggcagcaaggcaggcccccatctgtctcctcacccggaggcctctgcccg 2162

2163 ccccactcatgctcagggagagggtcttctggctttttccaccaggctccaggcaggcacaggctgggtgcccctacccc 2242

2243 aggcccttcacacacagggggcaggtgcttggctcagacctgccaaaagccatatccgggaggaccctgcccctgacctaa 2322

2323 gccgaccccaaaggccaaactgtccactcccctcagctcggacaccttctctcctcccagatccgagtaactcccaatctt 2402

2403 ctctctgcag AG CGC AAA TGT TGT GTC GAG TGC CCA CCG TGC CCA G gtaagccagcccaggcctcg 2468
 236          R   K   C   C   V   E   C   P   P   C   P   A                    247

2469 ccctccagctcaaggcgggacaggtgccctagagtagcctgcatcccagggacaggccccagctgggtgctgacacgtcca 2548

2549 cctccatctcttcctcag CA CCA CCT GTG GCA GGA CCG TCA GTC TTC CTC TTC CCC CCA AAA    2610
 248               P   P   V   A   G   P   S   V   F   L   F   P   P   K        261

2611 CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC ACG TGC GTG GTG GTG GAC GTG 2670
 262 P   K   D   T   L   M   I   S   R   T   P   E   V   T   C   V   V   V   D   V   281

2671 AGC CAG GAA GAC CCC GAG GTC CAG TTC AAC TGG TAC GTG GAT GGC GTG GAG GTG CAT AAT 2730
 282 S   Q   E   D   P   E   V   Q   F   N   W   Y   V   D   G   V   E   V   H   N   301

2731 GCC AAG ACA AAG CCG CGG GAG GAG CAG TTC AAC AGC ACG TAC CGT GTG GTC AGC GTC CTC 2790
 302 A   K   T   K   P   R   E   E   Q   F   N   S   T   Y   R   V   V   S   V   L   321

2791 ACC GTC CTG CAC CAG GAC TGG CTG AAC GGC AAG GAG TAC AAG TGC AAG GTC TCC AAC AAA 2850
 322 T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K   V   S   N   K   341

2851 GGC CTC CCG TCC TCC ATC GAG AAA ACC ATC TCC AAA GCC AAA G gtgggacccacggggtgcgagg 2915
 342 G   L   P   S   S   I   E   K   T   I   S   K   A   K   G                    356

2916 gccacacggacagaggccagctcggcccaccctctgccctgggagtgaccgctgtgccaaccttctgtccctacag GG  2992
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2993 CAG CCC CGA GAG CCA CAG GTG TAC ACC CTG CCC CCA TCC CAG GAG GAG ATG ACC AAG AAC 3052
 357 Q   P   R   E   P   Q   V   Y   T   L   P   P   S   Q   E   E   M   T   K   N   376

3053 CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAC CCC AGC GAC ATC GCC GTG GAG TGG 3112
 377 Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   396

3113 GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC 3172
 397 E   S   N   G   Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   416

3173 GGC TCC TTC TTC CTC TAC AGC AGG CTA ACC GTG GAC AAG AGC AGG TGG CAG GAG GGG AAT 3232
 417 G   S   F   F   L   Y   S   R   L   T   V   D   K   S   R   W   Q   E   G   N   436

3233 GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACA CAG AAG AGC CTC 3292
 437 V   F   S   C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   456

3293 TCC CTG TCT CTG GGT AAA TGA gtgccagggccattgaagcatttatcagggttattgtctcatgagcggatac 3365
 457 S   L   S   L   G   K   *                                                       463

3366 atatttgaatgtatttagaaaaataaacaaataagg                                           3400
```

2A2 HUMAN IgG 4 EXPRESSION PLASMID INSERT SEQUENCE

```
   1 gtgaccaatacaaaacaaaagcgccctcgtaccagcgaagaagggcagagatgccgtagtcaggtttagttcgtccgg  80

  81 cggcgggggatctgtatggtgcactctcagtacaatctgctctgatgccgcatagttaagccagtatctgctccctgctt 160

 161 gtgtgttggaggtcgctgagtagtgcgcgagcaaaatttaagctacaacaaggcaaggcttgaccgacaattgcatgaag 240

 241 aatctgcttagggttagggcgtttgcgctgcttcgcgatgtacgggccagatatacgcgttgacattgattattgactag 320

 321 ttattaatagtaatcaattacgggggtcattagttcatagcccatatatggagttccgcgttacataacttacggtaaatg 400

 401 gcccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaataggg 480

 481 actttccattgacgtcaatgggtggactatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaag 560
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 561 tacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagtacatgaccttatgggactttccta 640

 641 cttggcagtacatctacgtattagtcatcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatag 720

 721 cggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacggga 800

 801 ctttccaaaatgtcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagca 880

 881 gagctcgtttagtgaaccgtcaGAATTCTGTTGGGCTCGCGGTTGATTACAAACTCTTCGCGGTCTTTCCAGTACTCTTG 960

 961 GATCGGAAACCCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGATCGGAAAAC 1040

1041 CTCTCGACTGTTGGGgtgagtactccctctcaaaagcgggcatgacttctgcgctaagattgtcagtttccaaaaacgag 1120

1121 gaggatttgatattcacctggcccgcggtgatgcctttgagggtggccgcgtccatctggtcagaaaagacaatcttttt 1200

1201 gttgtcaagcttgaggtgtggcaggcttgagatctggccatacacttgagtgacaatgacatccactttgcctttctctc 1280

1281 cacagGTGTCCACTCCCAGGTCCAACTGCAGGTCGAC ATG GGA TGG AGC TAT ATC ATG TTC TTC TTG    1347
   1                                       M   G   W   S   Y   I   M   F   F   L      10

1348 GTA TCA ACA GCT ACA GTT GTC CAC TCC CAG GTA CAA CTG CAG CAG TCT GGG CCT CAG CTG  1407
  11 V   S   T   A   T   V   V   H   S   Q   V   Q   L   Q   Q   S   G   P   Q   L    30

1408 GTT AGG CCT GGG ACT TCA GTG AAG ATA TCC TGC AAG GCT TCT GGT TAC TCA TTC ACC AGC  1467
  31 V   R   P   G   T   S   V   K   I   S   C   K   A   S   G   Y   S   F   T   S    50

1468 TAT TGG ATG CAC TGG GTG AAG CAG AGG CCT GGA CAA GAT CTT GAG TGG ATT GGC ATG ATT  1527
  51 Y   W   M   H   W   V   K   Q   R   P   G   Q   D   L   E   W   I   G   M   I    70

1528 GAT CCA TCC GAT AGT GAA GTT AAA TTA AAT CAG AGG TTA AAG GAC AAG GCC ATA TTG ACT  1587
  71 D   P   S   D   S   E   V   K   L   N   Q   R   L   K   D   K   A   I   L   T    90

1588 GTT GAC AAA TCC TCC AAC ACA GCC TAC ATG CAA TTC AGC GGC CCG ACT TCT GAG GAC TCT  1647
  91 V   D   K   S   S   N   T   A   Y   M   Q   F   S   G   P   T   S   E   D   S    110
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1648 GCG GTC TAT TAC TGT ACA AGA GGG GAG GTT TCC TGG TTT GCT TAC TGG GGC CAG GGG ACT 1707
 111 A   V   Y   Y   C   T   R   G   E   V   S   W   F   A   Y   W   G   Q   G   T   130

1708 CTG GTC ACT GTC TCT GCA GCC TCC ACC AAG GGC CCA TCC GTC TTC CCC CTG GCG CCC TGC 1767
 131 L   V   T   V   S   A   A   S   T   K   G   P   S   V   F   P   L   A   P   C   150

1768 TCC AGG AGC ACC TCC GAG AGC ACA GCC GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC 1827
 151 S   R   S   T   S   E   S   T   A   A   L   G   C   L   V   K   D   Y   F   P   170

1828 GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG 1887
 171 E   P   V   T   V   S   W   N   S   G   A   L   T   S   G   V   H   T   F   P   190

1888 GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC 1947
 191 A   V   L   Q   S   S   G   L   Y   S   L   S   S   V   V   T   V   P   S   S   210

1948 AGC TTG GGC ACG AAG ACC TAC ACC TGC AAC GTA GAT CAC AAG CCC AGC AAC ACC AAG GTG 2007
 211 S   L   G   T   K   T   Y   T   C   N   V   D   H   K   P   S   N   T   K   V   230

2008 GAC AAG AGA GTT G gtgagaggccagcacagggagggagggtgtctgctggaagccaggctcagcccctcctgcctg 2082
 231 D   K   R   V   E                                                              235

2083 gacgcacccggctgtgcagccccagcccagggcagcaaggcatgccccatctgtctcctcacccggaggcctctgacca 2162

2163 ccccactcatgctcagggagagggtcttctggatttttccaccaggctcccggcaccacaggctggatgcccctacccca 2242

2243 ggccctgcgcatacagggcaggtgctgcgctcagacctgccaagagccatatccgggaggaccctgcccctgacctaagc 2322

2323 ccacccccaaaggccaaactctccactccctcagctcagacaccttctctcctcccagatctgagtaactcccaatcttct 2402

2403 ctctgcag AG TCC AAA TAT GGT CCC CCA TGC CCA TCA TGC CCA G gtaagccaacccaggcctcgcc 2468
          236  S   K   Y   G   P   P   C   P   S   C   P   A                    247

2469 ctccagctcaaggcgggacaggtgccctagagtagcctgcatccagggacaggccccagccgggtgctgacgcatccacc 2548

2549 tccatctcttcctcag CA CCT GAG TTC CTG GGG GGA CCA TCA GTC TTC CTG TTC CCC CCA AAA 2611
               248   P   E   F   L   G   G   P   S   V   F   L   F   P   P   K   262
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2612 CCC AAG GAC ACT CTC ATG ATC TCC CGG ACC CCT GAG GTC ACG TGC GTG GTG GTG GAC GTG 2671
 263 P   K   D   T   L   M   I   S   R   T   P   E   V   T   C   V   V   V   D   V   282

2672 AGC CAG GAA GAC CCC GAG GTC CAG TTC AAC TGG TAC GTG GAT GGC GTG GAG GTG CAT AAT 2731
 283 S   Q   E   D   P   E   V   Q   F   N   W   Y   V   D   G   V   E   V   H   N   302

2732 GCC AAG ACA AAG CCG CGG GAG GAG CAG TTC AAC AGC ACG TAC CGT GTG GTC AGC GTC CTC 2791
 303 A   K   T   K   P   R   E   E   Q   F   N   S   T   Y   R   V   V   S   V   L   322

2792 ACC GTC CTG CAC CAG GAC TGG CTG AAC GGC AAG GAG TAC AAG TGC AAG GTC TCC AAC AAA 2851
 323 T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K   V   S   N   K   342

2852 GGC CTC CCG TCC TCC ATC GAG AAA ACC ATC TCC AAA GCC AAA G gtgggacccacgggggtgcgagg 2916
 343 G   L   P   S   S   I   E   K   T   I   S   K   A   K   G                       357

2917 gccacacggacagaggccagctcggcccaccctctgccctgggagtgaccgctgtgccaacctctgtccctacag GG  2993

2994 CAG CCC CGA GAG CCA CAG GTG TAC ACC CTG CCC CCA TCC CAG GAG GAG ATG ACC AAG AAC 3053
 358 Q   P   R   E   P   Q   V   Y   T   L   P   P   S   Q   E   E   M   T   K   N   377

3054 CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC TAC CCC AGC GAC ATC GCC GTG GAG TGG 3113
 378 Q   V   S   L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   397

3114 GAG AGC AAT GGG CAG CCG GAG AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC 3173
 398 E   S   N   G   Q   P   E   N   Y   K   T   T   P   P   V   L   D   S   D   417

3174 GGC TCC TTC CTC TAC AGC AGG CTA ACC GTG GAC AAG AGC AGG TGG CAG GAG GGG AAT 3233
 418 G   S   F   L   Y   S   R   L   T   V   D   K   S   R   W   Q   E   G   N   437

3234 GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACA CAG AAG AGC CTC 3293
 438 V   F   S   C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   457

3294 TCC CTG TCT CTG GGT AAA TGA gtgccagggccattgaagcatttatcagggttattgtctcatgagcggatac 3366
 458 S   L   S   L   G   K   *                                                       464

3367 atatttgaatgtatttagaaaaataaacaaataggggttccgcgcacatttccccgaaaagtgccacctgacgcgttgac 3446

3447 attgattattgactagttattaatagtaatcaattacggggtcattagttcatagcccatatatggagttccgcgttaca 3526
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3527 taacttacggtaaatggccccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatgttccca 3606

3607 tagtaacgccaatagggactttccattgacgtcaatgggtggactatttacggtaaactgcccacttggcagtacatcaa 3686

3687 gtgtatcatatgccaagtacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagtacatgac 3766

3767 cttatgggactttcctacttggcagtacatctacgtattagtcatcgctattaccatggtgatgcggttttggcagtaca 3846

3847 tcaatgggcgtggatagcggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtttgttttgg 3926

3927 caccaaaatcaacgggactttccaaaatgtcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtg 4006

4007 ggaggtctatataagcagagctcgtttagtgaaccgtcaGAATTCTGTTGGGCTCGCGGTTGATTACAAACTCTTCGCGG 4086

4087 TCTTTCCAGTACTCTTGGATCGGAAACCCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCAT 4166

4167 CGACCGGATCGGAAAACCTCTCGACTGTTGGGgtgagtactccctctcaaaagcgggcatgacttctgcgctaagattgt 4246

4247 cagtttccaaaaacgaggaggatttgatattcacctggcccgcggtgatgcctttgagggtggccgcgtccatctggtca 4326

4327 gaaaagacaatctttttgttgtcaagcttgaggtgtggcaggcttgagatctggccatacacttgagtgacaatgacatc 4406

4407 cactttgcctttctctccacagGTGTCCACTCCCAGGTCCAACTGCAGGTCGAC ATG GGC TTC AAG ATG GAG   4478
   1                                                        M   G   F   K   M   E     6

4479 TCA CAT TTT CAG GTC TTT GTA TAC ATG TTG CTG TGG TTG TCT GGT GTT AAT GGA GAC ATT  4538
   7 S   H   F   Q   V   F   V   Y   M   L   L   W   L   S   G   V   N   G   D   I    26

4539 GTG ATG ACC CAG TCT CAA AAA TTC ATG TCC ACA TCA TTA GGA GAC AGG GTC AGC GTC ACC  4598
  27 V   M   T   Q   S   Q   K   F   M   S   T   S   L   G   D   R   V   S   V   T    46

4599 TGC AAG GCC AGT CAG AAT GTG GGT CCT AAT GTA GCC TGG TTT CAA CAG AAA CCA GGC CAG  4658
  47 C   K   A   S   Q   N   V   G   P   N   V   A   W   F   Q   Q   K   P   G   Q    66

4659 TCT CCT AAA ACA CTT ATT TAC TCG GCA TCC TTC CGC TAC AGT GGA GTC CCT GAT CGC TTC  4718
  67 S   P   K   T   L   I   Y   S   A   S   F   R   Y   S   G   V   P   D   R   F    86
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4719 ACA GGC AGT GGA TCT GGG ACA GAT TTC ACT CTC ACC ATC ACC AAT GTG CAG TCT GAA GAC 4778
  87 T   G   S   G   S   G   T   D   F   T   L   T   I   T   N   V   Q   S   E   D   106

4779 TTG GCA GAG TAT TTC TGT CAT CAA TAT AAC TCC TAT CCT CTC ACG TTC GGG GGG GGG ACC 4838
 107 L   A   E   Y   F   C   H   Q   Y   N   S   Y   P   L   T   F   G   G   G   T   126

4839 AAG CTG AAA ATA AAA CGA ACT GTG GCT GCA CCA TCT GTC TTC ATC TTC CCG CCA TCT GAT 4898
 127 K   L   K   I   K   R   T   V   A   A   P   S   V   F   I   F   P   P   S   D   146

4899 GAG CAG TTG AAA TCT GGA ACT GCC TCT GTT GTG TGC CTG CTG AAT AAC TTC TAT CCC AGA 4958
 147 E   Q   L   K   S   G   T   A   S   V   V   C   L   L   N   N   F   Y   P   R   166

4959 GAG GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC CTC CAA TCG GGT AAC TCC CAG GAG AGT 5018
 167 E   A   K   V   Q   W   K   V   D   N   A   L   Q   S   G   N   S   Q   E   S   186

5019 GTC ACA GAG CAG GAC AGC AAG GAC AGC ACC TAC AGC CTC AGC AGC ACC CTG ACG CTG AGC 5078
 187 V   T   E   Q   D   S   K   D   S   T   Y   S   L   S   S   T   L   T   L   S   206

5079 AAA GCA GAC TAC GAG AAA CAC AAA GTC TAC GCC TGC GAA GTC ACC CAT CAG GGC CTG AGC 5138
 207 K   A   D   Y   E   K   H   K   V   Y   A   C   E   V   T   H   Q   G   L   S   226

5139 TCG CCC GTC ACA AAG AGC TTC AAC AGG GGA GAG TGT TAG ctcgagcatgcaggcatgcaagcttggc 5205
 227 S   P   V   T   K   S   F   N   R   G   E   C   *                               239

5206 actggccgtcgtttacaacgtcgtgactgggaaaaccctggcgt                                    5250
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3F4 LIGHT CHAIN cDNA

```
4496/1
          c
ATG AAG TTG CCT GTT AGG CTG TTG GTG CTG ATG TTC TGG ATT CCT GTT TCC AGC AGT GAT
M   K   L   P   V   R   L   L   V   L   M   F   W   I   P   V   S   S   S   D
4556/21                                4586/31
GTT GTG ATG ACC CAA ACT CCA CTC TCC CTG CCT GTC AGT CTT GGA GAT CAA GCC TCC ATC
V   V   M   T   Q   T   P   L   S   L   P   V   S   L   G   D   Q   A   S   I
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4616/41                                                    4646/51
TCT TGC AGA TCT AGT CAG AGC CTT GTA CAC AGT AAT GGA AAC ACC TAT TTA CAG TGG TAC
S   C   R   S   S   Q   S   L   V   H   S   N   G   N   T   Y   L   Q   W   Y
4676/61                                                    4706/71
CTG CAG AAG CCA GGC CAG TCT CCA AAG CTC CTG ATC TAC AAA GTT TCC AAC CGA TTT TCT
L   Q   K   P   G   Q   S   P   K   L   L   I   Y   K   V   S   N   R   F   S
4736/81                                                    4766/91
GGG GTC CCA GAC AGG TTC AGT GGC AGT GGA TCA GGG ACA GAT TTC ACA CTC AAG ATC AGC
G   V   P   D   R   F   S   G   S   G   S   G   T   D   F   T   L   K   I   S
4796/101                                                   4826/111
AGA GTG GAG GCT GAG GAT CTG GGA GTT TAT TTC TGT TCT CAA AGT ACA CAT GTT CCG TTC
R   V   E   A   E   D   L   G   V   Y   F   C   S   Q   S   T   H   V   P   F
4856/121                                                   4886/131
ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA CGA ACT GTG GCT GCA CCA TCT GTC TTC
T   F   G   G   G   T   K   L   E   I   K   R   T   V   A   A   P   S   V   F
4916/141                                                   4946/151
ATC TTC CCG CCA TCT GAT GAG CAG TTG AAA TCT GGA ACT GCC TCT GTT GTG TGC CTG CTG
I   F   P   P   S   D   E   Q   L   K   S   G   T   A   S   V   V   C   L   L
4976/161                                                   5006/171
AAT AAC TTC TAT CCC AGA GAG GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC CTC CAA TCG
N   N   F   Y   P   R   E   A   K   V   Q   W   K   V   D   N   A   L   Q   S
5036/181                                                   5066/191
GGT AAC TCC CAG GAG AGT GTC ACA GAG CAG GAC AGC AAG GAC AGC ACC TAC AGC CTC AGC
G   N   S   Q   E   S   V   T   E   Q   D   S   K   D   S   T   Y   S   L   S
5096/201                                                   5126/211
AGC ACC CTG ACG CTG AGC AAA GCA GAC TAC GAG AAA CAC AAA GTC TAC GCC TGC GAA GTC
S   T   L   T   L   S   K   A   D   Y   E   K   H   K   V   Y   A   C   E   V
5156/221                                                   5186/231
ACC CAT CAG GGC CTG AGC TCG CCC GTC ACA AAG AGC TTC AAC AGG GGA GAG TGT TAG
T   H   Q   G   L   S   S   P   V   T   K   S   F   N   R   G   E   C   *
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3F4 HEAVY CHAIN cDNA

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1/1                                                        31/11
ATG AAG TGG AGC TGG GTT ATT CTC TTC CTC CTG TCA GTA ACT GCC GGC GTC CAC TCC CAG
M   K   W   S   W   V   I   L   F   L   L   S   V   T   A   G   V   H   S   Q
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61/21                                   91/31
GTT CAG GTC CAG CAG TCT GGG GCT GAG CTG GCA AGA CCT TGG GCT TCA GTG AAG TTG TCC
V   Q   V   Q   Q   S   G   A   E   L   A   R   P   W   A   S   V   K   L   S
121/41                                  151/51
TGC AAG GCT TCT GGC TAC AAT TTT AAT AGT TAC TGG ATG CAG TGG GTA AAA CAG AGG CCT
C   K   A   S   G   Y   N   F   N   S   Y   W   M   Q   W   V   K   Q   R   P
181/61                                  211/71
GGA CAG GGT CTG GAA TGG ATT GGG GCT ATT TAT CCT GGA GAT GGT GAT ACT AGC TAC ACT
G   Q   G   L   E   W   I   G   A   I   Y   P   G   D   G   D   T   S   Y   T
241/81                                  271/91
CAG AAG TTC AGG GGC AAG GCC ACA TTG ACT GCA GAT AAA TCC TCC AGC ACA GCC TAC ATG
Q   K   F   R   G   K   A   T   L   T   A   D   K   S   S   S   T   A   Y   M
301/101                                 331/111
CAA CTC AGC AGC TTG GCA TCT GAG GAC TCT GCG GTC TAT TAC TGT GCA AGA CGT ACG GTA
Q   L   S   S   L   A   S   E   D   S   A   V   Y   Y   C   A   R   R   T   V
361/121                                 391/131
GGA GGC TAC TTT GAC TAC TGG GGC CAA GGC ACC ACT CTC ACA GTC TCC TCA GCC TCC ACC
G   G   Y   F   D   Y   W   G   Q   G   T   T   L   T   V   S   S   A   S   T
421/141                                 451/151
AAG GGC CCA TCC GTC TTC CCC CTG GCG CCC TGC TCC AGG AGC ACC TCC GAG AGC ACA GCC
K   G   P   S   V   F   P   L   A   P   C   S   R   S   T   S   E   S   T   A
481/161                                 511/171
GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
A   L   G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S
541/181                                 571/191
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC
G   A   L   T   S   G   V   H   T   F   P   A   V   L   Q   S   S   G   L   Y
601/201                                 631/211
TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACG AAG ACC TAC ACC TGC
S   L   S   S   V   V   T   V   P   S   S   S   L   G   T   K   T   Y   T   C
661/221                                 691/231
AAC GTA GAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AGA GTT GAG TCC AAA TAT GGT
N   V   D   H   K   P   S   N   T   K   V   D   K   R   V   E   S   K   Y   G
721/241                                 751/251
CCC CCA TGC CCA TCA TGC CCA GCA CCT GAG TTC CTG GGG GGA CCA TCA GTC TTC CTG TTC
P   P   C   P   S   C   P   A   P   E   F   L   G   G   P   S   V   F   L   F
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781/261                                                    811/271
CCC CCA AAA CCC AAG GAC ACT CTC ATG ATC TCC CGG ACC CCT GAG GTC ACG TGC GTG GTG
P   P   K   P   K   D   T   L   M   I   S   R   T   P   E   V   T   C   V   V
841/281                                                    871/291
GTG GAC GTG AGC CAG GAA GAC CCC GAG GTC CAG TTC AAC TGG TAC GTG GAT GGC GTG GAG
V   D   V   S   Q   E   D   P   E   V   Q   F   N   W   Y   V   D   G   V   E
901/301                                                    931/311
GTG CAT AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TTC AAC AGC ACG TAC CGT GTG GTC
V   H   N   A   K   T   K   P   R   E   E   Q   F   N   S   T   Y   R   V   V
961/321                                                    991/331
AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAC GGC AAG GAG TAC AAG TGC AAG GTC
S   V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K   V
1021/341                                                   1051/351
TCC AAC AAA GGC CTC CCG TCC TCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC
S   N   K   G   L   P   S   S   I   E   K   T   I   S   K   A   K   G   Q   P
1081/361                                                   1111/371
CGA GAG CCA CAG GTG TAC ACC CTG CCC CCA TCC CAG GAG GAG ATG ACC AAG AAC CAG GTC
R   E   P   Q   V   Y   T   L   P   P   S   Q   E   E   M   T   K   N   Q   V
1141/381                                                   1171/391
AGC CTG ACC TGC CTG GTC AAA GGC TTC TAC CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC
S   L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   E   S
1201/401                                                   1231/411
AAT GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC
N   G   Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   G   S
1261/421                                                   1291/431
TTC TTC CTC TAC AGC AGG CTA ACC GTG GAC AAG AGC AGG TGG CAG GAG GGG AAT GTC TTC
F   F   L   Y   S   R   L   T   V   D   K   S   R   W   Q   E   G   N   V   F
1321/441                                                   1351/451
TCA TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACA CAG AAG AGC CTC TCC CTG
S   C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   S   L
1381/461
TCT CTG GGT AAA TGA
S   L   G   K   *
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3F4 (CHIMERIC) HUMAN G2/G4 CDNA

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1/1                                                 31/11
ATG AAG TGG AGC TGG GTT ATT CTC TTC CTC CTG TCA GTA ACT GCC GGC GTC CAC TCC CAG
M   K   W   S   W   V   I   L   F   L   L   S   V   T   A   G   V   H   S   Q
61/21                                               91/31
GTT CAG GTC CAG CAG TCT GGG GCT GAG CTG GCA AGA CCT TGG GCT TCA GTG AAG TTG TCC
V   Q   V   Q   Q   S   G   A   E   L   A   R   P   W   A   S   V   K   L   S
121/41                                              151/51
TGC AAG GCT TCT GGC TAC AAT TTT AAT AGT TAC TGG ATG CAG TGG GTA AAA CAG AGG CCT
C   K   A   S   G   Y   N   F   N   S   Y   W   M   Q   W   V   K   Q   R   P
181/61                                              211/71
GGA CAG GGT CTG GAA TGG ATT GGG GCT ATT TAT CCT GGA GAT GGT GAT ACT AGC TAC ACT
G   Q   G   L   E   W   I   G   A   I   Y   P   G   D   G   D   T   S   Y   T
241/81                                              271/91
CAG AAG TTC AGG GGC AAG GCC ACA TTG ACT GCA GAT AAA TCC TCC AGC ACA GCC TAC ATG
Q   K   F   R   G   K   A   T   L   T   A   D   K   S   S   S   T   A   Y   M
301/101                                             331/111
CAA CTC AGC AGC TTG GCA TCT GAG GAC TCT GCG GTC TAT TAC TGT GCA AGA CGT ACG GTA
Q   L   S   S   L   A   S   E   D   S   A   V   Y   Y   C   A   R   R   T   V
361/121                                             391/131
GGA GGC TAC TTT GAC TAC TGG GGC CAA GGC ACC ACT CTC ACA GTC TCC TCA GCC TCC ACC
G   G   Y   F   D   Y   W   G   Q   G   T   T   L   T   V   S   S   A   S   T
421/141                                             451/151
AAG GGC CCA TCC GTC TTC CCC CTG GCG CCC TGC TCC AGG AGC ACC TCC GAG AGC ACA GCC
K   G   P   S   V   F   P   L   A   P   C   S   R   S   T   S   E   S   T   A
481/161                                             511/171
GCC CTG GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA
A   L   G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S
541/181                                             571/191
GGC GCC CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC
G   A   L   T   S   G   V   H   T   F   P   A   V   L   Q   S   S   G   L   Y
601/201                                             631/211
TCC CTC AGC AGC GTG GTG ACC GTG CCC TCC AGC AAC TTC GGC ACC CAG ACC TAC ACC TGC
S   L   S   S   V   V   T   V   P   S   S   N   F   G   T   Q   T   Y   T   C
661/221                                             691/231
AAC GTA GAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG ACA GTT GAG CGC AAA TGT TGT
N   V   D   H   K   P   S   N   T   K   V   D   K   T   V   E   R   K   C   C
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                                                    751/251
721/241
GTC GAG TGC CCA CCG TGC CCA GCA CCA CCT GTG GCA GGA CCG TCA GTC TTC CTC TTC CCC
V   E   C   P   P   C   P   A   P   P   V   A   G   P   S   V   F   L   F   P
781/261                                             811/271
CCA AAA CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT GAG GTC ACG TGC GTG GTG GTG
P   K   P   K   D   T   L   M   I   S   R   T   P   E   V   T   C   V   V   V
841/281                                             871/291
GAC GTG AGC CAG GAA GAC CCC GAG GTC CAG TTC AAC TGG TAC GTG GAT GGC GTG GAG GTG
D   V   S   Q   E   D   P   E   V   Q   F   N   W   Y   V   D   G   V   E   V
901/301                                             931/311
CAT AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TTC AAC AGC ACG TAC CGT GTG GTC AGC
H   N   A   K   T   K   P   R   E   E   Q   F   N   S   T   Y   R   V   V   S
961/321                                             991/331
GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAC GGC AAG GAG TAC AAG TGC AAG GTC TCC
V   L   T   V   L   H   Q   D   W   L   N   G   K   E   Y   K   C   K   V   S
1021/341                                            1051/351
AAC AAA GGC CTC CCG TCC TCC ATC GAG AAA ACC ATC TCC AAA GCC AAA GGG CAG CCC CGA
N   K   G   L   P   S   S   I   E   K   T   I   S   K   A   K   G   Q   P   R
1081/361                                            1111/371
GAG CCA CAG GTG TAC ACC CTG CCC CCA TCC CAG GAG GAG ATG ACC AAG AAC CAG GTC AGC
E   P   Q   V   Y   T   L   P   P   S   Q   E   E   M   T   K   N   Q   V   S
1141/381                                            1171/391
CTG ACC TGC CTG GTC AAA GGC TTC TAC CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC AAT
L   T   C   L   V   K   G   F   Y   P   S   D   I   A   V   E   W   E   S   N
1201/401                                            1231/411
GGG CAG CCG GAG AAC AAC TAC AAG ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC
G   Q   P   E   N   N   Y   K   T   T   P   P   V   L   D   S   D   G   S   F
1261/421                                            1291/431
TTC CTC TAC AGC AGG CTA ACC GTG GAC AAG AGC AGG TGG CAG GAG GGG AAT GTC TTC TCA
F   L   Y   S   R   L   T   V   D   K   S   R   W   Q   E   G   N   V   F   S
1321/441                                            1351/451
TGC TCC GTG ATG CAT GAG GCT CTG CAC AAC CAC TAC ACA CAG AAG AGC CTC TCC CTG TCT
C   S   V   M   H   E   A   L   H   N   H   Y   T   Q   K   S   L   S   L   S
1381/461
CTG GGT AAA TGA
L   G   K   *
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3F4 HUMAN G2/G4 EXPRESSION PLASMID INSERT SEQUENCE

```
   1 gtgaccaatacaaaacaaaagcgcccctcgtaccagcgaagaaggggcagagatgccgtagtcaggtttagttcgtccgg 80
  81 cggcgggggatctgtatggtgcactctcagtacaatctgctctgatgccgcatagttaagccagtatctgctccctgctt 160
 161 gtgtgttggaggtcgctgagtagtgcgcgagcaaaatttaagctacaacaaggcaaggcttgaccgacaattgcatgaag 240
 241 aatctgcttagggttaggcgttttgcgctgcttcgcgatgtacgggccagatatacgcgttgacattgattattgactag 320
 321 ttattaatagtaatcaattacggggtcattagttcatagcccatatatggagttccgcgttacataacttacggtaaatg 400
 401 gcccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaataggg 480
 481 actttccattgacgtcaatgggtggactatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaag 560
 561 tacgccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagtacatgaccttatgggactttccta 640
 641 cttggcagtacatctacgtattagtcatcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatag 720
 721 cggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacggga 800
 801 ctttccaaaatgtcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagca 880
 881 gagctcgtttagtgaaccgtcaGAATTCTGTTGGGCTCGCGGTTGATTACAAACTCTTCGCGGTCTTTCCAGTACTCTTG 960
 961 GATCGGAAACCCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGATCGGAAAAC 1040
1041 CTCTCGACTGTTGGGgtgagtactccctctcaaaagcgggcatgacttctgcgctaagattgtcagtttccaaaaacgag 1120
1121 gaggatttgatattcacctggcccgcggtgatgcctttgagggtggccgcgtccatctggtcagaaaagacaatcttttt 1200
1201 gttgtcaagcttgaggtgtggcaggcttgagatctggccatacacttgagtgacaatgacatccactttgcctttctctc 1280
1281 cacagGTGTCCACTCCCAGGTCCAACTGCAGGTCGACCGGCTTGGTACCGAGCTCGGATCCGGACCATC ATG AAG    1355
   1                                                                      M   K      2
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1356 TGG AGC TGG GTT ATT CTC TTC CTC CTG TCA GTA ACT GCC GGC GTC CAC TCC CAG GTT CAG 1415
   3 W   S   W   V   I   L   F   L   L   S   V   T   A   G   V   H   S   Q   V   Q    22

1416 GTC CAG CAG TCT GGG GCT GAG CTG GCA AGA CCT TGG GCT TCA GTG AAG TTG TCC TGC AAG 1475
  23 V   Q   Q   S   G   A   E   L   A   R   P   W   A   S   V   K   L   S   C   K    42

1476 GCT TCT GGC TAC AAT TTT AAT AGT TAC TGG ATG CAG TGG GTA AAA CAG AGG CCT GGA CAG 1535
  43 A   S   G   Y   N   F   N   S   Y   W   M   Q   W   V   K   Q   R   P   G   Q    62

1536 GGT CTG GAA TGG ATT GGG GCT ATT TAT CCT GGA GAT GGT GAT ACT AGC TAC ACT CAG AAG 1595
  63 G   L   E   W   I   G   A   I   Y   P   G   D   G   D   T   S   Y   T   Q   K    82

1596 TTC AGG GGC AAG GCC ACA TTG ACT GCA GAT AAA TCC TCC AGC ACA GCC TAC ATG CAA CTC 1655
  83 F   R   G   K   A   T   L   T   A   D   K   S   S   S   T   A   Y   M   Q   L   102

1656 AGC AGC TTG GCA TCT GAG GAC TCT GCG GTC TAT TAC TGT GCA AGA CGT ACG GTA GGA GGC 1715
 103 S   S   L   A   S   E   D   S   A   V   Y   Y   C   A   R   R   T   V   G   G   122

1716 TAC TTT GAC TAC TGG GGC CAA GGC ACC ACT CTC ACA GTC TCC TCA GCC TCC ACC AAG GGC 1775
 123 Y   F   D   Y   W   G   Q   G   T   T   L   T   V   S   S   A   S   T   K   G   142

1776 CCA TCC GTC TTC CCC CTG GCG CCC TGC TCC AGG AGC ACC TCC GAG AGC ACA GCC GCC CTG 1835
 143 P   S   V   F   P   L   A   P   C   S   R   S   T   S   E   S   T   A   A   L   162

1836 GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC 1895
 163 G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S   G   A   182

1896 CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC 1955
 183 L   T   S   G   V   H   T   F   P   A   V   L   Q   S   S   G   L   Y   S   L   202

1956 AGC AGC GTG GTG ACC GTG CCC TCC AGC AAC TTC GGC ACC CAG ACC TAC ACC TGC AAC GTA 2015
 203 S   S   V   V   T   V   P   S   S   N   F   G   T   Q   T   Y   T   C   N   V   222

2016 GAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG ACA GTT G gtgagaggccagctcagggagggagg 2081
 223 D   H   K   P   S   N   T   K   V   D   K   T   V   E                           236

2082 gtgtctgctggaagccaggctcagccctcctgcctggacgcaccccggctgtgcagcccccagcccagggcagcaaggcag 2161
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2162 gccccatctgtctcctcacccggaggcctctgcccgccccactcatgctcagggagagggtcttctggctttttccacca 2241

2242 ggctccaggcaggcacaggctgggtgcccctaccccaggcccttcacacacaggggcaggtgcttggctcagacctgcca 2321

2322 aaagccatatccgggaggaccctgcccctgacctaagccgaccccaaaggccaaactgtccactccctcagctcggacac 2401

2402 cttctctcctcccagatccgagtaactcccaatcttctctctgcag AG CGC AAA TGT TGT GTC GAG TGC    2470
 237                                                R   K   C   C   V   E   C      243

2471 CCA CCG TGC CCA G gtaagccagcccaggcctcgccctccagctcaaggcgggacaggtgccctagagtagcctgc 2545
 244 P   P   C   P   A                                                                248

2546 atccagggacaggccccagctgggtgctgacacgtccacctccatctcttcctcag CA CCA CCT GTG GCA GGA  2618
 249                                                           P   P   V   A   G    253

2619 CCG TCA GTC TTC CTC TTC CCC CCA AAA CCC AAG GAC ACC CTC ATG ATC TCC CGG ACC CCT  2678
 254 P   S   V   F   L   F   P   P   K   P   K   D   T   L   M   I   S   R   T   P    273

2679 GAG GTC ACG TGC GTG GTG GTG GAC GTG AGC CAG GAA GAC CCC GAG GTC CAG TTC AAC TGG  2738
 274 E   V   T   C   V   V   V   D   V   S   Q   E   D   P   E   V   Q   F   N   W    293

2739 TAC GTG GAT GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TTC AAC  2798
 294 Y   V   D   G   V   E   V   H   N   A   K   T   K   P   R   E   E   Q   F   N    313

2799 AGC ACG TAC CGT GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAC GGC AAG  2858
 314 S   T   Y   R   V   V   S   V   L   T   V   L   H   Q   D   W   L   N   G   K    333

2859 GAG TAC AAG TGC AAG GTC TCC AAC AAA GGC CTC CCG TCC TCC ATC GAG AAA ACC ATC TCC  2918
 334 E   Y   K   C   K   V   S   N   K   G   L   P   S   S   I   E   K   T   I   S    353

2919 AAA GCC AAA G gtgggacccacggggtgcgagggccacacggacagaggccagctcggcccaccctctgccctggga 2994
 354 K   A   K   G                                                                    357

2995 gtgaccgctgtgccaacctctgtccctacag GG CAG CCC CGA GAG CCA CAG GTG TAC ACC CTG CCC   3060
 358                                   Q   P   R   E   P   Q   V   Y   T   L   P     368

3061 CCA TCC CAG GAG GAG ATG ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC  3120
 369 P   S   Q   E   E   M   T   K   N   Q   V   S   L   T   C   L   V   K   G   F    388
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3121 TAC CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG 3180
 389 Y   P   S   D   I   A   V   E   W   E   S   N   G   Q   P   E   N   N   Y   K   408

3181 ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AGG CTA ACC GTG 3240
 409 T   T   P   P   V   L   D   S   D   G   S   F   F   L   Y   S   R   L   T   V   428

3241 GAC AAG AGC AGG TGG CAG GAG GGG AAT GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG 3300
 429 D   K   S   R   W   Q   E   G   N   V   F   S   C   S   V   M   H   E   A   L   448

3301 CAC AAC CAC TAC ACA CAG AAG AGC CTC TCC CTG TCT CTG GGT AAA TGA gtgccagggccattga 3364
 449 H   N   H   Y   T   Q   K   S   L   S   L   S   L   G   K   *                   464

3365 agcatttatcagggttattgtctcatgagcggatac                                          3400
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3F4 HUMAN IgG4 EXPRESSION PLASMID INSERT SEQUENCE

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   1 gtgaccaatacaaaacaaaagcgcccctcgtaccagcgaagaggggcagagatgccgtagtcaggtttagttcgtccgg  80

  81 cggcgggggatctgtatggtgcactctcagtacaatctgtctgatgccgcatagttaagccagtatctgctccctgctt 160

 161 gtgtgttggaggtcgctgagtagtgcgcgagcaaaatttaagctacaacaaggcaaggcttgaccgacaattgcatgaag 240

 241 aatctgcttagggttaggcgttttgcgctgcttcgcgatgtacgggccagatatacgcgttgacattgattattgactag 320

 321 ttattaatagtaatcaattacgggggtcattagttcatagcccatatatggagttccgcgttacataacttacggtaaatg 400

 401 gcccgcctggctgaccgcccaacgacccccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaataggg 480

 481 actttccattgacgtcaatgggtggactatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaag 560

 561 tacgcccccctattgacgtcaatgacggtaaatggcccgcctggcattatgcccagtacatgaccttatgggactttccta 640

 641 cttggcagtacatctacgtattagtcatcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatag 720

 721 cggtttgactcacggggatttccaagtctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggga 800
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 801 ctttccaaaatgtcgtaacaactccgccccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagca 880

 881 gagctcgtttagtgaaccgtcaGAATTCTGTTGGGCTCGCGGTTGATTACAAACTCTTCGCGGTCTTTCCAGTACTCTTG 960

 961 GATCGGAAACCCGTCGGCCTCCGAACGGTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGATCGGAAAAC 1040

1041 CTCTCGACTGTTGGGgtgagtactccctctcaaaagcgggcatgacttctgcgctaagattgtcagtttccaaaaacgag 1120

1121 gaggatttgatattcacctggcccgcggtgatgcctttgagggtggccgcgtccatctggtcagaaaagacaatcttttt 1200

1201 gttgtcaagcttgaggtgtggcaggcttgagatctggccatacacttgagtgacaatgacatccactttgcctttctctc 1280

1281 cacagGTGTCCACTCCCAGGTCCAACTGCAGGTCGACCGGCTTGGTACCGAGCTCGGATCCGGACCATC ATG AAG    1355
   1                                                                      M   K      2

1356 TGG AGC TGG GTT ATT CTC TTC CTC CTG TCA GTA ACT GCC GGC GTC CAC TCC CAG GTT CAG  1415
   3 W   S   W   V   I   L   F   L   L   S   V   T   A   G   V   H   S   Q   V   Q    22

1416 GTC CAG CAG TCT GGG GCT GAG CTG GCA AGA CCT TGG GCT TCA GTG AAG TTG TCC TGC AAG  1475
  23 V   Q   Q   S   G   A   E   L   A   R   P   W   A   S   V   K   L   S   C   K    42

1476 GCT TCT GGC TAC AAT TTT AAT AGT TAC TGG ATG CAG TGG GTA AAA CAG AGG CCT GGA CAG  1535
  43 A   S   G   Y   N   F   N   S   Y   W   M   Q   W   V   K   Q   R   P   G   Q    62

1536 GGT CTG GAA TGG ATT GGG GCT ATT TAT CCT GGA GAT GGT GAT ACT AGC TAC ACT CAG AAG  1595
  63 G   L   E   W   I   G   A   I   Y   P   G   D   G   D   T   S   Y   T   Q   K    82

1596 TTC AGG GGC AAG GCC ACA TTG ACT GCA GAT AAA TCC TCC AGC ACA GCC TAC ATG CAA CTC  1655
  83 F   R   G   K   A   T   L   T   A   D   K   S   S   S   T   A   Y   M   Q   L    102

1656 AGC AGC TTG GCA TCT GAG GAC TCT GCG GTC TAT TAC TGT GCA AGA CGT ACG GTA GGA GGC  1715
 103 S   S   L   A   S   E   D   S   A   V   Y   Y   C   A   R   R   T   V   G   G    122

1716 TAC TTT GAC TAC TGG GGC CAA GGC ACC ACT CTC ACA GTC TCC TCA GCC TCC ACC AAG GGC  1775
 123 Y   F   D   Y   W   G   Q   G   T   T   L   T   V   S   S   A   S   T   K   G    142
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1776 CCA TCC GTC TTC CCC CTG GCG CCC TGC TCC AGG AGC ACC TCC GAG AGC ACA GCC GCC CTG  1835
 143 P   S   V   F   P   L   A   P   C   S   R   S   T   S   E   S   T   A   A   L    162

1836 GGC TGC CTG GTC AAG GAC TAC TTC CCC GAA CCG GTG ACG GTG TCG TGG AAC TCA GGC GCC  1895
 163 G   C   L   V   K   D   Y   F   P   E   P   V   T   V   S   W   N   S   G   A    182

1896 CTG ACC AGC GGC GTG CAC ACC TTC CCG GCT GTC CTA CAG TCC TCA GGA CTC TAC TCC CTC  1955
 183 L   T   S   G   V   H   T   F   P   A   V   L   Q   S   S   G   L   Y   S   L    202

1956 AGC AGC GTG GTG ACC GTG CCC TCC AGC AGC TTG GGC ACG AAG ACC TAC ACC TGC AAC GTA  2015
 203 S   S   V   V   T   V   P   S   S   S   L   G   T   K   T   Y   T   C   N   V    222

2016 GAT CAC AAG CCC AGC AAC ACC AAG GTG GAC AAG AGA GTT G gtgagaggccagcacagggagggagg  2081
 223 D   H   K   P   S   N   T   K   V   D   K   R   V   E                            236

2082 gtgtctgctggaagccaggctcagcccctcctgctggacgcaccccggctgtgcagccccagcccagggcagcaaggcat  2161

2162 gccccatctgtctcctcacccggaggcctctgaccacccccactcatgctcagggagagggtcttctggatttttccacca  2241

2242 ggctcccggcaccacaggctggatgcccctaccccaggcccctgcgcatacagggcaggtgctgcgctcagacctgccaag  2321

2322 agccatatccgggaggaccctgcccctgacctaagcccacccccaaaggccaaactctccactccctcagctcagacacct  2401

2402 tctctcctcccagatctgagtaactcccaatcttctctctgcag AG TCC AAA TAT GGT CCC CCA TGC CCA  2471
 237                                             S   K   Y   G   P   P   C   P    244

2472 TCA TGC CCA G gtaagccaacccaggcctcgccctccagctcaaggcgggacaggtgccctagagtagcctgcatcc  2547
 245 S   C   P   A                                                                  248

2548 agggacaggccccagccgggtgctgacgcatccacctccatctcttcctcag CA CCT GAG TTC CTG GGG GGA  2619
 249                                                    P   E   F   L   G   G    254

2620 CCA TCA GTC TTC CTG TTC CCC CCA AAA CCC AAG GAC ACT CTC ATG ATC TCC CGG ACC CCT  2679
 255 P   S   V   F   L   F   P   P   K   P   K   D   T   L   M   I   S   R   T   P    274

2680 GAG GTC ACG TGC GTG GTG GTG GAC GTG AGC CAG GAA GAC CCC GAG GTC CAG TTC AAC TGG  2739
 275 E   V   T   C   V   V   V   D   V   S   Q   E   D   P   E   V   Q   F   N   W    294
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2740 TAC GTG GAT GGC GTG GAG GTG CAT AAT GCC AAG ACA AAG CCG CGG GAG GAG CAG TTC AAC 2799
 295 Y   V   D   G   V   E   V   H   N   A   K   T   K   P   R   E   E   Q   F   N   314

2800 AGC ACG TAC CGT GTG GTC AGC GTC CTC ACC GTC CTG CAC CAG GAC TGG CTG AAC GGC AAG 2859
 315 S   T   Y   R   V   V   S   V   L   T   V   L   H   Q   D   W   L   N   G   K   334

2860 GAG TAC AAG TGC AAG GTC TCC AAC AAA GGC CTC CCG TCC TCC ATC GAG AAA ACC ATC TCC 2919
 335 E   Y   K   C   K   V   S   N   K   G   L   P   S   S   I   E   K   T   I   S   354

2920 AAA GCC AAA G gtgggacccacggggtgcgagggccacacggacagaggccagctcggcccacctctgccctggga 2995
 355 K   A   K   G                                                                   358

2996 gtgaccgctgtgccaacctctgtccctacag GG CAG CCC CGA GAG CCA CAG GTG TAC ACC CTG CCC 3061
 359                                   Q   P   R   E   P   Q   V   Y   T   L   P   369

3062 CCA TCC CAG GAG GAG ATG ACC AAG AAC CAG GTC AGC CTG ACC TGC CTG GTC AAA GGC TTC 3121
 370 P   S   Q   E   E   M   T   K   N   Q   V   S   L   T   C   L   V   K   G   F   389

3122 TAC CCC AGC GAC ATC GCC GTG GAG TGG GAG AGC AAT GGG CAG CCG GAG AAC AAC TAC AAG 3181
 390 Y   P   S   D   I   A   V   E   W   E   S   N   G   Q   P   E   N   N   Y   K   409

3182 ACC ACG CCT CCC GTG CTG GAC TCC GAC GGC TCC TTC TTC CTC TAC AGC AGG CTA ACC GTG 3241
 410 T   T   P   P   V   L   D   S   D   G   S   F   F   L   Y   S   R   L   T   V   429

3242 GAC AAG AGC AGG TGG CAG GAG GGG AAT GTC TTC TCA TGC TCC GTG ATG CAT GAG GCT CTG 3301
 430 D   K   S   R   W   Q   E   G   N   V   F   S   C   S   V   M   H   E   A   L   449

3302 CAC AAC CAC TAC ACA CAG AAG AGC CTC TCC CTG TCT CTG GGT AAA TGA gtgccagggccattga 3365
 450 H   N   H   Y   T   Q   K   S   L   S   L   S   L   G   K   *                   465

3366 agcatttatcagggttattgtctcatgagcggatacatatttgaatgtatttagaaaaataaacaaataggggttccgcg 3445

3446 cacatttcccgaaaagtgccacctgacgcgttgacattgattattgactagttattaatagtaatcaattacgggggtca 3525

3526 ttagttcatagcccatatatggagttccgcgttacataacttacggtaaatggcccgcctggctgaccgcccaacgacc 3605

3606 cccgcccattgacgtcaataatgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggac 3685
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3686 tatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacgg 3765

3766 taaatggcccgcctggcattatgcccagtacatgaccttatgggacttcctacttggcagtacatctacgtattagtca 3845

3846 tcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacggggatttccaagt 3925

3926 ctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatgtcgtaacaactccgc 4005

4006 cccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcagagctcgtttagtgaaccgtcaGAATT 4085

4086 CTGTTGGGCTCGCGGTTGATTACAAACTCTTCGCGGTCTTTCCAGTACTCTTGGATCGGAAACCCGTCGGCCTCCGAACG 4165

4166 GTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGATCGGAAAACCTCTCGACTGTTGGGgtgagtactccc 4245

4246 tctcaaaagcgggcatgacttctgcgctaagattgtcagtttccaaaaacgaggaggatttgatattcacctggccccgcg 4325

4326 gtgatgcctttgagggtggccgcgtccatctggtcagaaaagacaatcttttgttgtcaagcttgaggtgtggcaggct 4405

4406 tgagatctggccatacacttgagtgacaatgacatccactttgcctttctctcccacagGTGTCCACTCCCAGGTCCAACT 4485

4486 GCAGGTCGAC ATG AAG TTG CCT GTT AGG CTG TTG GTG CTG ATG TTC TGG ATT CCT GTT TCC  4546
          M  K  L  P  V  R  L  L  V  L  M  F  W  I  P  V  S      17

4547 AGC AGT GAT GTT GTG ATG ACC CAA ACT CCA CTC TCC CTG CCT GTC AGT CTT GGA GAT CAA 4606
  18 S  S  D  V  V  M  T  Q  T  P  L  S  L  P  V  S  L  G  D  Q      37

4607 GCC TCC ATC TCT TGC AGA TCT AGT CAG AGC CTT GTA CAC AGT AAT GGA AAC ACC TAT TTA 4666
  38 A  S  I  S  C  R  S  S  Q  S  L  V  H  S  N  G  N  T  Y  L      57

4667 CAG TGG TAC CTG CAG AAG CCA GGC CAG TCT CCA AAG CTC CTG ATC TAC AAA GTT TCC AAC 4726
  58 Q  W  Y  L  Q  K  P  G  Q  S  P  K  L  L  I  Y  K  V  S  N      77

4727 CGA TTT TCT GGG GTC CCA GAC AGG TTC AGT GGC AGT GGA TCA GGG ACA GAT TTC ACA CTC 4786
  78 R  F  S  G  V  P  D  R  F  S  G  S  G  S  G  T  D  F  T  L      97

4787 AAG ATC AGC AGA GTG GAG GCT GAG GAT CTG GGA GTT TAT TTC TGT TCT CAA AGT ACA CAT 4846
  98 K  I  S  R  V  E  A  E  D  L  G  V  Y  F  C  S  Q  S  T  H     117
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3686 tatttacggtaaactgcccacttggcagtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatgacgg 3765

3766 taaatggcccgcctggcattatgcccagtacatgaccttatgggactttcctacttggcagtacatctacgtattagtca 3845

3846 tcgctattaccatggtgatgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacggggatttccaagt 3925

3926 ctccaccccattgacgtcaatgggagtttgttttggcaccaaaatcaacgggactttccaaaatgtcgtaacaactccgc 4005

4006 cccattgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcagagctcgtttagtgaaccgtcaGAATT 4085

4086 CTGTTGGGCTCGCGGTTGATTACAAACTCTTCGCGGTCTTTCCAGTACTCTTGGATCGGAAACCCGTCGGCCTCCGAACG 4165

4166 GTACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGATCGGAAAACCTCTCGACTGTTGGGgtgagtactccc 4245

4246 tctcaaaagcgggcatgacttctgcgctaagattgtcagtttccaaaaacgaggaggatttgatattcacctggcccgcg 4325

4326 gtgatgcctttgagggtggccgcgtccatctggtcagaaaagacaatcttttgttgtcaagcttgaggtgtggcaggct 4405

4406 tgagatctggccatacacttgagtgacaatgacatccactttgcctttctctccacagGTGTCCACTCCCAGGTCCAACT 4485

4486 GCAGGTCGAC ATG AAG TTG CCT GTT AGG CTG TTG GTG CTG ATG TTC TGG ATT CCT GTT TCC  4546
          M  K  L  P  V  R  L  L  V  L  M  F  W  I  P  V  S     17

4547 AGC AGT GAT GTT GTG ATG ACC CAA ACT CCA CTC TCC CTG CCT GTC AGT CTT GGA GAT CAA 4606
  18  S  S  D  V  V  M  T  Q  T  P  L  S  L  P  V  S  L  G  D  Q     37

4607 GCC TCC ATC TCT TGC AGA TCT AGT CAG AGC CTT GTA CAC AGT AAT GGA AAC ACC TAT TTA 4666
  38  A  S  I  S  C  R  S  S  Q  S  L  V  H  S  N  G  N  T  Y  L     57

4667 CAG TGG TAC CTG CAG AAG CCA GGC CAG TCT CCA AAG CTC CTG ATC TAC AAA GTT TCC AAC 4726
  58  Q  W  Y  L  Q  K  P  G  Q  S  P  K  L  L  I  Y  K  V  S  N     77

4727 CGA TTT TCT GGG GTC CCA GAC AGG TTC AGT GGC AGT GGA TCA GGG ACA GAT TTC ACA CTC 4786
  78  R  F  S  G  V  P  D  R  F  S  G  S  G  S  G  T  D  F  T  L     97

4787 AAG ATC AGC AGA GTG GAG GCT GAG GAT CTG GGA GTT TAT TTC TGT TCT CAA AGT ACA CAT 4846
  98  K  I  S  R  V  E  A  E  D  L  G  V  Y  F  C  S  Q  S  T  H    117
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4847 GTT CCG TTC ACG TTC GGA GGG GGG ACC AAG CTG GAA ATA AAA CGA ACT GTG GCT GCA CCA 4906
 118 V   P   F   T   F   G   G   G   T   K   L   E   I   K   R   T   V   A   A   P   137

4907 TCT GTC TTC ATC TTC CCG CCA TCT GAT GAG CAG TTG AAA TCT GGA ACT GCC TCT GTT GTG 4966
 138 S   V   F   I   F   P   P   S   D   E   Q   L   K   S   G   T   A   S   V   V   157

4967 TGC CTG CTG AAT AAC TTC TAT CCC AGA GAG GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC 5026
 158 C   L   L   N   N   F   Y   P   R   E   A   K   V   Q   W   K   V   D   N   A   177

5027 CTC CAA TCG GGT AAC TCC CAG GAG AGT GTC ACA GAG CAG GAC AGC AAG GAC AGC ACC TAC 5086
 178 L   Q   S   G   N   S   Q   E   S   V   T   E   Q   D   S   K   D   S   T   Y   197

5087 AGC CTC AGC AGC ACC CTG ACG CTG AGC AAA GCA GAC TAC GAG AAA CAC AAA GTC TAC GCC 5146
 198 S   L   S   S   T   L   T   L   S   K   A   D   Y   E   K   H   K   V   Y   A   217

5147 TGC GAA GTC ACC CAT CAG GGC CTG AGC TCG CCC GTC ACA AAG AGC TTC AAC AGG GGA GAG 5206
 218 C   E   V   T   H   Q   G   L   S   S   P   V   T   K   S   F   N   R   G   E   237

5207 TGT TAG ctcgagcatgcaggcatgcaagcttggcactggccgtcgtttacaacgtcgtgactgggaaaaccctggcg 5284
 238 C   *                                                                          239

5285 ttacccaacttaatcg                                                              5300
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Cloning of Porcine CD86 (B7-2) RT-PCR was used to amplify an internal segment of the porcine CD86 gene from RNA isolated from LPS stimulated porcine PBLs. A second PCR fragment encoding a truncated N-terminus was prepared using the same cDNA template and an anchor dependent 5' RACE PCR cloning kit (CLONTECH, San Diego, CA). These porcine PCR products were fused by overlapping PCR and ligated into a plasmid vector for sequencing.

The cloned portion of porcine CD86 comprises 577 nucleotides. the encoded polypeptide is 192 amino acids long. The partial gene fragment was subsequently fused to the carboxy terminal 49 amino acids of the human CD86 IgC domain by overlapping PCR in which the 5' primer was constructed so as to encode the first 4 N-terminal amino acid residues of human CD86. to facilitate efficient secretion from mammalian cells. The 3' primer included fifteen nucleotides encoding a 5 histidine tag sequence.

The sequence of the chimeric human/porcine CD86 is shown below. Amino acid residues 1-4 and 197-245 are from human CD86. Residues 1-25 are believed to encode a signal sequence. Primers used for cloning had sequences corresponding to (separately) nucleotides 166-184, nucleotides 574-595, nucleotides 1-33, nucleotides 585-764, and nucleotides 728-764. The porcine CD86 sequence of the invention spans nucleotides 19-597.

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TCT AGA ATG GAT CCC CAG TGC ACT ATG GGA CTG AGA AAC ATT CTC GTT  48
      Met Asp Pro Gln Cys Thr Met Gly Leu Arg Asn Ile Leu Val
        1               5                  10

GGG ATG GTC CTC CTG CTC TCT GGT GCT GCC TCC TTG AAA AGT CAG GCA  96
Gly Met Val Leu Leu Leu Ser Gly Ala Ala Ser Leu Lys Ser Gln Ala
  15                  20                  25                  30

TAT TTC AAT GAG ACT GGA GAA CTG CCG TGC CAT TTT ACA AAC TCG CAG 144
Tyr Phe Asn Glu Thr Gly Glu Leu Pro Cys His Phe Thr Asn Ser Gln
                  35                  40                  45

AAC CTA AGC CTG GAT GAG CTG GTA GTA TTT TGG CAG GAC CAG GAT AAC 192
Asn Leu Ser Leu Asp Glu Leu Val Val Phe Trp Gln Asp Gln Asp Asn
              50                  55                  60

CTG GTT CTC TAC GAG CTA TAC CGA GGC CAA GAG AAG CCT CAT AAT GTT 240
Leu Val Leu Tyr Glu Leu Tyr Arg Gly Gln Glu Lys Pro His Asn Val
          65                  70                  75

AAT TCC AAG TAT ATG GGT CGC ACA AGC TTT GAC CAG GCC ACC TGG ACC 288
Asn Ser Lys Tyr Met Gly Arg Thr Ser Phe Asp Gln Ala Thr Trp Thr
      80                  85                  90

CTG AGA CTC CAC AAC GTT CAA ATC AAG GAC AAG GGC TCA TAT CAA TGT 336
Leu Arg Leu His Asn Val Gln Ile Lys Asp Lys Gly Ser Tyr Gln Cys
  95                 100                 105                 110

TTC ATC CAT CAT AAA GGG CCG CAT GGA CTT GTT CCT ATC CAC CAG ATG 384
Phe Ile His His Lys Gly Pro His Gly Leu Val Pro Ile His Gln Met
                 115                 120                 125

AGT TCT GAC CTA TCA GTG CTT GCT AAC TTC AGT CAA CCT GAA ATA AAC 432
Ser Ser Asp Leu Ser Val Leu Ala Asn Phe Ser Gln Pro Glu Ile Asn
             130                 135                 140
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CTA CTT ACT AAT CAC ACA GAA AAT TCT GTC ATA AAT TTG ACC TGC TCA 480
Leu Leu Thr Asn His Thr Glu Asn Ser Val Ile Asn Leu Thr Cys Ser
        145                 150                 155

TCT ACA CAA GGC TAC CCA GAA CCC CAG AGG ATG TAT ATG TTG CTA AAT 528
Ser Thr Gln Gly Tyr Pro Glu Pro Gln Arg Met Tyr Met Leu Leu Asn
    160                 165                 170

ACG AAG AAT TCA ACC ACT GAG CAT GAT GCT GAC ATG AAG AAA TCT CAA 576
Thr Lys Asn Ser Thr Thr Glu His Asp Ala Asp Met Lys Lys Ser Gln
175                 180                 185                 190

GAT AAT GTC ACA GAA CTG TAT GAC GTT TCC ATC AGC TTG TCT GTT TCA 624
Asp Asn Val Thr Glu Leu Tyr Asp Val Ser Ile Ser Leu Ser Val Ser
                195                 200                 205

TTC CCT GAT GTT ACG AGC AAT ATG ACC ATC TTC TGT ATT CTG GAA ACT 672
Phe Pro Asp Val Thr Ser Asn Met Thr Ile Phe Cys Ile Leu Glu Thr
            210                 215                 220

GAC AAG ACG CGG CTT TTA TCT TCA CCT TTC TCT ATA GAG CTT GAG GAC 720
Asp Lys Thr Arg Leu Leu Ser Ser Pro Phe Ser Ile Glu Leu Glu Asp
        225                 230                 235

CCT CAG CCT CCC CCA GAC CAC CAT CAC CAT CAT TAA TGC AT      764
Pro Gln Pro Pro Pro Asp His His His His His  *
    240                 245                 250
```


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What is claimed is:

1. An isolated antibody which binds to a porcine cell interaction protein selected from the group consisting of P-selectin, VCAM, and CD86 but not to a human cell interaction protein selected from the group consisting of P-selectin, VCAM, and CD86.

2. A method for treating rejection of a xenografted porcine organ, tissue, or cell comprising administering the antibody of Claim 1 to said organ, tissue, or cell.

3. A method for detecting rejection of a porcine organ, tissue, or cell that has been xenografted into a patient comprising assaying a body fluid of the patient for the presence of an antigen immunoreactive with the antibody of Claim 1.

4. The method of Claim 3 in which the body fluid is blood.

5. The isolated antibody of Claim 1 wherein the antibody is a recombinant antibody and comprises a chain coded for by a sequence selected from the sequences of pages 59-79.

6. An isolated nucleic acid molecule comprising:

(a) a sequence selected from the sequences of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, and SEQ ID NO:14;

(b) a sequence complementary to (a); or

(c) both (a) and (b);

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said molecule being substantially free of nucleic acid molecules not containing (a), (b), or (c).

7. An isolated nucleic acid molecule comprising:

(a) any of the CDR encoding regions of the antibody sequences of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:11, or SEQ ID NO:12,; or

(b) a sequence complementary to (a); or

(c) both (a) and (b);

said molecule being substantially free of nucleic acid molecules not containing (a), (b), or (c).

8. An antibody comprising the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4

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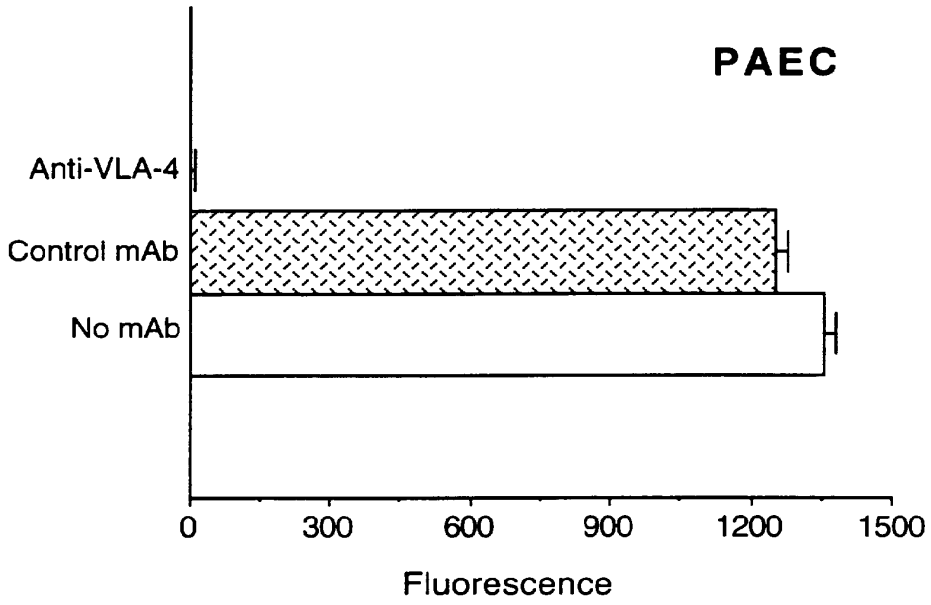

Fig. 1a

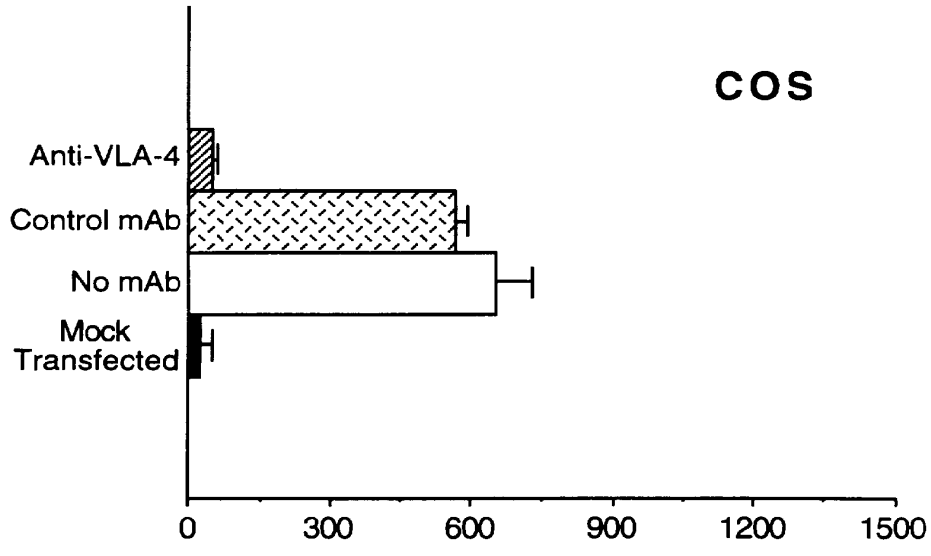

Fig. 1b

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Fig. 2B

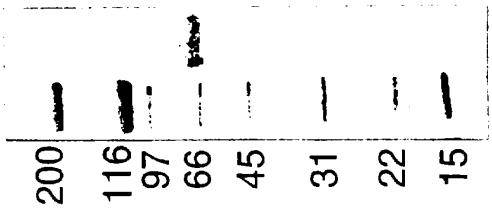
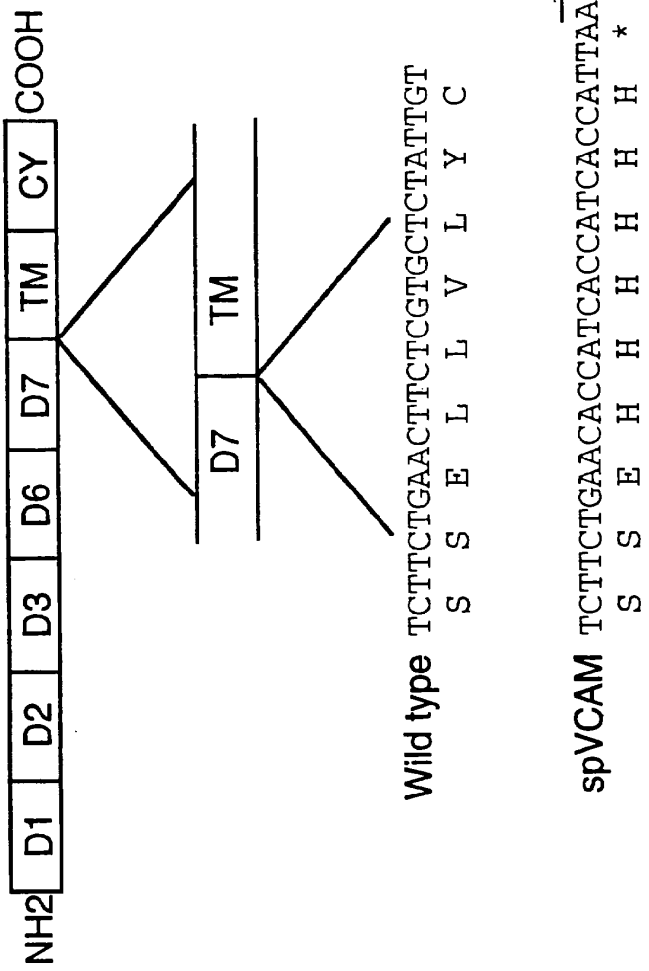


Fig. 2A



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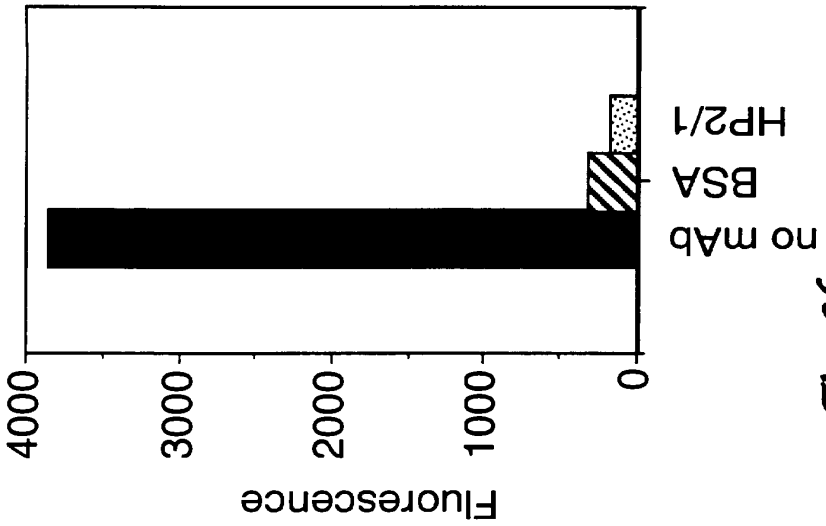

Fig. 3b

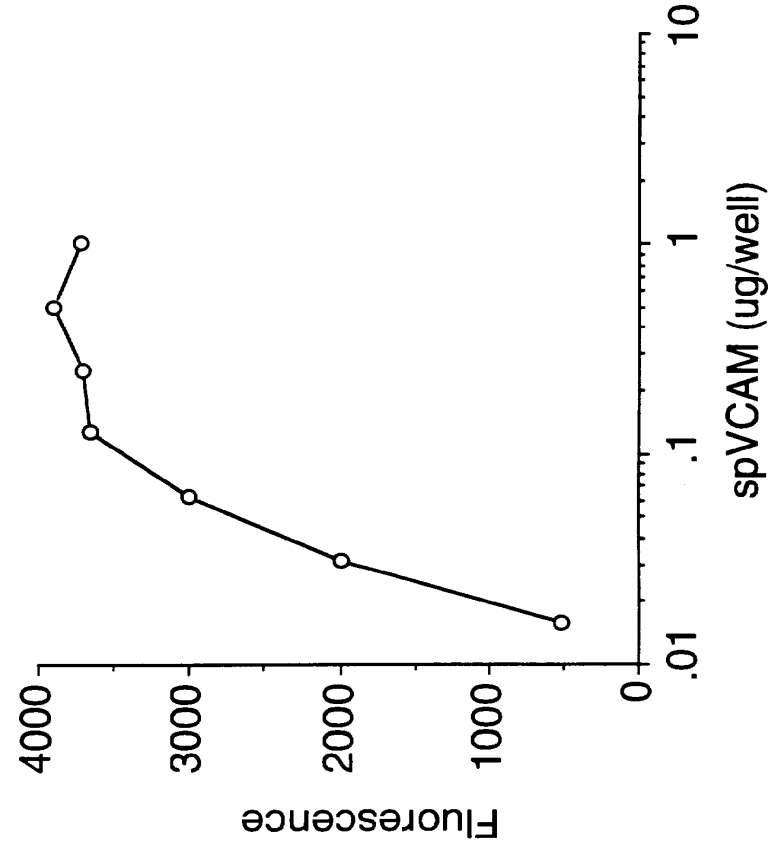

Fig. 3a

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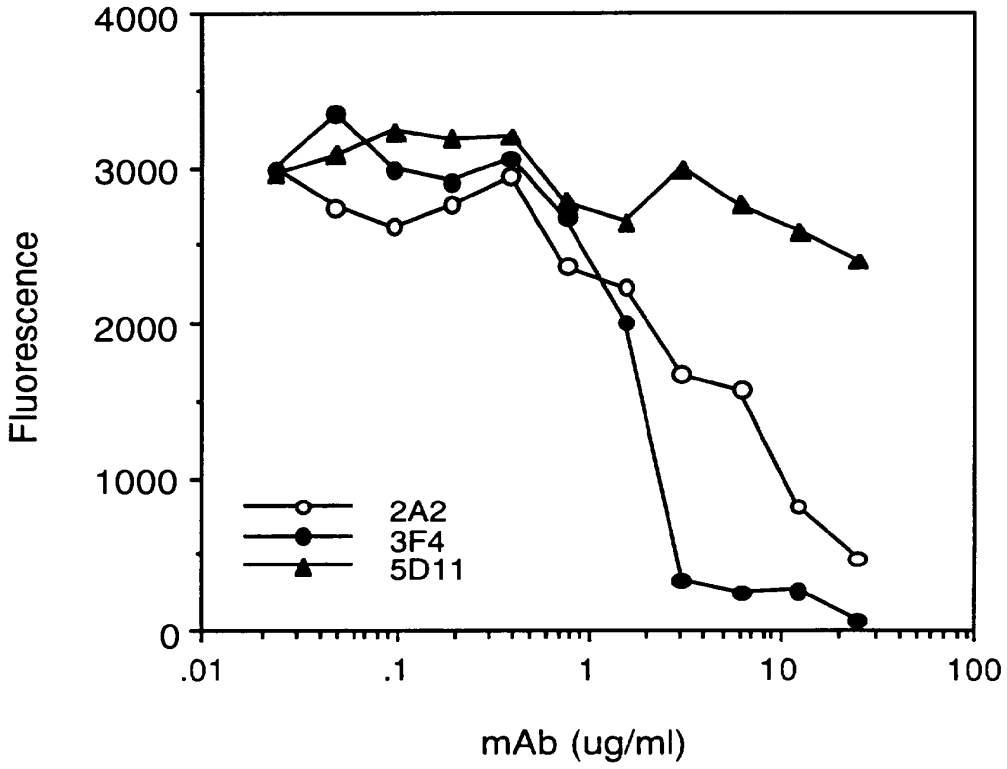

Fig. 4

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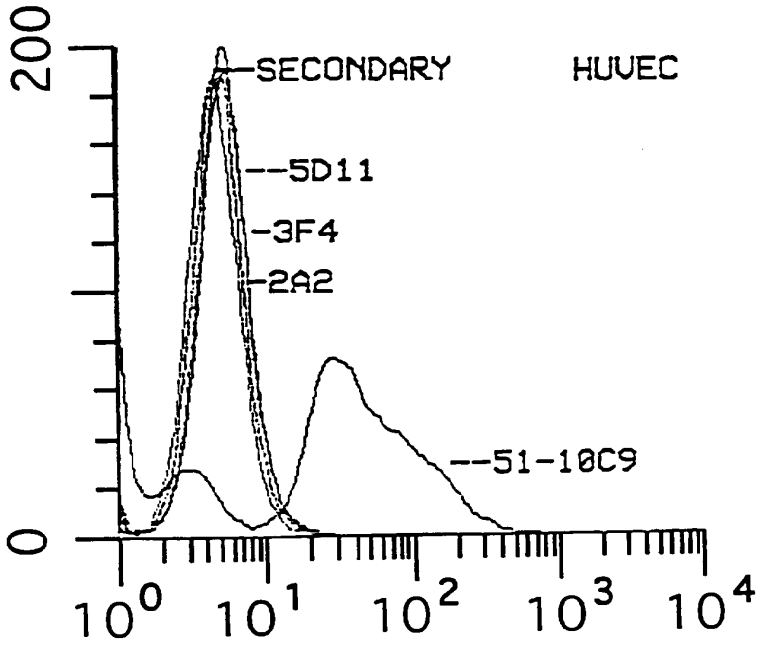

Fig. 5a

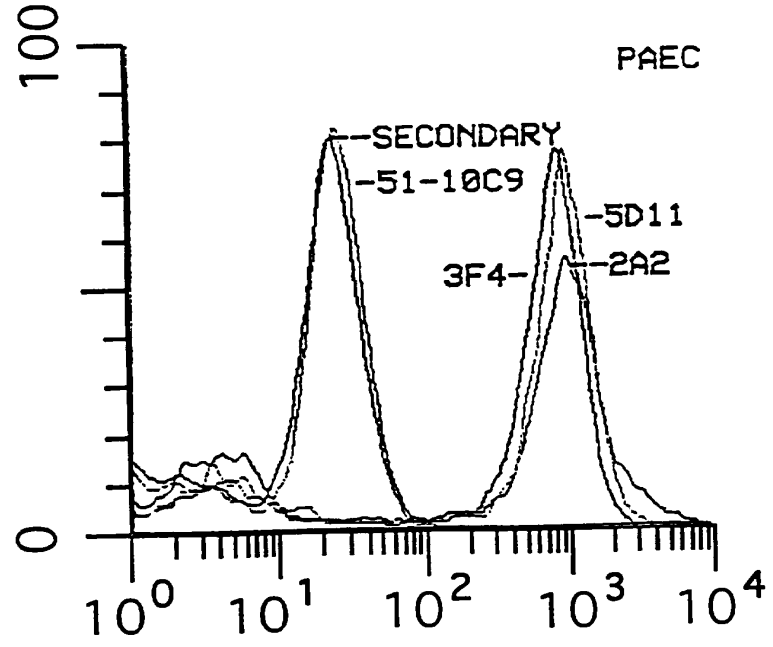

Fig. 5b

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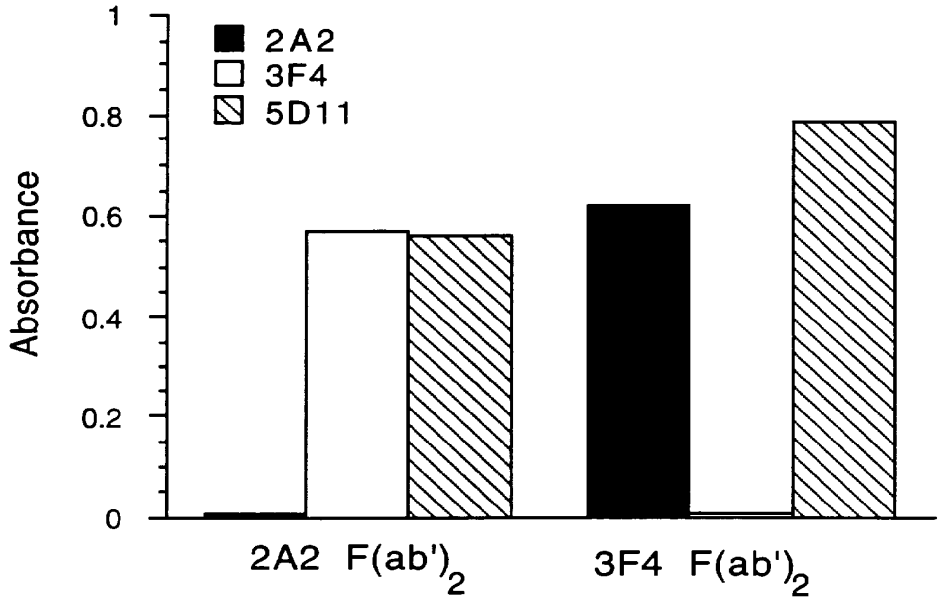

Fig. 6

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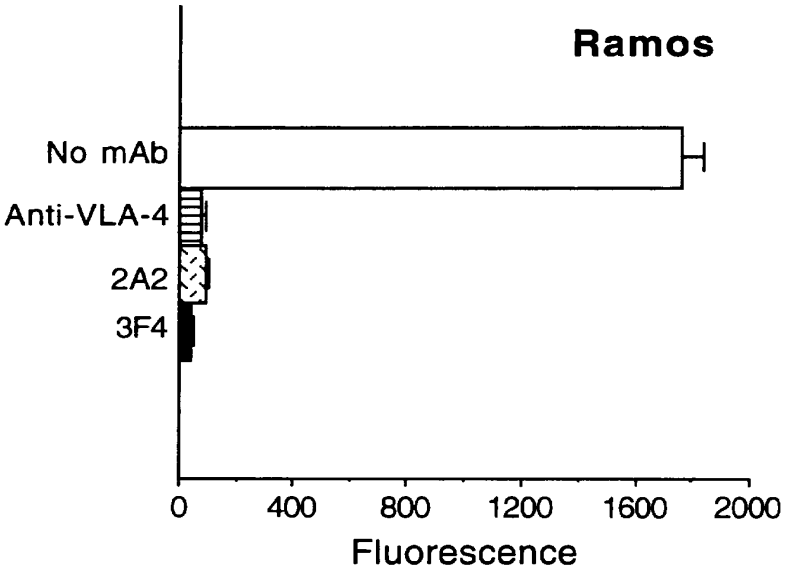

Fig. 7a

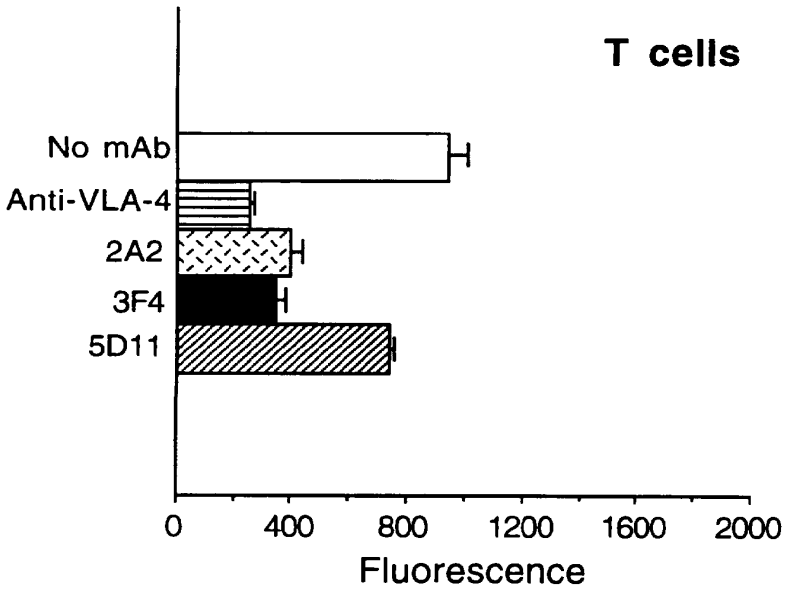

Fig. 7b

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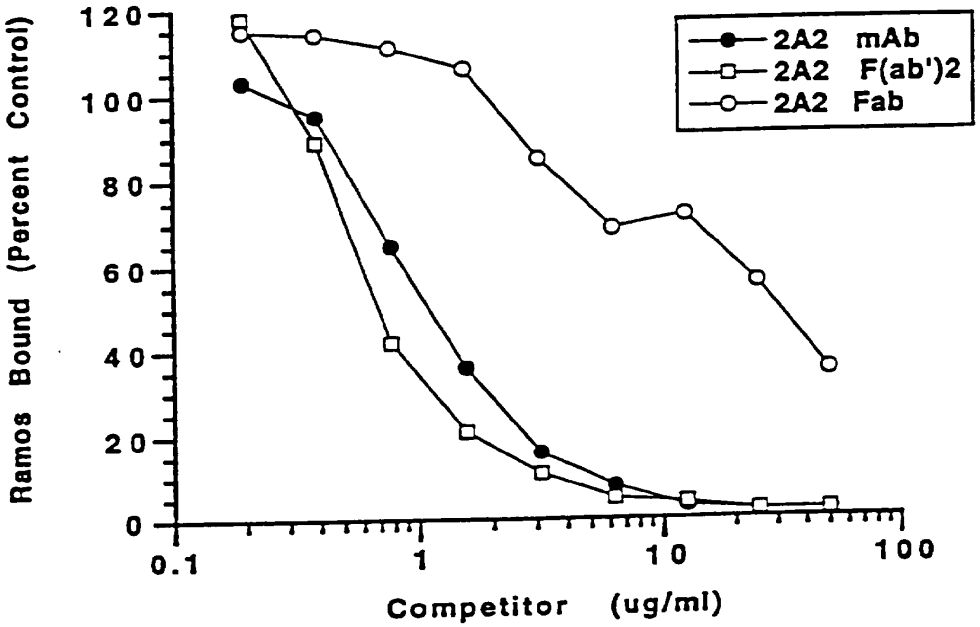

Fig. 8a

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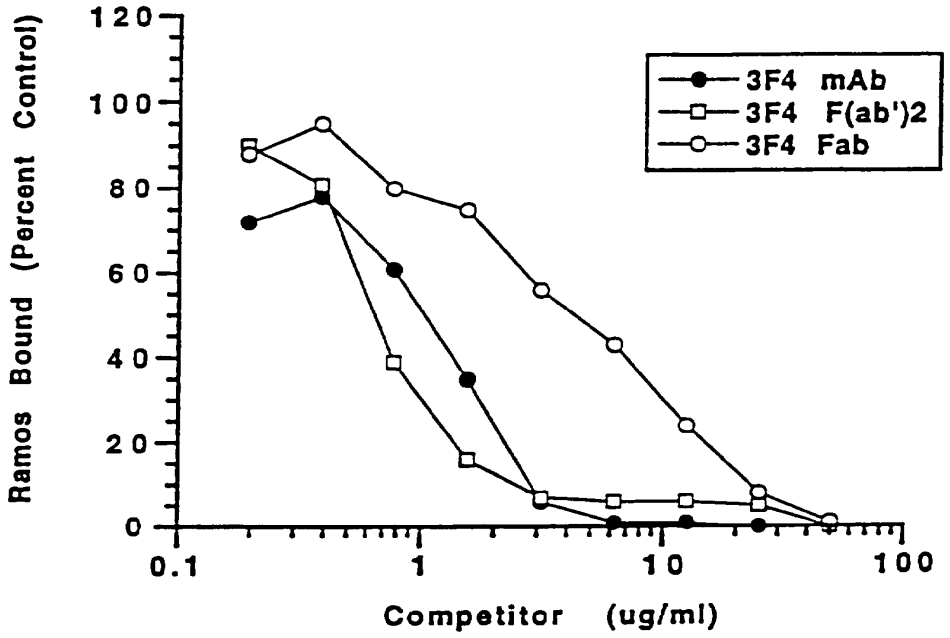
Ramos Bound (Percent Control)
120
100
80
60
40
20
0
0.1
1
10
100
Competitor (ug/ml)
3F4 mAb
3F4 F(ab')2
3F4 Fab

Fig. 8b

VARIABLE LIGHT

```
                                                                  24
D V V M T Q T P L S L P V S L G D Q A S I S C R S 3F4
D I V M T Q S Q K F M S T S L G D R V S V T C K A 2A2

          31 a c d e f   34
S Q S L V H S N G N T Y L Q W Y L Q K P G Q S P K 3F4
S Q N V G P - - - - - N V A W F Q Q K P G Q S P K 2A2

          50          56
L L I Y K V S N R F S G V P D R F S G S G S G T D 3F4
T L I Y S A S F R Y S G V P D R F T G S G S G T D 2A2

                                                  89
F T L K I S R V E A E D L G V Y F C S Q S T H V P 3F4
F T L T I T N V Q S E D L A E Y F C H Q Y N S Y P 2A2

 97
F T F G G G T K L E I K 3F4
L T F G G G T K L K I K 2A2
```

VARIABLE HEAVY

```
Q V Q V Q Q S G A E L A R P W A S V K L S C K A S 3F4
Q V Q L Q Q S G P Q L V R P G T S V K I S C K A S 2A2

          31    35                                        50
G Y N F N S Y W M Q W V K Q R P G Q G L E W I G A 3F4
G Y S F T S Y W M H W V K Q R P G Q D L E W I G M 2A2

 52 a                          65
I Y P G D G D T S Y T Q K F R G K A T L T A D K S 3F4
I D P S D S E V K L N Q R L K D K A I L T V D K S 2A2

              82 a b c                                95
S S T A Y M Q L S S L A S E D S A V Y Y C A R R T 3F4
S N T A Y M Q F S G P T S E D S A V Y Y C T R G E 2A2

    100 a 102
V G G Y F D Y W G Q G T T L T V S S 3F4
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Fig. 9

SUBSTITUTE SHEET (RULE 26)

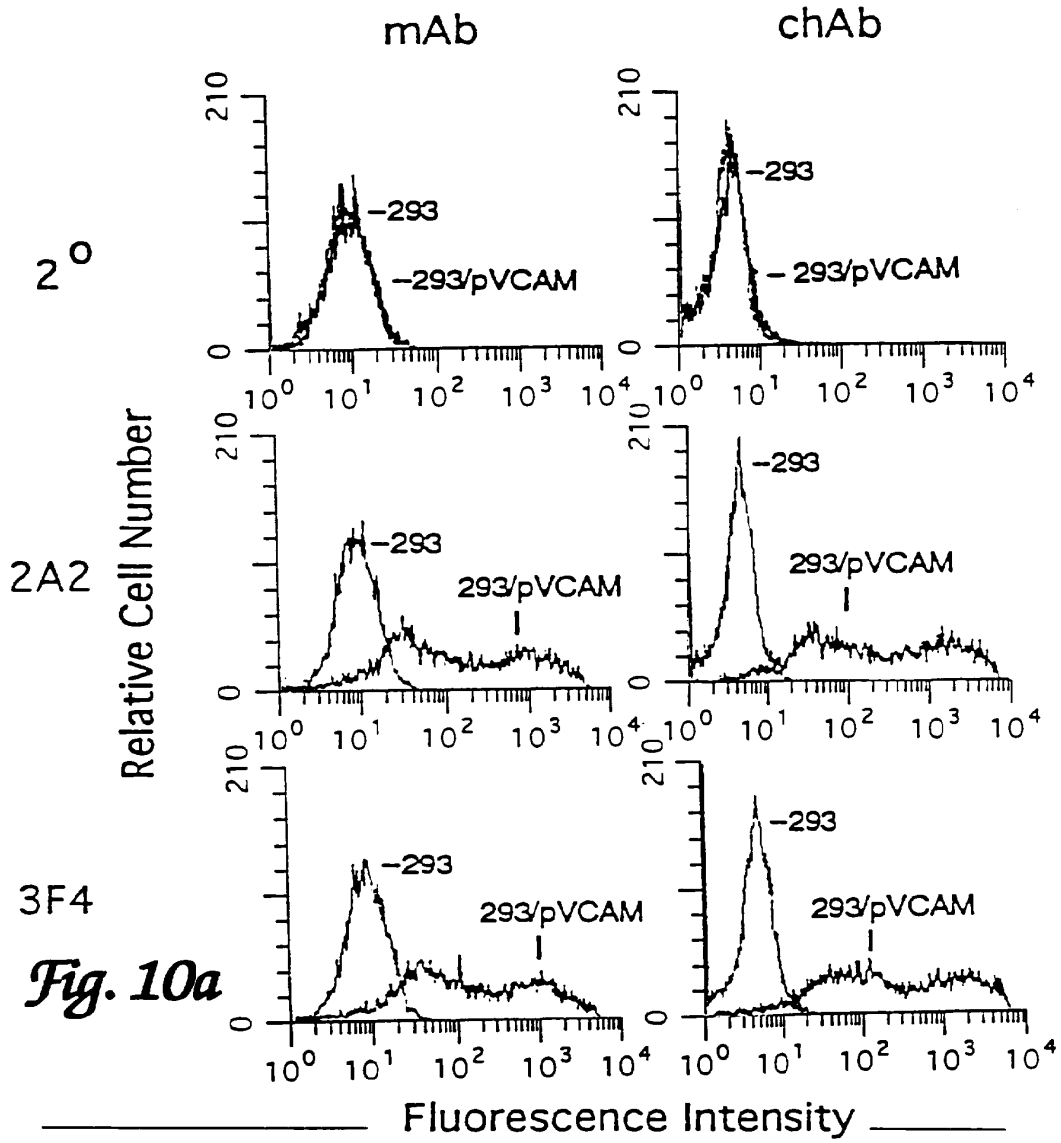

Fig. 10a

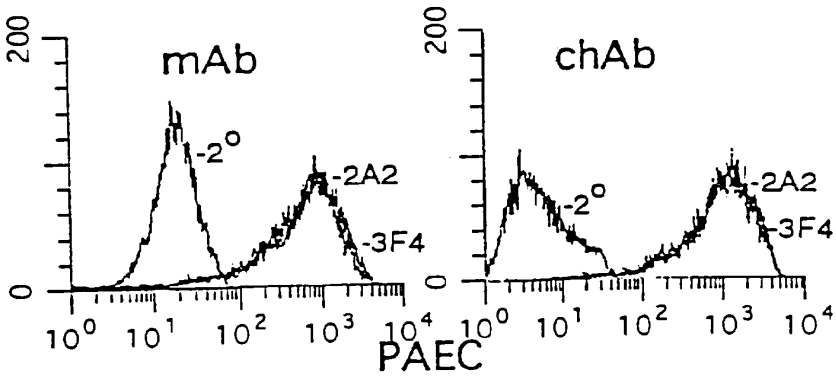

Fig. 10b

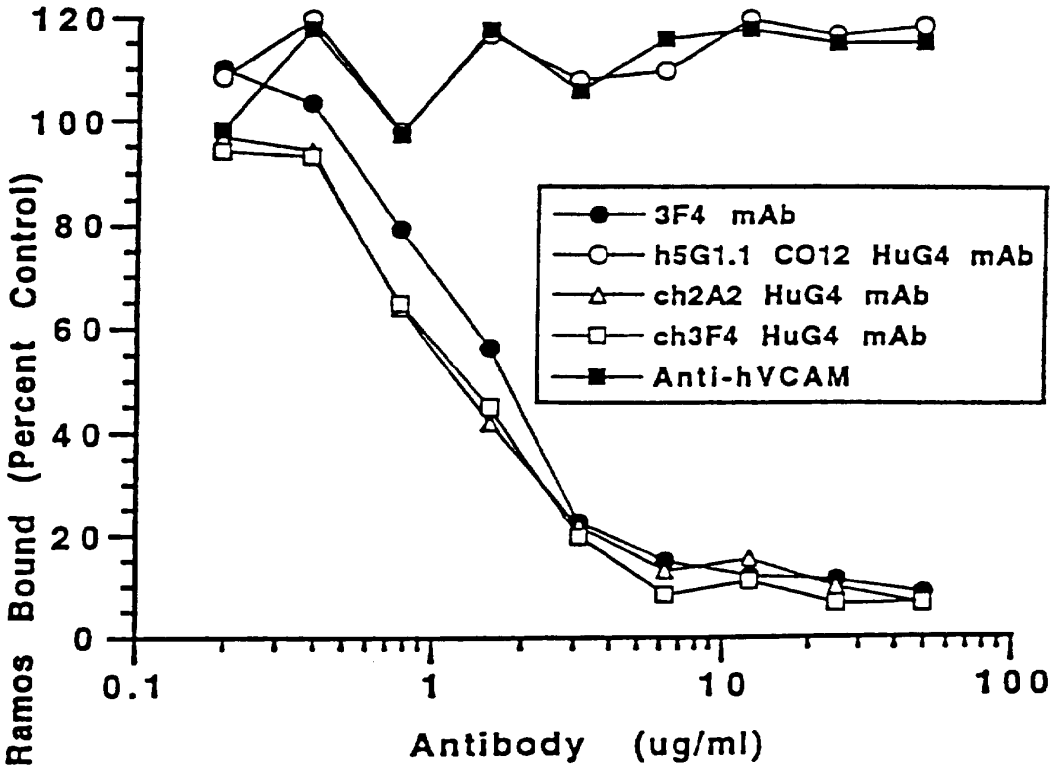

Fig. 11

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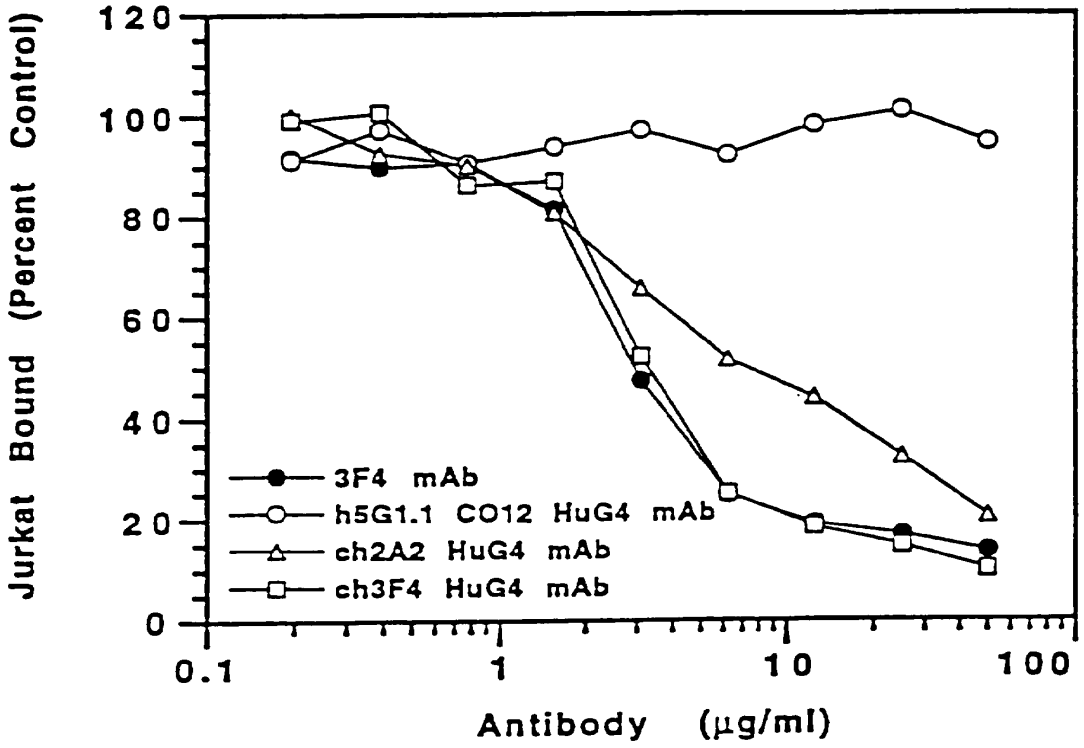

Fig. 12

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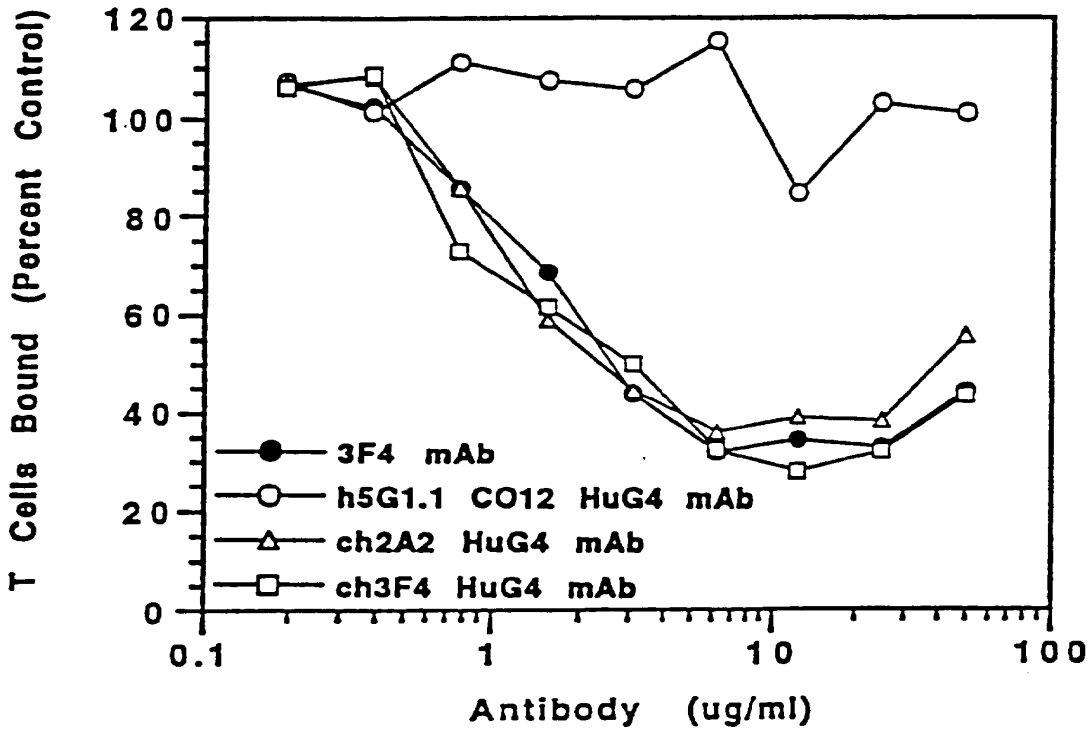

Fig. 13

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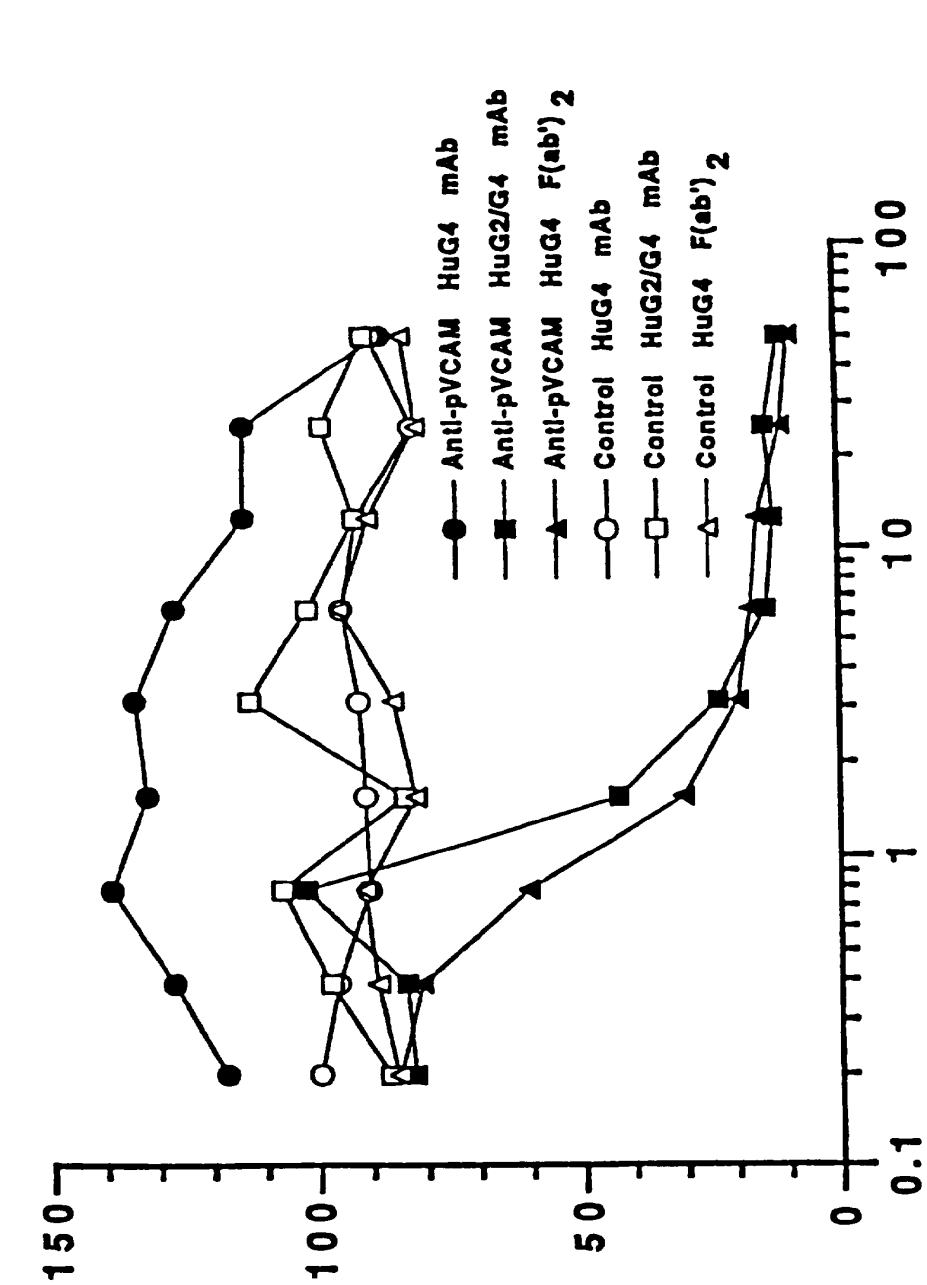

Fig. 14

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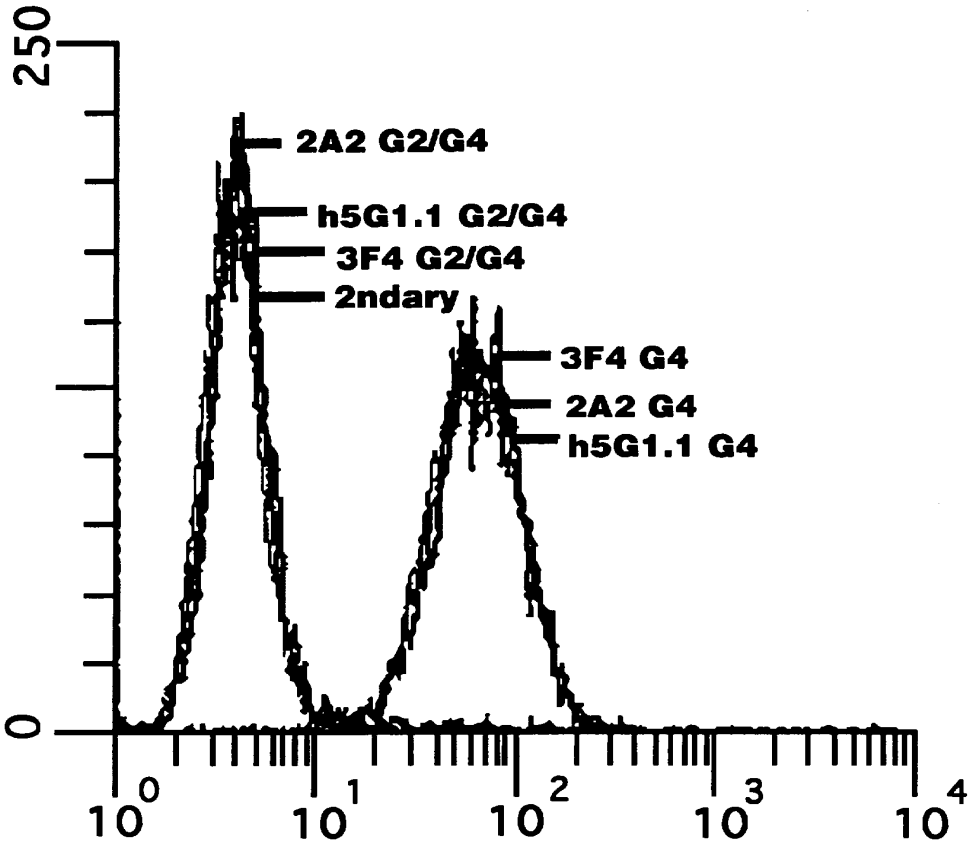

Fig. 15

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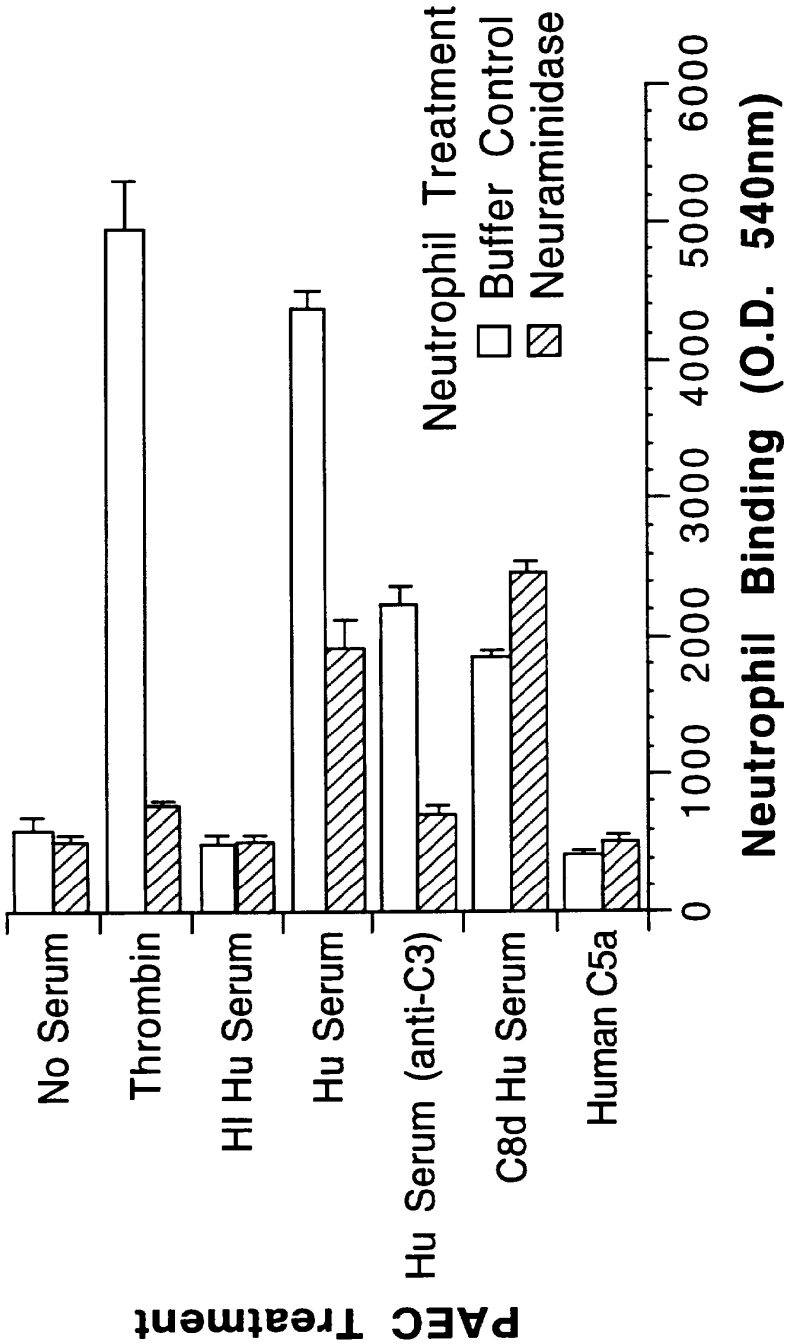

Fig. 16

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```
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    Hu **N*QI**LYQ*****V*GIS***C******E*T***E***

Lec Po WTYNYSTSAYSWNTSRVFCQRYFTDLVAIQNKKEIAYLNDVIPYYSSYYWIGMRKINNKWIW
    Hu ***H***K*****I**KY**NRY*********N**D***K*L**********I**N*KT**

    Po VGIKKTLTQEAENWAKNEPNNESNNQDCVEMYIKSPLAPGKWNDEPCVKRKRAL
    Hu *****A**N******D*****KR**E****I*****S********H*L*K*H**

EGF Po CYTASCQSTSCSKQGECTETIGNYTCSCYSGFYGPRCEYVKE
    Hu *******DM********L***********P*****E****R*

CR1 Po CGEFKLPQYVLINCSHPLGNFSFNSQCSFHCAEGYTLNGPSELECLASGNWTHPPPQCVAVQ
    Hu ***LE***H**M******************TD**QV****K*******I**NK****L*A*

CR2 Po CPALKSPEKGNMACLHSEKAFQYQSSCNFSCEEGYALVGPEVVQCQASGMWTAPVPVCKAIT
    Hu **P**I**R***I****A****H****S******F**********T***V****A*****VQ

CR3 Po Absent
    Hu CQHLEAPSEGIMDCVHPLTAFAYGSSCKFECQPGYRVRGLDMLRCIDSGHWSAPLPTCEAIS

CR4 Po CEPLESPVRGSMDCFPSSRAFQYNTSCSFRCAKGFTLRGADIVRCSNLGQWTAPAPVCQALQ
    Hu ********H*****S**L*****D*N******E**M*****I***D***************

CR5 Po CQDLPAPEKAQVNCSHPFGAFRYQSTCSFTCDEGSSLVGASVLQCLETGNWSAPAPECQ
    Hu *****V*NE*R**************V*****N**LL**********A****NSVP****

    Po GISIVSAPPPEVR
    Hu A*P

CR6 Po Absent
    Hu CTPLLSPQNGIMTCVQPLGSSSYKSTCQFICDEGYSLSGPERLDCTRSGRWTDSPPMCEAIK

CR7 Po Absent
    Hu CPELFAPEQGSLDCSDTRGEFNVGSTCHFSCNNGFKLEGPNNVECTTSGRWSATPPTCK

    Po Absent
    Hu GIASLPTGLQ

CR8 Po CPALITPEQGIMHCQHHLGTFGLNITCYFRCKTGFTIMGNNALRCRSSGQWTAVAPVCRAVK
    Hu ****T**G****Y*R**P****F******G*NA***LI*DST*SC*P*******T*A*****

CR9 Po CYELHITGPIVMNCSNPWGSFSYGSTCSFHCPEGQLLNGSELTVCKENGEWSTIMPTCL
    Hu *S***VNK**A*****L**N*****I*****L********AQ*A*QE**H****V***Q

    Po AGPLTIQE
    Hu ********

TM  Po ALTYFGGAVASTTGLVMGGTLLALL
    Hu ************I**I*********

CYT Po RKRRRQKDDGKSPLSPQSHLGTYGVFTNAAFDPNP
    Hu ***F*******C**N*H****************S*
```

SUBSTITUTE SHEET (RULE 26)

Fig. 17

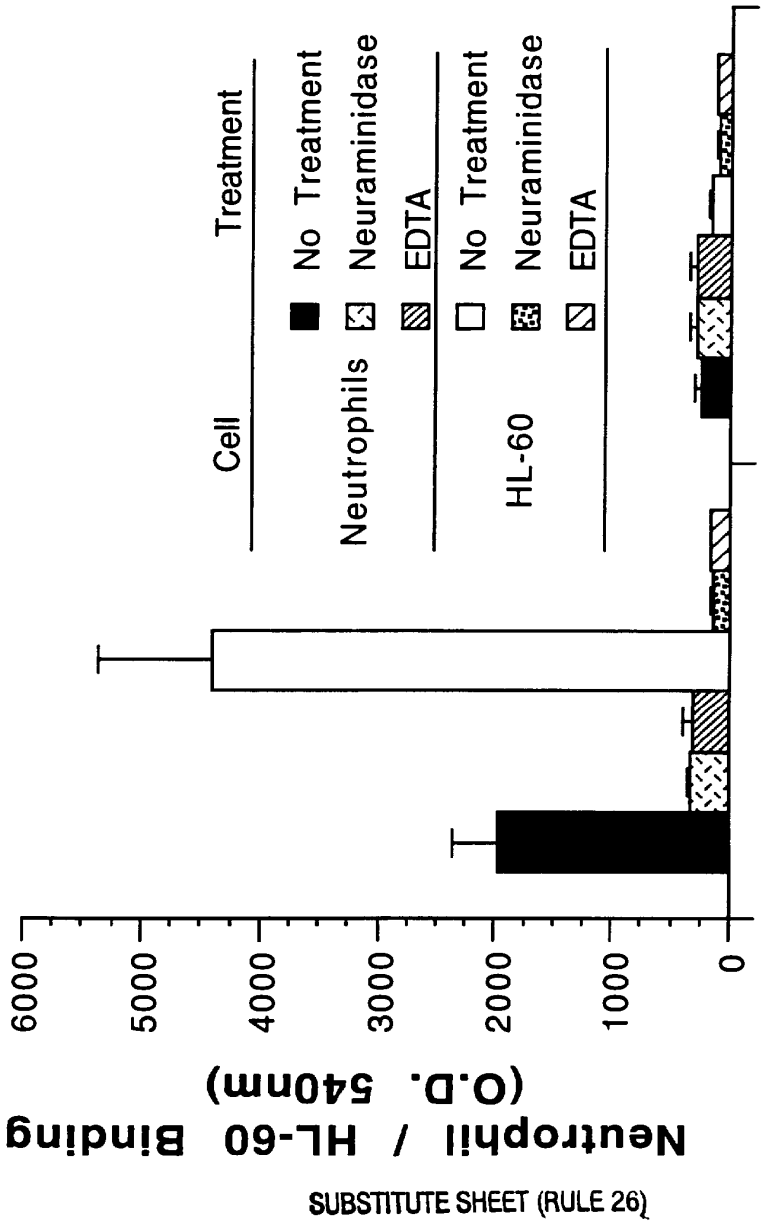

Fig. 18

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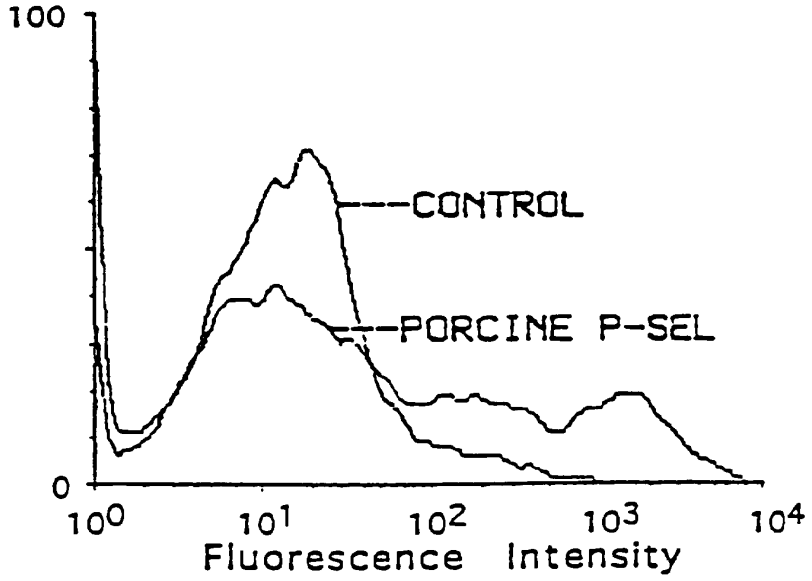

Fig 19a

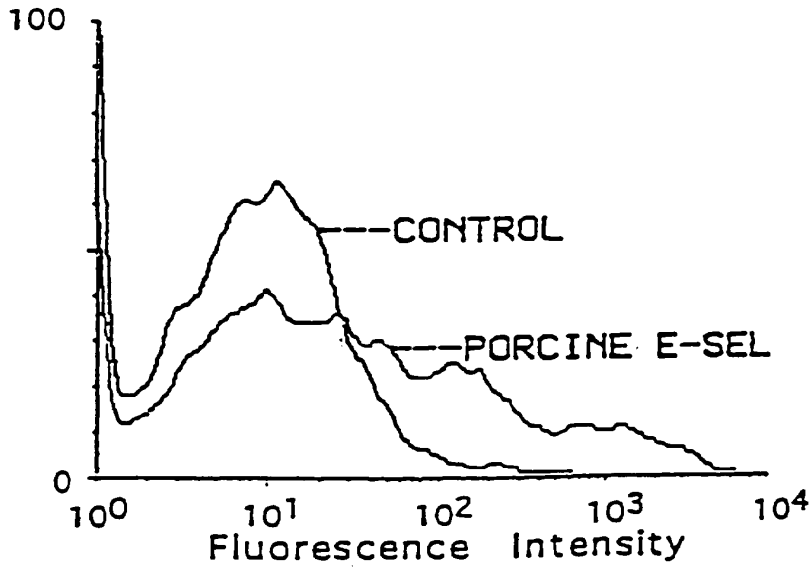

Fig. 19b

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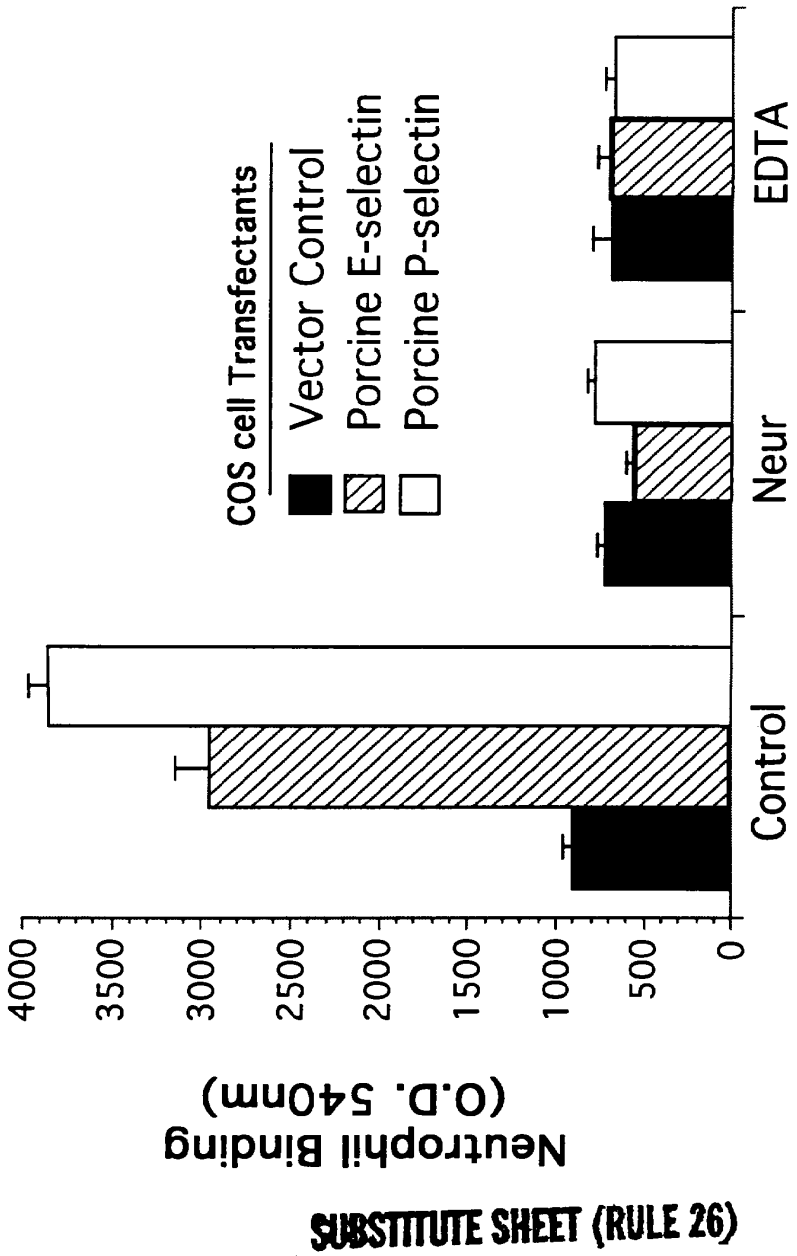
COS cell Transfectants
Vector Control
Porcine E-selectin
Porcine P-selectin
Control
Neur
EDTA
Neutrophil Binding
(O.D. 540nm)
0
500
1000
1500
2000
2500
3000
3500
4000

Fig. 20

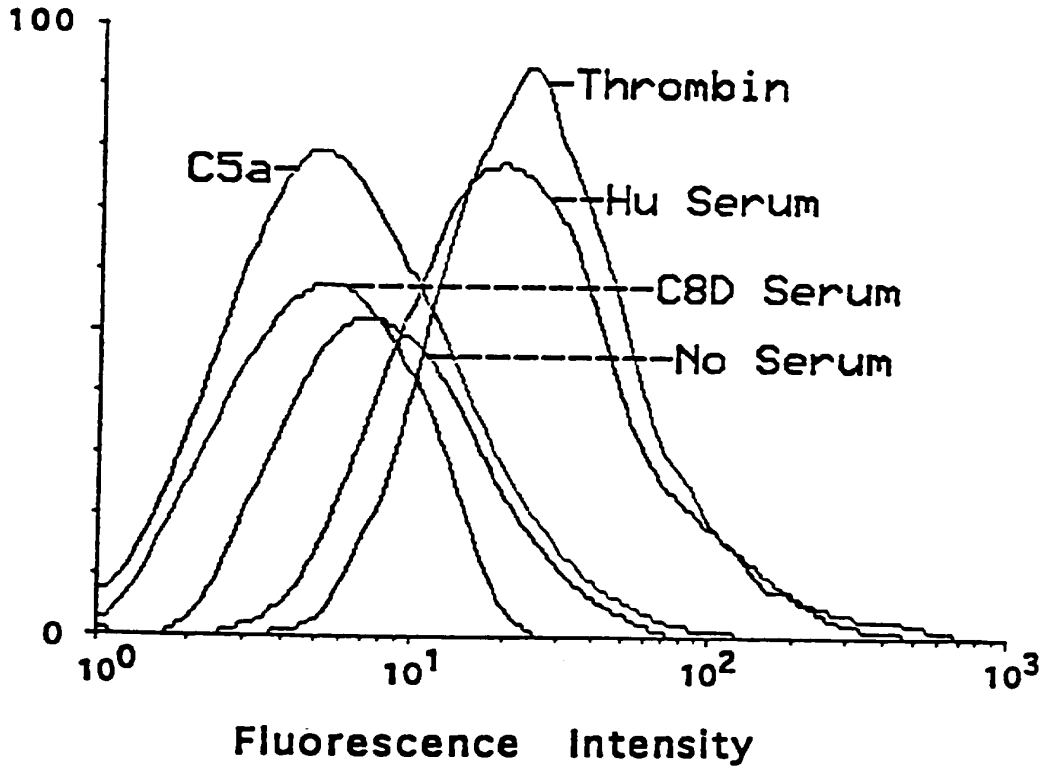

Fig. 21

Samsung Bioepis Exhibit No. 1002
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15575

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07K 16/00, 16/18, 16/28, 16/46
US CL : 530/387.1, 387.2, 388.1, 388.22, 388.7, 388.73
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : C07K 16/00, 16/18, 16/28, 16/46

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG, BIOSIS, CA, EMBASE, MEDLINE, WPI
search terms: porcine, swine, pig, vcam, cd86, p selectin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Biochem. Biophys. Res. Commun., Volume 201, Number 2, issued 15 June 1994, Tsang et al., "Cloning and Expression Kinetics of Porcine Vascular Cell Adhesion Molecule", pages 805-812, see entire document.	1-4
X --- Y	Xenotransplantation, Volume 2, issued 1995, Kumagai-Braesch et al., "Identification of Swine and Primate Cellular Adhesion Molecules (CAM) Using Mouse Anti-Human Monoclonal Antibodies", pages 88-97, see entire document.	1-4 -------- 1-4, 8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 DECEMBER 1996	Date of mailing of the international search report 15 JAN 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PHILLIP CAMPBELL Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/15575

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 5-7
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

SEQUENCE SEARCH COULD NOT BE PERFORMED BECAUSE OF DEFECTIVE DISKETTE SUBMISSION.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

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(71) Applicant *(for all designated States except US)*: **ALEXION PHARMACEUTICALS, INC.** [US/US]; 352 Knotter Drive, Cheshire, CT 06410 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ROTHER, Russell, P.** [US/US]; 25 Blue Trail Drive, Prospect, CT 06712 (US). **FAAS-KNIGHT, Susan** [US/US]; 14 Stonewood Drive, Old Lyme, CT 06371 (US). **WU, Dayang** [US/US]; 755 Devonwood Drive, Cheshire, CT 06410 (US). **SQUINTO, Stephen, P.** [US/US]; 16 Coachman Lane, Bethany, CT 06524 (US). **EVANS, Mark, J.** [US/US]; 617 Twin Bridge Road, Radnor, PA 19087 (US).

(74) Agent: **MARK, Farber**; Alexion Pharmaceuticals, Inc., 352 Knotter Drive, Cheshire, CT 06410 (US).

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(54) Title: ANTIBODIES AND FUSION PROTEINS THAT INCLUDE ENGINEERED CONSTANT REGIONS

(57) Abstract: Antibodies and/or fusion proteins contain a region that includes an IgG2-derived portion and an IgG4-derived portion.

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ANTIBODIES AND FUSION PROTEINS THAT INCLUDE ENGINEERED CONSTANT REGIONS

RELATED CASES

This application claims priority to U.S. Provisional Applications 60/475,202 and 60/563,500 filed May 30, 2003 and April 19, 2004, respectively, the entire disclosures of which are incorporated herein by this reference.

BACKGROUND

1. Technical Field

The present disclosure relates to the field of genetically engineered antibodies and fusion proteins. More specifically this disclosure relates to antibodies and/or fusion proteins containing a region that includes an IgG2-derived portion and an IgG4-derived portion.

2. Background of Related Art

Antibodies are produced by B lymphocytes and defend against infections. The basic structure of an antibody consists of two identical light polypeptide chains and two identical heavy polypeptide chains linked together by disulphide bonds. The first domain located at the amino terminus of each chain is variable in amino acid sequence, providing the vast spectrum of antibody binding specificities found in each individual. These are known as variable heavy (VH) and variable light (VL) regions. The other domains of each chain are relatively invariant in amino acid sequence and are known as constant heavy (CH) and constant light (CL) regions. The major classes of antibodies are IgA, IgD, IgE, IgG and IgM; and these classes may be further divided into

subclasses (isotypes). For example, the IgG class has four subclasses, namely, IgG1, IgG2, IgG3, and IgG4. Of the various human antibody classes, only human IgG1, IgG2, IgG3 and IgM are known to effectively activate the complement system.

The differences between antibody classes are derived from differences in the heavy chains. Class switching is known to occur during antibody maturation. The basic antibody molecule is a bifunctional structure wherein the variable regions bind antigen while the remaining constant regions elicit certain effector functions. The hinge region is particularly sensitive to proteolytic cleavage; such proteolysis yields two or three fragments depending on the precise site of cleavage. The hinge region allows the antigen binding regions (each made up of a light chain and the first two domains of a heavy chain) to move or rotate freely relative to the rest of the antibody, which includes the remaining heavy chain domains. Although the constant regions do not form the antigen binding sites, the arrangement of the constant domains and hinge region confer segmental flexibility on the molecule which allows it to bind with the antigen.

The interaction between the antigen and the antibody takes place by the formation of multiple bonds and attractive forces such as hydrogen bonds, electrostatic forces and Van der Waals forces. Together these form considerable binding energy which allows the antibody to bind the antigen. Antibody binding affinity and avidity have been found to affect the physiological and pathological properties of antibodies.

The advent of genetic engineering technology has led to various means of producing unlimited quantities of uniform antibodies (monoclonal antibodies) which, depending upon the isotype, exhibit varying degrees of effector function. For example, certain murine isotypes (IgG1, IgG2) as well as human isotypes (particularly IgG1) can

bind to Fc receptors on cells such as monocytes, B cells and NK cells, thereby activating the cells to release cytokines; such antibody isotypes are also potent in activating complement, with local or systemic inflammatory consequences. When antibodies bearing these Fc receptor-binding constant regions are injected in vivo, a transient but significant systemic release of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin 2 (IL-2) and/or other cytokines may be released as a consequence of activation of multiple cell types including lymphocytes or monocytes through Fc receptor-antibody engagement. The release of cytokines is usually accompanied by high fever, chills and headache, but less frequently may progress to more severe and potentially life-threatening symptoms, such as pulmonary edema, meningitis, neurotoxicity, hypotension and respiratory distress (cytokine release syndrome or CRS). The murine antibody OKT3 is one antibody that has been observed to cause significant cytokine release leading to CRS. The human CD3 moiety consists of at least four invariant polypeptide chains, which are non-covalently associated with the T cell receptors (TCR) on the surface of T-cells, typically referred to as the T cell receptor complex. The T cell receptor complex plays an important role in the T-cell activation upon antigen binding to the T cell receptor. Some anti-CD3 antibodies, such as OKT3, can activate T-cells in the absence of antigen-TCR ligation. Such activation depends upon the interaction between the Fc portion of the mAb and the Fc receptors on accessory cells, enabling crosslinking of CD3 complexes on the T-cells. Soluble anti-CD3 mAbs do not stimulate T-cells to proliferate *in vitro* unless they are bound to plastic (which artificially promotes CD3 cross-linking) or bound to Fc receptor- bearing cells.

It would be desirable to reduce antibody-mediated cell activation events such as, for example, cytokine release in settings where these events are not warranted and/or harmful. Numerous laboratories have attempted to reduce the negative effects associated with potent effector function, such as that observed with OKT3, by engineering antibodies with different constant regions that exhibit features such as reduced Fc receptor binding, lack of complement activation, etc.

Therefore it is an object herein to reduce effector function in engineered antibodies through the incorporation of unique constant regions.

SUMMARY

Recombinant antibodies having engineered heavy chain constant regions are described herein. The engineered constant regions include an IgG2-derived portion and an IgG4-derived portion. Preferably, the IgG2-derived portion includes at least the heavy chain constant region 1 and hinge region and the IgG4-derived portion includes most of the heavy chain constant region 2 and the entire heavy chain constant region 3. Antibodies that bind cell surface molecules or soluble molecules that bind to cell surface molecules having an engineered heavy chain constant region in accordance with this disclosure, reduce unwanted antibody-mediated cell activation and inflammatory events (including reduced complement activation) resulting from Fc–receptor antibody engagement.

In another aspect, this disclosure relates to a process for producing an antibody heavy chain which includes the steps of: (a) producing an expression vector having a DNA sequence which includes a sequence that encodes an antibody heavy chain

containing a variable region and a constant region; (b) having said constant region comprised of a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies; (c) transfecting a host cell with the vector; and (d) culturing the transfected cell line to produce an engineered antibody heavy chain molecule which associates with antibody light chains to produce a functional antibody molecule.

In another aspect, this disclosure relates to methods for reducing antibody-mediated cell activation and inflammatory events through binding cell surface molecules or soluble molecules that bind to cell surface molecules using antibodies having an engineered heavy chain constant region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies, associated with light chains to produce a functional antibody molecule.

In another embodiment, an engineered constant region that includes an IgG2-derived portion and an IgG4-derived portion in accordance with this disclosure is used as the Fc region of a fusion protein. The fusion proteins include a non-Fc component fused to an Fc region that is engineered to include an IgG2-derived portion and an IgG4-derived portion. Preferably, the IgG2-derived portion includes at least the heavy chain constant region 1 and hinge region and the IgG4-derived portion includes most of the heavy chain constant region 2 and the entire heavy chain constant region 3. Preferably the fusion proteins in accordance with this disclosure maintain the function of the non-Fc component and/or have increased half-life compared to the non-Fc component alone and/or lack unwanted antibody Fc-mediated cell activating and

inflammatory properties including events resulting from Fc–receptor antibody engagement and complement activation.

Recombinant DNA molecules encoding such fusion proteins are also provided. Upon heterologous expression in transfected mammalian cells, the fusion proteins are potently secreted in stable form, and display desired properties characteristic of the antibody and non-Fc component predecessor molecules. These fusion proteins can be used in applications conventionally associated with monoclonal antibodies, including flow cytometry, immunohisto-chemistry, cell-based assays and immunoprecipitation.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 A, B, and C schematically shows examples of a chimeric (FIG. 1A), humanized (FIG. 1B) or fully human (FIG. 1C) recombinant antibody, respectively, having an engineered heavy chain constant region in accordance with this disclosure.

Figure 2 shows the amino acid sequence (SEQ ID NO: 1) of an engineered heavy chain constant region in accordance with this disclosure and the nucleotide sequence (SEQ ID NO: 2) that encodes that engineered heavy chain constant region.

Figures 3A and 3B show the human IgG2 (GenBank Accession number V00554), and human IgG4 (GenBank Accession number K01316) amino acid and nucleic acid sequences, respectively. Figure 3C shows a schematic map of the plasmid pBR322 (GenBank Accession number J01749)..

Figure 4A shows a graphic map of the vector APEX-1 3F4V_HHuGamma4. Figure 4B shows the complete nucleotide sequence of the vector (SEQ ID NO: 3) and indicates the amino acid (SEQ ID NO: 4) and nucleotide sequences of the hIgG4 insert adjacent

to an irrelevant VH region (labeled 3F4VH). The locations of the signal sequence, CH1, hinge, CH2 and CH3 regions are indicated.

Figure 5A shows a graphic map of the vector APEX-1 3F4V_HHuG2/G4. Figure 5B shows the nucleotide sequence of the vector (SEQ ID NO: 5) and the amino acid (SEQ ID NO: 6) and nucleic acid sequence of the G2/G4 insert, and indicates the locations of the signal sequence, irrelevant Vh (herein labeled 3F4Vh), CH1, hinge, CH2 and CH3 regions.

Figure 6 shows the complete nucleotide and amino acid sequence of the OKT3 heavy chain variable region (GenBank Accession number A22261).

Figure 7 shows the complete nucleotide and amino acid sequence of the OKT3 light chain variable region (GenBank Accession number A22259).

Figure 8 shows the complete nucleotide (SEQ ID NO: 7) and amino acid (SEQ ID NO:8) sequences of the murine OKT3 heavy chain variable region, constructed using Expression Strategy #1, and including the murine immunoglobulin promoter, a murine signal sequence with intron at the 5' ends, and a splice donor site (Bam HI) at the 3' ends. Restriction enzyme sites are indicated.

Figure 9 shows the complete nucleotide (SEQ ID NO: 9) and amino acid (SEQ ID NO:10) sequences of the murine OKT3 light chain variable region, constructed using Expression Strategy #1, and including the murine immunoglobulin promoter, a murine signal sequence with intron at the 5' ends, and a splice donor site (Bam HI) at the 3' ends. Restriction enzyme sites are indicated.

Figure 10 shows the complete nucleotide sequence (SEQ ID NO: 11).of the HuG2/G4 fragment excised from the APEX-1 3F4V_HHuG2/G4 vector and modified for

insertion into a PUC 19 cloning vector by the addition, at the 5' end, of a Bam HI site and 5' untranslated inron sequences from native human IgG4 and, at the 3' end, of a Bgl II site and 3' untranslated sequence from natural human IgG4.

Figure 11 shows a graphic map of the heavy chain expression vector pSVgptHuG2/G4 used in Expression System #1.

Figure 12 shows a graphic map of the expression vector pSVgptHuCk used in Expression System #1.

Figures 13 A, B, and C show the nucleotide (SEQ ID NO: 12) and amino acid (SEQ ID NO: 13) sequences of the OKT3 heavy chain variable region and huG2/G4 constant region constructed using Expression Strategy #2. The construct lacks the 5' leader intron and employs the original OKT3 signal sequence (indicated). Restriction enzyme sites are also indicated.

Figures 14 A-D show the entire nucleic acid sequence of the APEX-3P G2/G4 expression vector used in Expression System #2 (SEQ ID NO: 14) , including the amino acid sequence (SEQ ID NO: 15) of the G2/G4 insert and indicated restriction sites.

Figures 15 A and B show the entire nucleic acid sequence of the expression vector APEX-3PmOKT3VhG2G4 (SEQ ID NO: 16), used in Expression System #2, including the amino acid sequence (SEQ ID NO: 17) of the OKT3 variable heavy region and G2/G4 insert. Restriction enzyme sites are indicated.

Figures 16 A -F show the entire nucleic acid sequence of PUC19 (SEQ ID NO: 18) and the amino acid sequence (SEQ ID NO: 19) of the OKT3Vk and human Ck expression cassettes used in Expression System #2. Restriction enzyme sites are indicated.

Figure 17 shows the entire nucleic acid sequence of the shuttle vector, LITMUS 28 (SEQ ID NO: 20), and the amino acid sequences of the OKT3VkhCk insert (SEQ ID NO: 21) used in Expression System #2.

Figures 18 A and B show the entire nucleic acid sequence of APEX-3 OKT3Vk+Ck (SEQ ID NO: 22) and the amino acid sequences of the OKT3Vk and Ck insert (SEQ ID NO: 23) used in Expression System #2. Restriction enzyme sites are indicated.

Figures 19 A and B show the results of tests evaluating the ability of an antibody containing the G2/G4 heavy chain constant region to bind to the FcγRI receptor on U937 cells.

Figure 20 shows the results of tests evaluating the ability of an antibody containing the G2/G4 heavy chain constant region to bind to the FcγRII receptor on K562 cells.

Figure 21 shows the results of tests designed to evaluate the ability of an antibody containing the G2/G4 heavy chain constant region to induce cytokine production in human PBL.

Figure 22 shows the results of tests designed to evaluate the ability of an antibody containing the G2/G4 heavy chain constant region to induce the upregulation of activation markers on human T cells.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

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Recombinant antibodies are described with engineered heavy chain constant regions that serve to reduce antibody-mediated cell activation and inflammation events resulting from antibody-Fc receptor interactions. The engineered heavy chain constant region includes a portion derived from one or more human antibodies of the IgG2 sub-class and a portion derived from one or more human antibodies of the IgG4 sub-class. As those skilled in the art will appreciate, an antibody heavy chain includes a variable region and a constant region. The heavy chain constant region includes the heavy chain constant region 1 (CH1), hinge region, heavy chain constant region 2 (CH2) and heavy chain constant region 3 (CH3). At least a portion of one of the CH1, hinge region, CH2 or CH3 are derived from a human IgG2 antibody in the present engineered heavy chains, with at least a portion of the balance of the engineered heavy chain being derived from a human IgG4 antibody. Preferably, the entire engineered heavy chain is derived from a combination of human IgG2 and IgG4 portions.

It should be understood that two or more, non-contiguous portions of the heavy chain constant region can be derived from an IgG2 antibody. In such circumstances, the portions can be derived from the same or from different antibodies (i.e. those with different allotypes) within the IgG2 subclass. Likewise, two or more, non-contiguous portions of the heavy chain constant region can be derived from an IgG4 antibody (note that there is only one known IgG4 allotype).

In a particularly useful embodiment shown schematically in Figure 1, the engineered heavy chain constant region includes a CH1 and hinge region derived from one or more human antibodies of the IgG2 sub-class and CH2 and CH3 regions derived primarily from an antibody of the IgG4 sub-class. The engineered antibody can be in

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the form of a mouse-human chimeric antibody (Figure 1A), a humanized antibody (Figure 1B) or a fully human antibody (Figure 1C).

It should be understood that the portion derived from an IgG2 antibody and the portion derived from an IgG4 antibody need not terminate precisely at the junction between constant regions and/or the hinge region. For instance, in the working examples presented below (see Figure 2), the portion derived from an IgG2 antibody extends beyond the hinge region by a few amino acids into the constant region 2, with the balance of the heavy chain constant region being the portion derived from an IgG4 antibody.

One example of an engineered heavy chain constant region in accordance with this disclosure has the sequence shown in Figure 2 (SEQ ID NO: 1). Figure 2 also shows the nucleotide sequence (SEQ ID NO: 2) that encodes the engineered heavy chain constant region.

The IgG2 and IgG4 portions of the heavy chain constant region are chosen to reduce cell interactions that can result in excessive cytokine release, potentially leading to cytokine release syndrome (CRS). The engineered heavy chain constant region in accordance with the present disclosure also reduces the ability of the antibody to elicit inflammatory events such as cell activation, cytokine release and complement activation.

The heavy chain variable region of the antibody is selected for its binding specificity and can be of any type, such as, for example, non-human, humanized or fully human. Where the heavy chain variable region of the antibody is non-human (such as, for example, murine) and is combined recombinantly with an engineered heavy chain

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constant region in accordance with this disclosure, the resulting recombinant antibody is referred to as a chimeric antibody (see Figure 1A). Where the heavy chain variable region of the antibody is humanized and is combined recombinantly with an engineered heavy chain constant region in accordance with this disclosure, the resulting recombinant antibody is referred to as a humanized antibody (see Figure 1B). Where the heavy chain variable region of the antibody is human and is combined recombinantly with an engineered heavy chain constant region in accordance with this disclosure, the resulting recombinant antibody is referred to as a fully human antibody (see Figure 1C). In the embodiment shown in Figure 1B, the variable region of the heavy chain is humanized and includes human framework regions and non-human (in this case murine) complementary determining regions (CDRs). It should be understood that the framework regions can be derived from one source or more than one source and that the CDRs can be derived from one source or more than one source. Methods for humanization of antibodies are known to those skilled in the art and are disclosed, for example, in U.S. Patent Nos. 6,479,284; 6,407,213; 6,350,861; 6,180,370; 6,548,640; and commonly owned, pending U.S. Patent Application Serial No. PCT/US 02/ 38450, Filed December 3, 2002. The disclosures of each of these patents and patent applications are incorporated herein in their entirety by this reference.

The light chain of the antibody can be human, non-human or humanized. In the embodiment shown in Figure 1B, the light chain is humanized and includes human framework regions, non-human (in this case murine) CDRs and a human constant region. It should be understood that the framework regions can be derived from one

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source or more than one source and that the CDRs can be derived from one source or more than one source.

The antibody containing the engineered heavy chain constant region is selected based on its ability to bind to a cell surface molecule or a soluble molecule that binds to a cell surface molecule. Thus, for example, the antibody can be selected based on its ability to bind cell surface molecules such as cytokine receptors (e.g., IL-2R, TNF-αR, IL-15R, etc.); adhesion molecules (e.g., E-selectin, P-selectin, L-selectin, VCAM, ICAM, etc.); cell differentiation or activation antigens (e.g., CD3, CD4, CD8, CD20, CD25, CD40, etc.), and others. Alternatively, the antibody can be selected based on its ability to bind a soluble molecule that binds to cell surface molecules. Such soluble molecules include, but are not limited to, cytokines and chemokines (e.g., interleukin-1 (IL-1), IL-2, IL-3, IL-5, IL-6, etc.); growth factors (e.g., EGF, PGDF, GM-CSF, HGF, IGF, etc.); molecules inducing cell differentiation (e.g., EPO, TPO, SCF, PTN, etc.), and others.

The term "antibody" as used herein includes whole antibodies and antibody fragments that include at least two of CH1, hinge region, CH2 or CH3. Whole monoclonal antibodies are preferred.

In general, the construction of the antibodies disclosed herein is achieved by using recognized manipulations utilized in genetic engineering technology. For example, techniques for isolating DNA, making and selecting vectors for expressing the DNA, purifying and analyzing nucleic acids, specific methods for making recombinant vector DNA, cleaving DNA with restriction enzymes, ligating DNA, introducing DNA including vector DNA into host cells by stable or transient means, culturing the host cells in

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selective or non-selective media to select and maintain cells that express DNA, are generally known in the field.

The monoclonal antibodies disclosed herein may be derived using the hybridoma method (Kohler et al., Nature, 256:495, 1975), or other recombinant DNA methods well known in the art. In the hybridoma method, a mouse or other appropriate host animal is immunized with a protein which elicits the production of antibodies by the lymphocytes. Alternatively, lymphocytes may be immunized in vitro. The lymphocytes produced in response to the antigen are then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). The hybridoma cells are then seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. Preferred myeloma cells are those that fuse efficiently, support stable production of antibody by the selected antibody-producing cells, and are not sensitive to a medium such as HAT medium (Sigma Chemical Company, St. Louis, Mo., Catalog No. H-0262). Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, Calif. USA, and SP-20, NS0 or X63-Ag8-653 cells available from the American Type Culture Collection, Rockville, Md. USA.

The hybridoma cells are grown in a selective culture medium (e.g., HAT) and surviving cells expanded and assayed for production of monoclonal antibodies directed against the antigen. The binding specificity of monoclonal antibodies produced by hybridoma cells may be determined by assays such as immunoprecipitation,

radioimmunoassay (RIA), flow cytometry, cell activation assays or enzyme-linked immunoabsorbent assay (ELISA).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). In addition, the hybridoma cells may be grown in vivo as ascites tumors in an animal. The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, or mammalian cells that do not otherwise produce immunoglobulin proteins, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Antibodies or antibody fragments can also be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., Nature, 348:552-554 (1990). Other publications have described the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., Bio/Technology, 10:779-783 (1992)), as well as combinatorial infection and in vivo recombination as a strategy for constructing very large phage libraries (Waterhouse et

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al., Nuc. Acids. Res., 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The antibodies described herein are then modified by combining the coding sequence for the present engineered IgG2/IgG4-derived human heavy-chain constant domains with the coding sequence for a heavy chain variable domain. Where the present recombinant antibody is based on a particular murine antibody, for example, an engineered heavy chain constant region in accordance with this disclosure can be substituted in place of the homologous murine sequences. Alternatively, a functional antibody fragment can be identified (e.g., through the panning of a human phage library, an scFv library or a Fab library) onto which the present engineered IgG2/IgG4-derived human heavy-chain constant domains can be engineered.

In another aspect, this disclosure provides recombinant expression vectors which include the synthetic, genomic or cDNA-derived nucleic acid fragments necessary to produce the engineered heavy chain constant region. The nucleotide sequence coding for any of the engineered heavy chain constant regions or antibodies containing the engineered heavy chain constant regions in accordance with this disclosure can be inserted into an appropriate vector which contains the necessary elements for the transcription and translation of the inserted protein-coding sequence. Any suitable host cell vector may be used for expression of the DNA sequences coding for the chimeric or CDR-grafted heavy and light chains. Bacterial (e.g. E.coli) and other microbial systems may be used. Eukaryotic (e.g. mammalian) host cell expression systems may also be used to obtain antibodies of the present invention. Suitable mammalian host cell

include COS cells and CHO cells (Bebbington C R (1991) Methods 2 136-145); and myeloma or hybridoma cell lines (for example NSO cells (Bebbington, et al., Bio Technology, 10: 169-175 (1992)).

The antibodies containing the engineered heavy chain constant region can also be used as separately administered compositions given in conjunction with therapeutic agents. For diagnostic purposes, the antibodies may either be labeled or unlabeled. Unlabeled antibodies can be used in combination with other labeled antibodies (second antibodies) that are reactive with the engineered antibody, such as antibodies specific for human immunoglobulin constant regions. Alternatively, the antibodies can be directly labeled. A wide variety of labels may be employed, such as radionuclides, fluors, enzymes, enzyme substrates, enzyme co-factors, enzyme inhibitors, ligands (particularly haptens), etc. Numerous types of immunoassays are available and are well known to those skilled in the art.

The present engineered antibodies can be administered to a patient in a composition comprising a pharmaceutical carrier. A pharmaceutical carrier can be any compatible, non-toxic substance suitable for delivery of the antibodies to the patient. Sterile water, alcohol, fats, waxes, and inert solids may be included in the carrier. Pharmaceutically accepted adjuvants (buffering agents, dispersing agent) may also be incorporated into the pharmaceutical composition.

The antibody compositions may be administered to a patient in a variety of ways. Preferably, the pharmaceutical compositions may be administered parenterally, e.g., subcutaneously, intramuscularly or intravenously. Thus, compositions for parental administration may include a solution of the antibody, antibody fragment or a cocktail

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thereof dissolved in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers can be used, e.g., water, buffered water, 0.4% saline, 0.3% glycine , etc. These solutions are sterile and generally free of particulate matter. These compositions may be sterilized by conventional, well known sterilization techniques. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, etc. The concentration of antibody or antibody fragment in these formulations can vary widely, e.g., from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., in accordance with the particular mode of administration selected.

Actual methods for preparing parenterally administrable compositions and adjustments necessary for administration to subjects will be known or apparent to those skilled in the art and are described in more detail in, for example, *Remington's Pharmaceutical Science*, 17th Ed., Mack Publishing Company, Easton, Pa (1985), which is incorporated herein by reference.

In another embodiment the present disclosure provides fusion proteins that include a non-Fc component fused to an Fc region that is engineered to include an IgG2-derived portion and an IgG4-derived portion. The Fc region can be an engineered constant region in accordance with any of the various embodiments described above with respect to antibodies. The Fc region can include all or any portion of a CH1, hinge, CH2 and CH3 domain, provided that the Fc region includes at least one IgG2-derived

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portion and at least one IgG4-derived portion. Preferably, the IgG2-derived portion includes at least the heavy chain constant region 1 and hinge region and the IgG4-derived portion includes most of the heavy chain constant region 2 and the entire heavy chain constant region 3. A linker may optionally be provided between the non-Fc component and the Fc region. The linker, when present, can be from 3 to 25 amino acids long. In particularly useful embodiments, the linker assists in maintaining proper folding and therefore function of the non-Fc component.

Preferably the fusion proteins in accordance with this disclosure maintain the function of the non-Fc portion of the protein and/or have increased half-life compared to the non-Fc portion alone. In addition, the fusion proteins in accordance with this disclosure preferably lack unwanted antibody Fc-mediated cell activating and inflammatory properties including events resulting from Fc–receptor antibody engagement and complement activation. Also, the fusion proteins in accordance with certain embodiments of this disclosure which include the hinge region have the ability to form disulfide bonds with other fusion protein molecules, thereby resulting in dimer formation which may increase the avidity of the non-Fc portion for the molecule to which it binds.

Fusion proteins in accordance with this disclosure may be readily secreted in stable form by mammalian cells transfected with DNA that codes for the molecule. In addition, they are amenable to rapid, efficient purification to homogeneity, for example, using protein A. Because these molecules therefore are obtainable in a commercially useful amount and form, they are advantageous substitutes for monoclonal antibodies

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in contexts such as flow cytometry, immunohistochemistry, immunoprecipitation, cell-based assays and enzyme-linked immunoadsorbant assays (ELISAs).

Any peptide or protein that exhibits a useful property is suitable for use as the non-Fc component to be combined with the present engineered antibody constant region to prepare the fusion protein. Peptide or protein activities and uses include, but are not limited to, serving as a protein agonist or antagonist, binding a receptor, binding a membrane bound surface molecule, binding a soluble protein, binding a ligand, binding an enzyme or structural protein, activating or inhibiting a receptor, targeted drug delivery, or any enzymatic activity. Those peptides or proteins whose utility can be increased from the enhanced stability and half-life conferred upon them when presented in combination with an Fc domain are usually selected. It should be understood that "biological activity" as used herein includes any activity associated with a molecule having activity in a biological system, including, but not limited to, the stimulatory or inhibitory activity triggered by protein-protein interactions as well as the kinetics surrounding such interactions including the stability of a protein-protein complex. Thus, non-limiting examples of molecules suitable for use as the non-Fc component include cytokines, hormones, enzymes, ligands, growth factors, receptors and antibody fragments.

Suitable non-Fc components suitable for use in preparing the present fusion proteins include: peptides that bind to receptors which are activated by ligand-induced homo-dimerization including active fragments displaying G-CSF activity, GHR activity and prolactin activity as described in Whitty and Borysenko, *Chem Biol.*, (1999) Apr 6(4):R107-18; other examples of suitable peptides include a nerve growth factor

mimetic from the CD loop as described in Zaccaro et al., *Med. Chem.* (2000) 43(19): 3530-40; an IL-2 mimetic as described in Eckenberg, et al., *J. Immunol.* (2000) 165(8):4312-8; glucogon-like peptide-1 as described in Evans et al., *Drugs R.D.* (1999) 2(2): 75-94; tetrapeptide I (D-lysine-L-asparaginyl-L-prolyl-L-tyrosine) which stimulates mitogen activated B cell proliferation as described in Gagnon et al., *Vaccine* (2000) 18(18):1886-92; the binding domain of human cytotoxic T-lymphocyte-associated antigen 4. Peptides which exhibit receptor antagonistic activity are also contemplated. For example, N-terminal peptide of vMIP-II as an antagonist of CXCR4 for HIV therapy as described in Luo et al., *Biochemistry* (2000) 39(44):13545-50; antagonist peptide ligand (AFLARAA) of the thrombin receptor for antithrombotic therapy as described in Pakala et al., *Thromb. Res.* (2000) 100(1): 89-96; peptide CGRP receptor antagonist CGRP (8-37) for attenuating tolerance to narcotics as described in Powell et al., *Br. J. Pharmacol.* (2000) 131(5): 875-84; parathyroid hormone (PTH)-1 receptor antagonist known as tuberoinfundibular peptide (7-39) as described in Hoare et al., *J. Pharmacol. Exp. Ther.* (2000) 295(2):761-70; opioid growth factor as described in Zagon et al., *Int. J. Oncol.* (2000) 17(5): 1053-61; high affinity type I interleukin 1 receptor antagonists as disclosed in Yanofsky, et al., *Proc. Natl. Acad. Sci. USA*, Vol. 93, pp. 7381-7386, July 1996 and Vigers, et al., *J. Biol. Chem.*, Vol 275, No 47, pages 36927-36933, 2000; and acid fibroblast growth factor binding peptide as described in Fan et al., *IUBMB Life* (2000) 49 (6) 545-48. Further examples of biologically active peptides which can be fused with a Fc region in accordance with this disclosure include proteins secreted by the heart as part of the body's response to congestive heart failure, such as, for example, human brain natriuretic peptide (hBNP) as described in Mukoyama, et al., *J.*

Clin. Invest. 87(4): 1402-12 (1991) and Clemens, et al., *J. Pharmacol. Exp. Ther.* 287(1): 67-71(1998). Additional examples of biologically active peptides which can be used in accordance with this disclosure include proteins which have the potential to preserve or improve beta-cell function (e.g., by inducing glucose-dependent insulinotropic effect), such as, for example, exendin-4, GLP-1 (7-36), GPL-2 (1-34), glucagons or PACAP-38 (see, Raufman, et al., *J. Biol. Chem.* 267(30): 21432-7 (1992). It should also be understood that antibody fragments can also be employed as the non-Fc component of the fusion protein. Thus, for example, the non-Fc component can be an sc-Fv, F(ab) or $F(ab)^1_2$. As another example, the non-Fc component can be an antibody variable region into which a mimetic peptide has been inserted into or in place of one or more CDR regions as described in WO 02/46238A2, the disclosure of which is incorporated herein in its entirety by this reference.

Thus, for example, the non-Fc component used to make the fusion protein can be a growth factor. Examples of growth factors include platelet-derived growth factor (PDGF), keratinocyte growth factor (KGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), insulin, nerve growth factor (NGF), insulin-like growth factor (IGF), transforming growth factor (TGF), hepatic growth factor (HGF), fibroblast growth factor (FGF), the product of the Wnt-2 proto-oncogne (wnt-2). Aaronson, supra; Norman et al., HORMONES, pp. 719-748 (Academic Press 1987). Also, see generally, Heath (ed.), GROWTH FACTORS, IRL Press (1990).

I. PRODUCTION OF FUSION PROTEINS

A. Construction of Fusion Protein Expression Vectors

Any technique within the purview of those skilled in the art can be used to produce fusion proteins which comprise an IgG2-derived portion and an IgG4-derived portion and a non-Fc portion. Suitable techniques include, but are not limited to those methods disclosed in U.S. Patent Nos. 5,670,625; 5,726,044; and 6,403,769. In one such technique, where the fusion protein is secreted in stable form by mammalian cells, DNA sequences coding for the fusion protein are subcloned into an expression vector which is used to transfect mammalian cells. General techniques for producing fusion proteins comprising antibody sequences are described in Coligan et al. (eds.), CURRENT PROTOCOLS IN IMMUNOLOGY, at pp. 10.19.1-10.19.11 (Wiley Interscience 1992), the contents of which are hereby incorporated by reference. See also METHODS: A COMPANION TO METHODS IN ENZYMOLOGY, Volume 2 (No. 2), Academic Press (1991), and ANTIBODY ENGINEERING: A PRACTICAL GUIDE, W. H. Freeman and Company (1992), in which commentary relevant to production of fusion proteins is dispersed throughout the respective texts. The present methods are not limited to any particular method of expression. Expression thus can be achieved using eukaryotic (e.g., mammalian, insect) or prokaryotic (e.g., bacteria) cells, and the fusion proteins can be secreted by the cells or recovered from periplasm or inclusion bodies within the cells.

Thus, one of the steps in the construction of fusion proteins is to subclone portions of the fusion proteins into cloning vectors. In this context, a "cloning vector" is a DNA molecule, such as a plasmid, cosmid or bacteriophage, that can replicate autonomously in a host prokaryotic cell. Cloning vectors typically contain one or a small

number of restriction endonuclease recognition sites at which foreign DNA sequences can be inserted in a determinable fashion without loss of an essential biological function of the vector, as well as a marker gene-that is suitable for use in the identification and selection of cells transformed with the cloning vector. Marker genes typically include genes that provide tetracycline resistance or ampicillin resistance. Suitable cloning vectors are described by Sambrook et al. (eds.), MOLECULAR CLONING: A LABORATORY MANUAL, Second Edition (Cold Spring Harbor Press 1989) (hereafter "Sambrook"); by Ausubel et al. (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (Wiley Interscience 1987) (hereafter "Ausubel"); and by Brown (ed.), MOLECULAR BIOLOGY LABFAX (Academic Press 1991). Suitable cloning vectors are commercially available.

The DNA sequence encoding the Fc region of the fusion protein can be obtained using any technique within the purview of those skilled in the art. DNA sequences encoding the non-Fc portion of the fusion protein can also be synthesized using techniques within the purview of those skilled in the art, such as PCR with RNA isolated from cells that produce the non-antibody protein. The DNA can include introns or can be engineered to remove some or all introns.

DNA sequences encoding the non-Fc component of the fusion protein are subcloned in frame with the N-terminus of the Fc region portion of the fusion protein Subcloning is performed in accordance with techniques within the purview of those skilled in the art, such as the use of restriction enzyme digestion to provide appropriate termini, the use of alkaline phosphatase treatment to avoid undesirable joining of DNA molecules, and ligation with appropriate ligases. Techniques for such manipulation are

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described by Sambrook and Ausubel, and are well-known in the art. Techniques for amplification of cloned DNA in bacterial hosts and isolation of cloned DNA from bacterial hosts also are well-known.

It should, of course be understood that the Fc region can be cloned onto the amino terminus of the non-Fc component, if desired.

The cloned fusion protein is cleaved from the cloning vector and inserted into an expression vector. Suitable expression vectors typically contain (1) prokaryotic DNA elements coding for a bacterial replication origin and an antibiotic resistance marker to provide for the growth and selection of the expression vector in a bacterial host; (2) eukaryotic DNA elements that control initiation of transcription, such as a promoter; and (3) DNA elements that control the processing of transcripts, such as a transcription termination/polyadenylation sequence.

A fusion protein in accordance with this disclosure can be expressed in eukaryotic cells, such as mammalian, insect and yeast cells. Mammalian cells are especially preferred eukaryotic hosts because mammalian cells provide suitable post-translational modifications such as glycosylation. Examples of mammalian host cells include Chinese hamster ovary cells (CHO-K1; ATCC CCL61), rat pituitary cells (GH_1 ; ATCC CCL82), HeLa S3 cells (ATCC CCL2.2), rat hepatoma cells (H-4-II-E; ATCC CRL1548) SV40-transformed monkey kidney cells (COS-1; ATCC CRL 1650) and murine embryonic cells (NIH-3T3; ATCC CRL 1658).

For a mammalian host, the transcriptional and translational regulatory signals may be derived from viral sources, such as adenovirus, cytomegalovirus, bovine papilloma virus, simian virus, or the like, in which the regulatory signals are associated

with a particular gene which has a high level of expression. Suitable transcriptional and translational regulatory sequences also can be obtained from mammalian genes, such as actin, collagen, myosin, and metallothionein genes.

Transcriptional regulatory sequences include a promoter region sufficient to direct the initiation of RNA synthesis. Suitable eukaryotic promoters include the promoter of the mouse metallothionein I gene (Hamer et al., J. Molec. Appl. Genet. 1: 273 (1982)]; the TK promoter of herpes virus (McKnight, Cell 31: 355 (1982)); the SV40 early promoter (Benoist et al., Nature 290: 304 (1981)); the Rous sarcoma virus promoter (Gorman et al., Proc. Nat'l Acad. Sci. USA 79: 6777 (1982)); and the cytomegalovirus promoter (Foecking et al., Gene 45: 101 (1980)).

Alternatively, a prokaryotic promoter, such as the bacteriophage T3 RNA polymerase promoter, can be used to control fusion gene expression if the prokaryotic promoter is regulated by a eukaryotic promoter. Zhou et al., Mol. Cell. Biol. 10: 4529 (1990); Kaufman et al., Nucl. Acids Res. 19: 4485 (1991).

An expression vector can be introduced into host cells using a variety of techniques including calcium phosphate transfection, liposome-mediated transfection, electroporation, and the like. Preferably, transfected cells are selected and propagated wherein the expression vector is stably integrated in the host cell genome to produce stable transformants. Techniques for introducing vectors into eukaryotic cells and techniques for selecting stable transformants using a dominant selectable marker are described by Sambrook, by Ausubel, by Bebbington, "Expression of Antibody Genes in Nonlymphoid Mammalian Cells," in 2 METHODS: A COMPANION TO METHODS IN

ENZYMOLOGY 136 (1991), and by Murray (ed.), GENE TRANSFER AND EXPRESSION PROTOCOLS (Humana Press 1991).

Stable transformants that produce a fusion protein can be identified using a variety of methods. For example, stable transformants can be screened using an antibody that binds either to the non-antibody portion of the fusion protein or to the antibody portion of the fusion protein. The use of immunoprecipitation to identify cells is a technique well known to those skilled in the art.

After fusion protein-producing cells have been identified, the cells are cultured and fusion proteins are isolated from culture supernatants. Suitable isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography and ion exchange chromatography. Protein A is a particularly useful way to isolate fusion proteins from supernatants.

Routine assays can be performed to determine whether the non-Fc portion of the fusion protein retains it functionality.

Fusion proteins can be detectably labeled with any appropriate marker moiety, for example, a radioisotope, an enzyme, a fluorescent label, a chemiluminescent label, a bioluminescent labels or a paramagnetic label. Methods of making and detecting such detectably-labeled fusion proteins are well-known to those of ordinary skill in the art.

In vitro and in situ detection methods may be used to assist in the diagnosis or staging of a pathological condition. The present disclosure also contemplates the use of fusion proteins for in vivo diagnosis.

The fusion proteins in accordance with this disclosure can be formulated into pharmaceutically acceptable compositions and administered in the manner described above for the antibody embodiments.

The following examples are intended to illustrate but not limit the invention. While they are typical of those that might be used, other procedures known to those skilled in the art may alternatively be used.

EXAMPLE 1

Anti-CD3 Antibody With an Engineered Heavy Chain Constant Region

The variable heavy chain of OKT3 was joined through standard recombinant DNA methodology to a genomic DNA cassette containing the first heavy chain constant region (CH1), the hinge linker region, and the first few amino acids from the second heavy chain constant region(CH2) from human IgG2. Next, a cassette containing the balance of the second heavy chain constant region (CH2) and third heavy chain constant region (CH3) from human IgG4 was added. The IgG2 hinge region and following amino acids were chosen to minimize antibody binding to Fc-gamma receptors and the IgG4 regions were chosen to prevent antibody-mediated complement activation.

Preparation of Engineered Heavy Chain Constant Region

Genomic DNA encoding either the human IgG2 heavy chain constant region (GenBank accession # V00554; see Figure 3A) or the human IgG4 heavy chain constant region (GenBank accession # K01316; see Figure 3B) were provided, as inserts in the bacterial carrier plasmid pBR322 (see Figure 3C), by Dr. Ed Max of the FDA. Restriction enzyme analysis and complete DNA sequencing confirmed that the

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correct sequences of human IgG4 and IgG2 constant regions were obtained. The IgG4-derived inserts were released from the plasmid by performing restriction digests with HindIII and XhoI. The inserts were purified, excised, and subjected to further restriction analysis to confirm the published sequence of the human IgG4 genomic DNA. The genomic IgG4 insert (HindIII/SmaI restriction fragment; the SmaI site is in the 3' untranslated region approximately 30 bp 3' of the translation stop site) was then subcloned by ligation into the expression cassette APEX-1 (see Figure 4A and 4B, APEX-1 3F4V_HHuGamma4). DNA sequence analysis was performed to confirm the correct sequence of the human IgG4 desired regions.

The pBR322 plasmid containing genomic DNA encoding human IgG2 was used as the source of IgG2 CH1, hinge region and the first part of CH2, which were excised with PmlI and Bst EII and subcloned into APEX-1 3F4V_HGamma4 to replace the corresponding IgG4 derived sequences (see Figure 5A). The sequence of the resulting chimeric IgG2/IgG4 human constant region is shown in Figure 5B (APEX-1 3F4V_HHuG2/G4).

Preparation of a Chimeric Antibody based upon murine OKT3 variable regions and the human G2/G4 heavy chain constant region

The murine mAb OKT3 heavy and light chain variable sequences have been previously determined and deposited in the GenBank database (Accession numbers A22261 (Figure 6) and A22259 (Figure7), respectively). A chimeric antibody was generated with the OKT3 variable regions and the HuG2/G4 constant region using two different expression systems. The heavy and light chain variable regions were

constructed by gene synthesis using overlapping 40 mer oligonucleotides and a ligase chain reaction for insertion into PUC 19 cloning vectors. For Expression System #1, sequences including the murine immunoglobulin promoter and a murine leader sequence with the leader intron, were added at the 5' ends, and sequences including the splice donor site were added at the 3' ends by PCR to form expression cassettes for the heavy and light chain (kappa) variable regions as HindIII to BamHI fragments. The complete DNA and amino acid sequences of the constructed murine OKT3 heavy chain variable region and the murine OKT3 light chain variable region used in Expression System #1 are shown in Figures 8 and 9, respectively.

The previously described engineered heavy chain constant region was next modified for insertion into a separate PUC19 cloning vector as follows: 5' untranslated intron sequence from native human IgG4 with a 5' BamHI site was added at the 5' end, and 3' untranslated sequence from natural human IgG4 with 3' EcoRI and BglII sites was added at the 3' end. The HuG2/G4 constant region was excised as a BamHI to BglII fragment from Puc 19, inserted into the unique BamHI site of the heavy chain expression vector pSVgpt.HuG2G4 and the correct orientation selected. The complete nucleic acid sequence of the BamHI to BglII HuG2/G4 fragment is shown in Figure 10.

Similarly, the constructed murine OKT3 heavy chain variable region was excised from PUC 19 as a HindIII to BamHI fragment and transferred to the pSVgpt.HuG2G4 expression vector containing the HuG2/G4 insert. The DNA sequence was confirmed to be correct. A schematic map of the heavy chain expression vector pSVgpt.HuG2G4 is

shown in Figure 11, and indicates the position of the HuG2/G4 constant region relative to the constructed OKT3 variable heavy region contained within the vector.

The constructed murine OKT3 light chain variable region was also excised from PUC 19 as a HindIII to BamHI fragment and transferred to the expression vector pSVhygHuCκ containing the human kappa constant region (HuCk) as shown in Figure 12.

A second expression system containing a modified version of the murine OKT3 variable heavy chain region joined to the human G2/G4 constant region was also generated. This version (Expression System #2) included the original OKT3 signal sequence and did not contain the immunoglobulin promoter and intron sequences described in the previous construct. The chimeric antibody was constructed by gene synthesis and ligated into the PUC19 cloning vector containing the previously described G2/G4 constant region. The sequences of the OKT3 VH and human G2/G4 inserts (Expression System #2) are shown in Figure 13.

The G2/G4 constant region was excised from Puc19 by digestion with BamHI/BglII and gel isolated. This fragment was then ligated into the expression vector APEX-3P at the BamHI site to generate APEX3PG2/G4 (see Figure 14). The murine OKT3VH was isolated with BsiWI/BamHI digestion from the above PUC 19 vector and modified by adding a BamHI site on its 5' end with a BamHI-BsiWI adapter. The cohesive-end adaptor duplex used to generate BamHI/BsiWI had the following sequences:

Adaptor 5'------G A T C C G C G G C C G C----------3' (Seq. ID No.50)
Adaptor 3'---------- G C G C C G G C G C A T G------- 5' (Seq. ID NO: 51)

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The APEX-3PG2/G4 vector was then opened with BamHI and the modified OKT3 V_H region inserted to generate the expression vector APEX-3PmOKT3VhG2G4 (Figure 15). Similarly, an alternative OKT3 light chain cassette containing the original murine OKT3 VK signal sequence and variable kappa sequence (no intron) was ligated to a human kappa light chain constant region. This was accomplished by constructing OKT3 VK gene sequences by gene synthesis and ligating the sequence, as a HindIII-BamHI fragment, to human kappa constant region gene sequences previously inserted into the PUC19 cloning vector. The resulting plasmid sequence is shown in Figure. 16. Next, the OKT3VK sequence was excised from this vector with BsiWI/EcoRI, and the hCK was excised with BsgI/EcoRI from the same vector. To transfer the two fragments into the expression vector APEX-3P, a commercially available shuttle vector, LITMUS 28 was used (New England Biolabs, Inc., Beverly, MA). LITMUS 28 was opened with BsiWI/EcoRI digestion and ligated with the OKT3 VK fragment to generate LITMUS28mOKT3 (vector not shown), which was then opened with EcoRI/BsgI digestion and ligated to the hCK fragment above to generate LITMUS28mOKT3VKhCK (Figure 17). The construct was then digested with BglII/BamHI to isolate the entire mOKT3VKhCK fragment. The expression vector APEX-3P was opened with BamHI and ligated with the mOKT3VKhCK fragment to generate APEX-3OKT3VK+CK (Figure 18).

Evaluation of the Ability of the Chimeric Antibody Containing a Human G2/G4 Constant Region to Bind to the Human Receptor for IgG (FcγRI)

Antibodies such as OKT3, directed against the CD3 epsilon component of the T cell receptor complex, can activate human T cells by cross-linking the TCR. However, cross-linking has been shown to require accessory cells, which bind the Fc portion of the antibody through high and low affinity Fc receptors. The antibody produced in accordance with this Example was tested to evaluate binding to the human high affinity receptor for IgG (FcγRI). Cells of the U937 line were incubated with the indicated concentrations of biotinylated hIgG (Sigma) for 15 minutes at 4°C, washed, incubated with streptavidin-phycoerythrin (SA-PE) for 15 minutes at 4°C, washed, and then analyzed by flow cytometry using a Becton Dickenson FACS Calibur flow cytometer. As seen in Figures 19A, the resulting binding curve indicated that a concentration of approximately 2-4ng/mL biotinylated hIgG was appropriate for further competition studies. U937 cell were incubated with 3.0ng/mL biotinylated hIgG together with the indicated concentrations of competing antibodies for 30 minutes on ice, washed, incubated with SA-PE for 15 minutes, washed, and then analyzed by flow cytometry (Figure 19B). Preparations of mOKT3, hIgG$_1$ and hIgG$_4$ efficiently blocked binding of the biotinylated hIgG to the target cells, indicating that they bound the FcγRI receptor. However, the recombinant chimeric antibody of this Example (containing an engineered IgG2/IgG4 human constant region) did not compete for binding to the FcγRI receptor on these cells, indicating that antibodies containing this modified constant region do not bind FcγRI.

Evaluation Of Binding To The Low Affinity Human Receptor For IgG (FcγRII)

The chimeric antibody containing an engineered IgG2/IgG4 human constant region produced in accordance with this Example was tested with respect to the ability to bind the human low affinity receptor for IgG (FcγRII). In order to reveal binding to low affinity Fc receptors, antibody preparations were first complexed by incubation with equimolar concentrations of fluorescein isothiocyanate (FITC) - labeled rabbit Fab'2 anti-human Fab'2 antibodies overnight at 4°C. Cells of the K562 line, which bear both allotypes of the human low affinity receptor for IgG (FcγRII), were incubated with the indicated concentrations of antibody complexes for 30 minutes on ice, washed, and analyzed for bound antibodies by flow cytometry using a Becton Dickenson FACS Calibur flow cytometer. As seen in Figure 20, human IgG_1 antibody complexes demonstrated efficient binding to the K562 cells, while $hIgG_2$ antibody complexes demonstrated much lower levels of binding. Human IgG4 and the chimeric OKT3 hG2/G4 recombinant antibody formed antibody complexes that were unable to bind the low affinity FcγRII receptors on these cells. Binding of the FITC- rabbit Fab'2 anti-human Fab'2 antibodies alone is also indicated.

Evaluation Of Ability To Induce Cytokine Production In PBL

A chimeric antibody of Example 1 directed against human CD3 and containing an engineered IgG2/IgG4 human constant region was evaluated for its ability to induce cytokine production in peripheral blood leukocytes (PBL). Freshly isolated human peripheral blood from a panel of donors was enriched for the leukocyte fraction by Ficoll-Hypaque density sedimentation. The resulting PBL were incubated with the

indicated concentrations of anti-CD3 antibodies bearing either a murine IgG2a constant region (OKT3) or a human $IgG_{G2/G4}$ constant region (OKT3 hG2/G4) (see, Figure 21). Supernatants were collected at 24 and 36 hours and evaluated for the accumulation of TNF-α (A), and IL-2 (B) by sandwich ELISA. The graphs shown in Figure 21 represent the time point at which peak levels of a given cytokine were observed (e.g. 24 hours for IL-2 and 36 hours for TNF-α). The OKT3 antibody, which binds both human FcγRI and FcγRII receptors, induced potent levels of both cytokines. However, the chimeric recombinant antibody OKT3 hG2/G4, which binds to the same CD3 epsilon epitope as OKT3 but which has lost its ability to bind Fc receptors, were unable to stimulate the production of significant levels of any of the cytokines examined.

Evaluation Of Ability To Activate Target T Cells From Human PBL

A chimeric antibody of Example 1 directed against human CD3 and containing an engineered IgG2/IgG4 human constant region was evaluated for the ability to activate target T cells from human PBL. CD25 is the receptor for interleukin-2 (IL-2) and its expression is upregulated on the surface of T cells activated through the T cell receptor complex. Similarly, CD69 is also an early T cell activation marker whose levels of expression increase upon T cell receptor engagement. Thus both markers serve as sensitive measures of T cell activation. Freshly isolated human peripheral blood from a panel of donors was enriched for the leukocyte fraction by Ficoll-Hypaque density sedimentation. The resulting PBL were incubated in the absence or presence of the indicated concentrations of anti-CD3 antibodies bearing either a murine IgG2a constant

region (OKT3) or a human $IgG_{G2/G4}$ constant region (OKT3 hG2/G4); see Figure 22). Cells were harvested at 24 hours, washed, and incubated with FITC-conjugated monoclonal antibodies specific for human CD25 and human CD69 on ice for 30 minutes. The cells were washed and analyzed for antibody binding by flow cytometry using a Becton Dickenson FACS Calibur flow cytometer. Data are shown in Figures 22A and 22B for one representative donor, with the percentage of cells expressing CD25 (A) or CD69 (B) indicated.

Generation And Expression Of
A Human L-SIGN-Fc Fusion Protein
With Human G2G4 Fc Portion

A human L-SIGN-human G2G4 fusion protein is generated by fusing two PCR fragments derived from cDNA coding for the human L-SIGN (as the non Fc component) and the Fc portion of human immunoglobulin HuG2G4. Oligonucleotides P1, cagatgtgatatcTCCAAGGTCCCCAGCTCCCTAAG (SEQ ID NO: 52), and P2, tgggctcgagTTCGTCTCTGAAGCAGGCTGCG (SEQ ID NO: 53), are used to amplify the extracellular portion of hL-SIGN from human spleen cDNA library (The regions of the primer that are complementary to the human L-SIGN are indicated with capital letters). P1 contains an upstream *EcoRV* restriction endonuclease site to fuse with a leader sequence (KLV56). In P2, a downstream *XhoI* restriction endonuclease site is used to fuse with the hG2G4 Fc region. The primers P3, agacgaactcGAGCGC AAATGTTGTGTCGAGT (SEQ ID NO: 54), and P4, cggccctggcactcaTTTACCCAGA GACAGGGAGAGGCT (SEQ ID NO: 55), are used to amplify the human G2G4 hybrid Fc region from Glu [99] of the hinge domain to the carboxyl terminus by using a plasmid

containing the human G2G4 constant region. Capital letters indicates complementary regions to the human G2G4 sequence. In P3, an upstream *XhoI* restriction endonuclease site is designed to ligate with hL-SIGN . P4 contains downstream sequences for one stop codon and *NgoMIV* restriction endonuclease site. The PCR amplified human L-SIGN and human G2G4 Fc region fragments are TA cloned into pCR2.1 vector and accurate sequence confirmed. The resulting plasmid pCR2.1hL-SIGN is digested with *EcRV/XhoI*, and the plasmid pCR2.1hG2G4 is digested with *XhoINgoMIV* . The resulting L-SIGN and hG2G4 fragments are ligated into a modified Apex3P plasmid (Alexion Pharmaceuticals, Inc.). *EcoRV/NgoMIV* contains a KLV56 leader with a Kozak sequence and ATG corresponding to the codon for the initiating methionine (5'— CGCCCTTCCACC ATGGACATGAGGGTCCCCGCTCAGCTCCTGGGGCTC CTGCTACTCTGGCTCCGAGGTGCCAGATGT—3' (SEQ ID NO: 56)).

Cell culture and protein purification

293 EBNA human embryonic kidney cells transfected with Apex3P-hL-SIGNhG2G4 are grown in DMEM (Cellgro #10-013-CV) with 10% heat inactivated FBS, 100 IU/ml penicillin, 100 □g/ml streptomycin, 2 mM glutamine with 250 ug/ml G418 Sulfate and 1 ug/ml puromycin. Cells are grown and selected at 37°C and 5% CO_2. Confluent T-175 flasks of selected cells are washed with 15 ml HBSS in order to remove serum proteins before the addition of 30 ml IS Pro serum free medium (Irvine Scientific, Santa Ana, CA, Catalog # 91103) supplemented with L-Glutamine (amount noted on bottle) and

penicillin/streptomycin to each flask. Two to three day supernatants are concentrated and purified by Protein A chromatography.

Throughout this specification, various publications and patent disclosures are referred to. The teachings and disclosures thereof, in their entireties, are hereby incorporated by reference into this application to more fully describe the state of the art to which the present invention pertains.

Although preferred and other embodiments of the invention have been described herein, further embodiments may be perceived by those skilled in the art without departing from the scope of the invention as defined by the following claims.

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We claim:

1. A method for reducing antibody-mediated cell activation or inflammation events comprising administering an antibody which binds to either a cell surface molecule or a soluble molecule that binds to a cell surface molecule, the antibody including an engineered heavy chain constant region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

2. A method as in claim 1 wherein at least the CH1 and hinge regions are derived from one or more human IgG2 antibodies and at least a portion of the CH2 and CH3 regions are derived from one or more human IgG4 antibodies.

3. A method as in claim 1 wherein the antibody binds to a human complement component.

4. A method as in claim 1 wherein the antibody binds to a cytokine receptor.

5. A method as in claim 1 wherein the antibody binds to an adhesion molecule.

6. A method as in claim 1 wherein the antibody binds to a cell differentiation antigen.

7. A method as in claim 1 wherein the antibody binds to a cell activation antigen.

8. A method as in claim 1 wherein the antibody binds to a soluble molecule that binds to cell surface molecules.

9. A method as in claim 1 wherein the antibody binds to a cytokine.

10. A method as in claim 1 wherein the antibody binds to a chemokine.

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11. A method as in claim 1 wherein the antibody binds to a growth factor.

12. A method as in claim 1 wherein the antibody binds to a molecule that induces cell differentiation.

13. A method as in claim 1 wherein the antibody binds to a molecule that induces cell activation.

14. A method as in claim 1 wherein the antibody binds to a cell surface molecule.

15. A method for preventing or reducing cytokine release comprising administering an antibody which binds to either a cell surface molecule or a soluble molecule that binds to a cell surface molecule, the antibody including an engineered heavy chain constant region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

16. A method for preventing or reducing the severity of cytokine release syndrome comprising administering an antibody which binds to either a cell surface molecule or a soluble molecule that binds to a cell surface molecule, the antibody including an engineered heavy chain constant region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

17. A fusion protein comprising a non-Fc component and an Fc region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

18. The fusion protein of claim 17 wherein the Fc region includes at least a portion of a CH_1 region.

19. The fusion protein of claim 17 wherein the Fc region does not include any portion of a CH_1 region.

20. The fusion protein of claim 17 wherein the Fc region includes at least a part of a hinge region.

21. The fusion protein of claim 17 wherein the non-Fc component comprises an antibody fragment.

22. The fusion protein of claim 17 wherein the non-Fc component is a member selected from the group consisting of single chain, scFv, f(ab) and $F(ab)'_2$.

23. The fusion protein of claim 17 wherein the non-Fc component comprises a variable region of an antibody having a mimetic peptide inserted within or in place of at least a portion of at least one CDR.

24. The fusion protein of claim 17 wherein the non-Fc component comprises a peptide.

25. The fusion protein of claim 17 wherein the non-Fc component comprises a protein or fragment thereof.

26. The fusion protein of claim 17 wherein the non-Fc component comprises a member selected from the group consisting of cytokines, hormones, enzymes, ligands, growth factors, receptors and antibody fragments.

27. The fusion protein of claim 17 wherein the non-Fc component comprises a member selected from the group consisting of peptides displaying G-CSF activity,

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peptides displaying GHR activity, peptides displaying prolactin activity, nerve growth factor mimetics, IL-2 mimetics, glucogon-like peptide-1, tetrapeptide I (D-lysine-L-asparaginyl-L-prolyl-L-tyrosine), N-terminal peptide of vMIP-II, antagonist peptide ligand (AFLARAA) of the thrombin receptor, peptide CGRP, receptor antagonist CGRP, parathyroid hormone (PTH)-1 receptor antagonist, acid fibroblast growth factor binding peptide, human brain natriuretic peptide (hBNP), exendin-4, GLP-1 (7-36), GPL-2 (1-34), glucagons, PACAP-38, platelet-derived growth factor (PDGF), keratinocyte growth factor (KGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), insulin, nerve growth factor (NGF), insulin-like growth factor (IGF), transforming growth factor (TGF), hepatic growth factor (HGF), fibroblast growth factor (FGF), the product of the Wnt-2 proto-oncogne (wnt-2) and the binding domain of human cytotoxic T-lymphocyte-associated antigen 4.

28. A method of increasing the half life of a non-Fc component by fusing the non-Fc component to an Fc region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

29. A method of increasing the avidity of a non-Fc component for a molecule to which the non-Fc component binds by fusing the non-Fc component to an Fc region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

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30. A method of forming a dimer of a non-Fc component by fusing the non-Fc component to an Fc region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

31. A method of facilitating purification of a non-Fc component by fusing the non-Fc component to an Fc region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

32. A method of reducing or eliminating Fc receptor binding and complement activation associated with a Fc fusion protein comprising fusing a non-Fc component to an Fc region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

33. A method as in claim 32 wherein the Fc receptor binding and complement activation is reduced or eliminated in vitro.

34. A method of improving expression of a non-Fc component in mammalian cells by creating a Fc fusion protein having the non-Fc component fused to an Fc region having a first portion derived from one or more human IgG2 antibodies and a second portion derived from one or more human IgG4 antibodies.

35. The fusion protein of claim 17 wherein the Fc region is attached to an amino terminus of the non-Fc component.

36. The fusion protein of claim 17 wherein the Fc region is attached to the carboxy terminus of the non-Fc component.

37. Nucleic acid encoding a fusion protein in accordance with claim 17.

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38. Nucleic acid as in claim 37 which includes introns.

39. Nucleic acid as in claim 37 which does not include introns.

40. An expression vector containing nucleic acid in accordance with claim 37.

41. A host cell transfected with an expression vector in accordance with claim 39.

42. A composition comprising a fusion protein in accordance with claim 17 and a pharmaceutically acceptable carrier.

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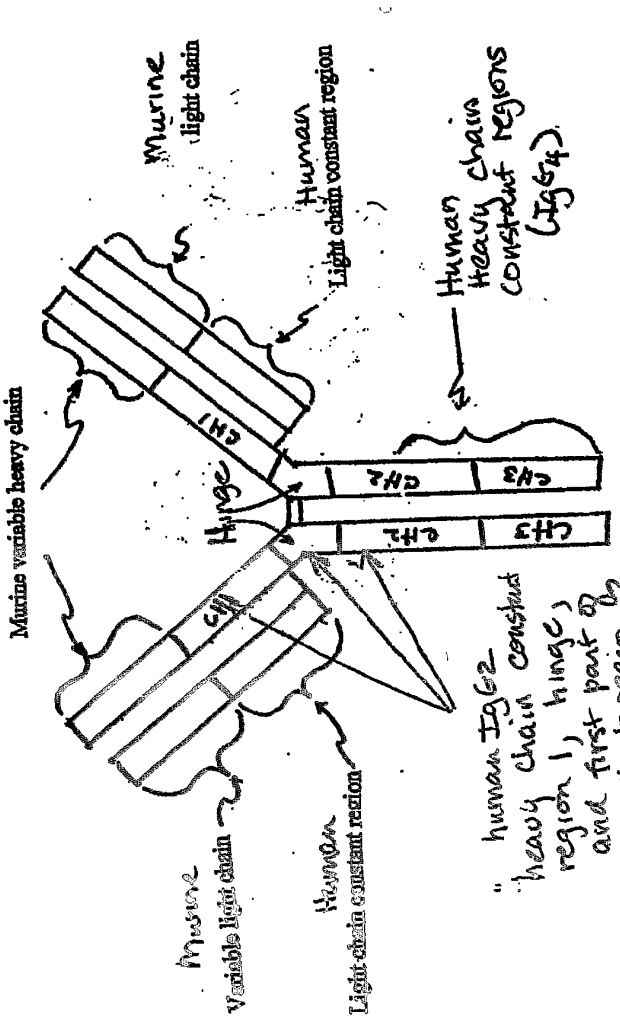

Fig. 1A Chimeric Recombinant Antibody

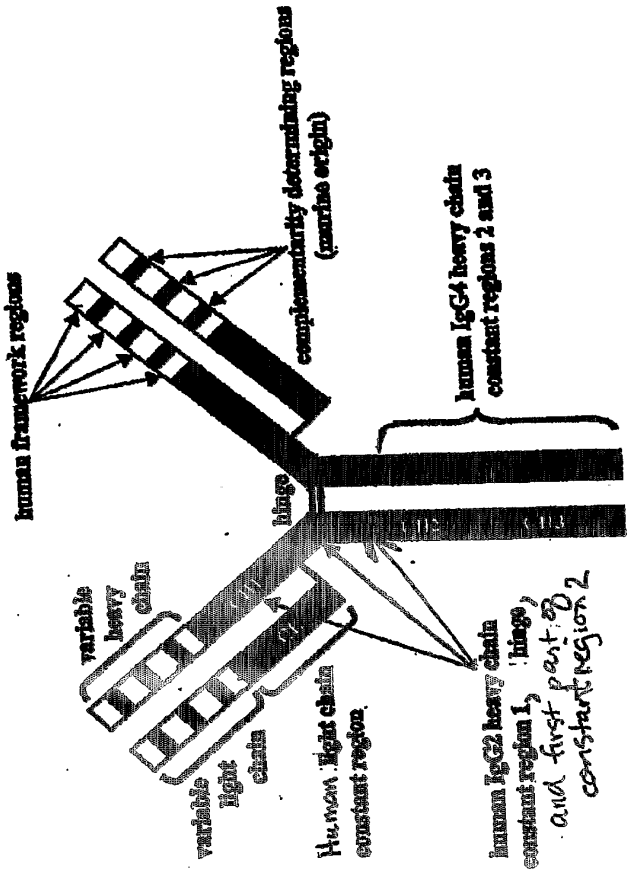

Fig. 1B Humanized Recombinant Antibody

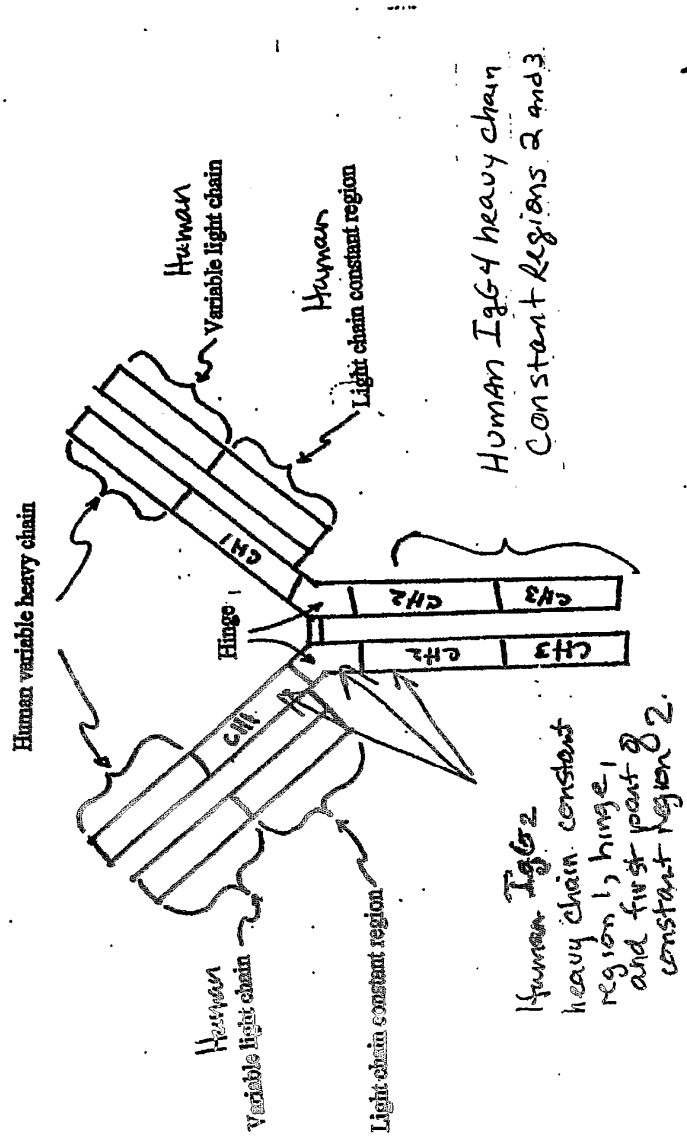

Fig. 1C - Fully Human Monoclonal Antibody

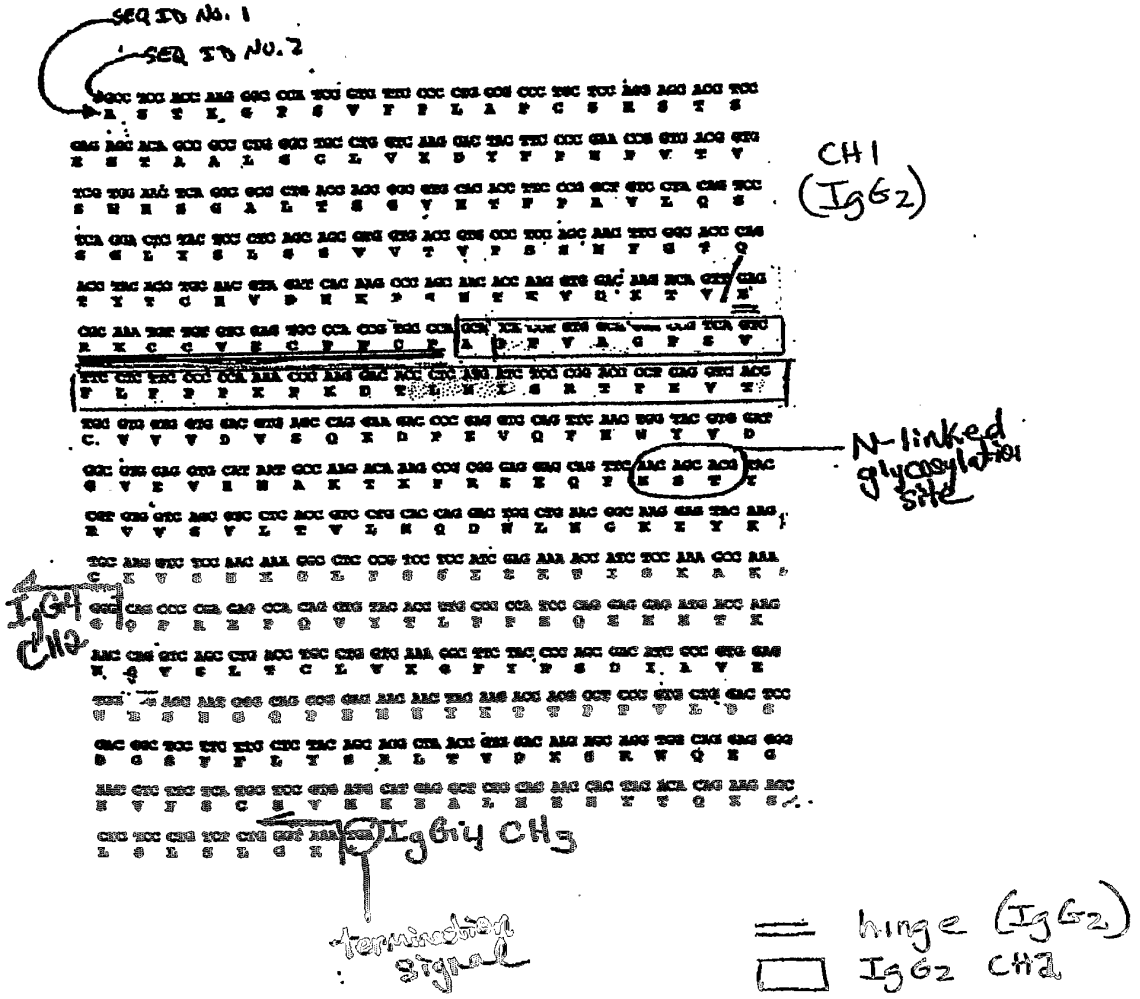
SEQ ID No. 1
SEQ ID NO. 2
CH1 (IgG2)
N-linked glycosylation site
IgG4 CH3
terminating signal
hinge (IgG2)
IgG2 CH2

Fig. 2

Figure 3A
Human IgG2 amino acid and nucleic acid sequence
GenBank Accession #V00554

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS
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TLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDW
LNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK (Seq. ID. NO. 3)

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121  ctggaccctc gtggatagac aagaaccgag gggcctctgc gcctgggccc agctctgtcc
181  cacaccgcgg tcacatggca ccacctctct tgcagcctcc accaagggcc catcggtctt
241  ccccctggcg ccctgctcca ggagcacctc cgagagcaca gccgccctgg gctgcctggt
301  caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgctc tgaccagcgg
361  cgtgcacacc ttcccagctg tcctacagtc ctcaggactc tactccctca gcagcgtggt
421  gaccgtgccc tccagcaact tcggcaccca gacctacacc tgcaacgtag atcacaagcc
481  cagcaacacc aaggtggaca agacagttgg tgagaggcca gctcagggag ggagggtgtc
541  tgctggaagc caggctcagc cctcctgcct ggacgcaccc cggctgtgca gccccagccc
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661  tgctcaggga gagggtcttc tggctttttc caccaggctc caggcaggca caggctgggt
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781  catatccggg aggaccctgc ccctgaccta agccgacccc aaaggccaaa ctgtccactc
841  cctcagctcg gacaccttct ctcctcccag atccgagtaa ctcccaatct tctctctgca
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1141 gtgcgtggtg gtggacgtga gccacgaaga ccccgaggtc cagttcaact ggtacgtgga
1201 cggcgtggag gtgcataatg ccaagacaaa gccacgggag gagcagttca acagcacgtt
1261 ccgtgtggtc agcgtcctca ccgttgtgca ccaggactgg ctgaacggca aggagtacaa
1321 gtgcaaggtc tccaacaaag gcctcccagc ccccatcgag aaaaccatct ccaaaaccaa
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1861 gcacgtaccc cgtgtacata cttcccaggc acccagcatg gaaataaagc acccagcgct
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1981 tgagtggcat gagggaggca gagtgggtc (Seq. ID. NO. 4)
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Figure 3B
Human IgG4 Amino Acid and Nucleic Acid Sequence
GenBank Accession #K01316

STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
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AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSLGK (Seq. ID. No 5)

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   1 agctttctgg ggcaggccgg gcctgacttt ggctgggggc agggaggggg ctaaggtgac
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 121 tggaccatcg cggatagaca agaaccgagg ggcctctgcg ccctgggccc agctctgtcc
 181 cacaccgcgg tcacatggca ccacctctct tgcagcttcc accaagggcc catccgtctt
 241 ccccctggcg ccctgctcca ggagcacctc cgagagcaca gccgccctgg gctgcctggt
 301 caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc tgaccagcgg
 361 cgtgcacacc ttcccggctg tcctacagtc ctcaggactc tactccctca gcagcgtggt
 421 gaccgtgccc tccagcagct tgggcacgaa gacctacacc tgcaacgtag atcacaagcc
 481 cagcaacacc aaggtggaca agagagttgg tgagaggcca gcacagggag ggagggtgtc
 541 tgctggaagc caggctcagc cctcctgcct ggacgcaccc cggctgtgca gccccagccc
 601 agggcagcaa ggcatgcccc atctgtctcc tcacccggag gcctctgacc accccactca
 661 tgctcaggga gagggtcttc tggatttttc caccaggctc ccggcaccac aggctggatg
 721 cccctacccc aggccctgcg catacagggc aggtgctgcg ctcagacctg ccaagagcca
 781 tatccgggag gaccctgccc ctgacctaag cccaccccaa aggccaaact ctccactccc
 841 tcagctcaga cacttctct cctcccagat ctgagtaact cccaatcttc tctctgcaga
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 961 cagctcaagg cgggacaggt gccctagagt agcctgcatc cagggacagg ccccagccgg
1021 gtgctgacgc atccacctcc atctcttcct cagcacctga gttcctgggg ggaccatcag
1081 tcttcctgtt ccccccaaaa cccaaggaca ctctcatgat ctcccggacc cctgaggtca
1141 cgtgcgtggt ggtggacgtg agccaggaag accccgaggt ccagttcaac tggtacgtgg
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1321 agtgcaaggt ctccaacaaa ggcctcccgt cctccatcga gaaaaccatc tccaaagcca
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1621 gagaacaact acaagaccac gcctcccgtg ctggactccg acggctcctt cttcctctac
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Figure 3C. Schematic map of the E.coli plasmid cloning vector pBR322 (GenBank Accession #J01749.

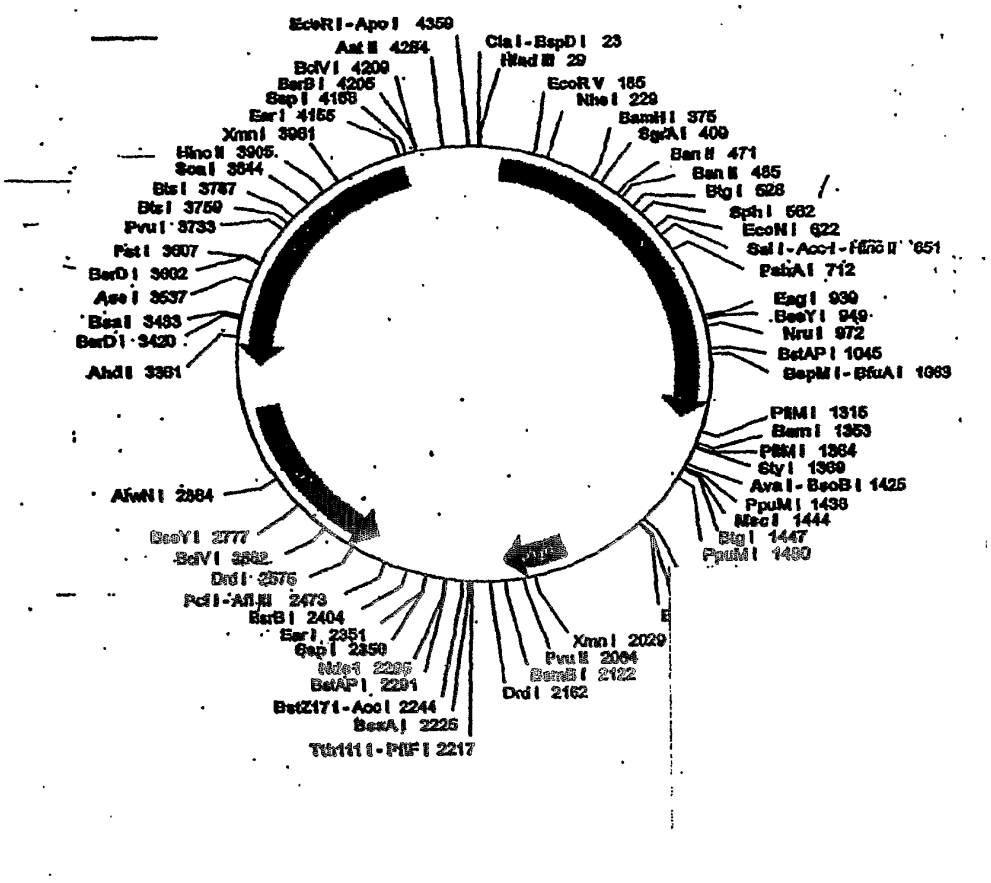

Figure 4A. Schematic map of the vector Apex-1 3F4V_HHuGamma4.

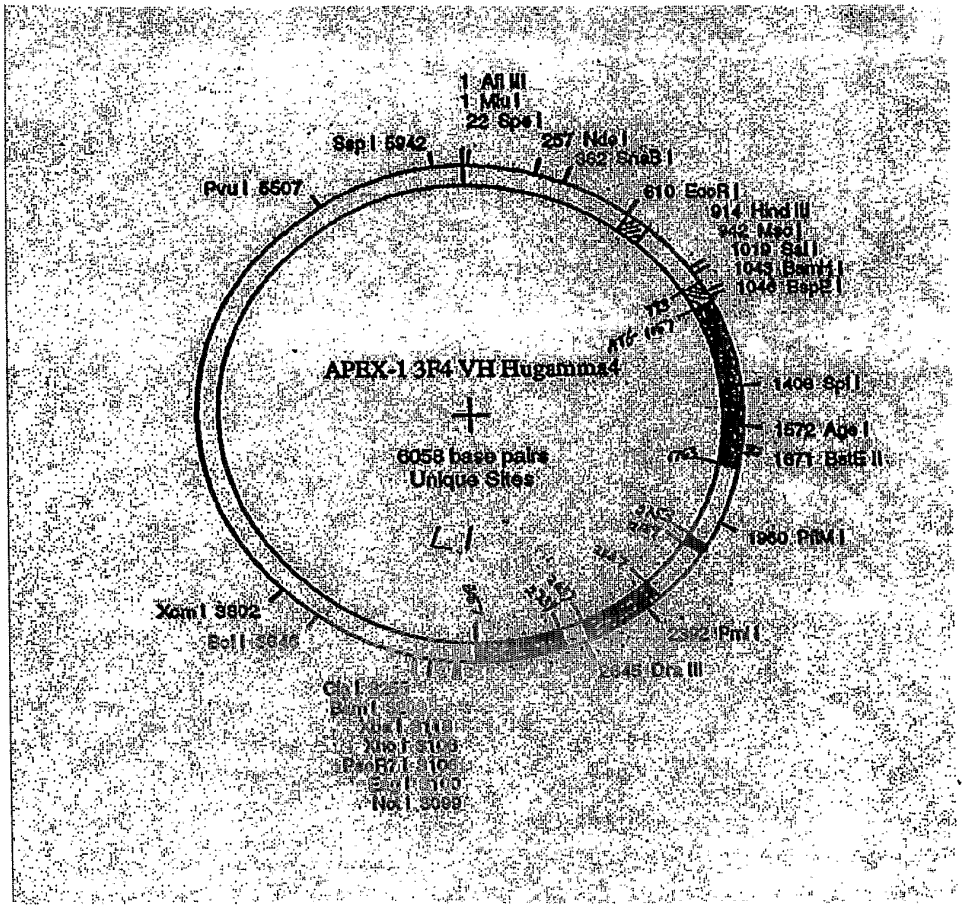

Figure 4B. Vector sequence (APEX-1 3F4V_HHuGamma4)

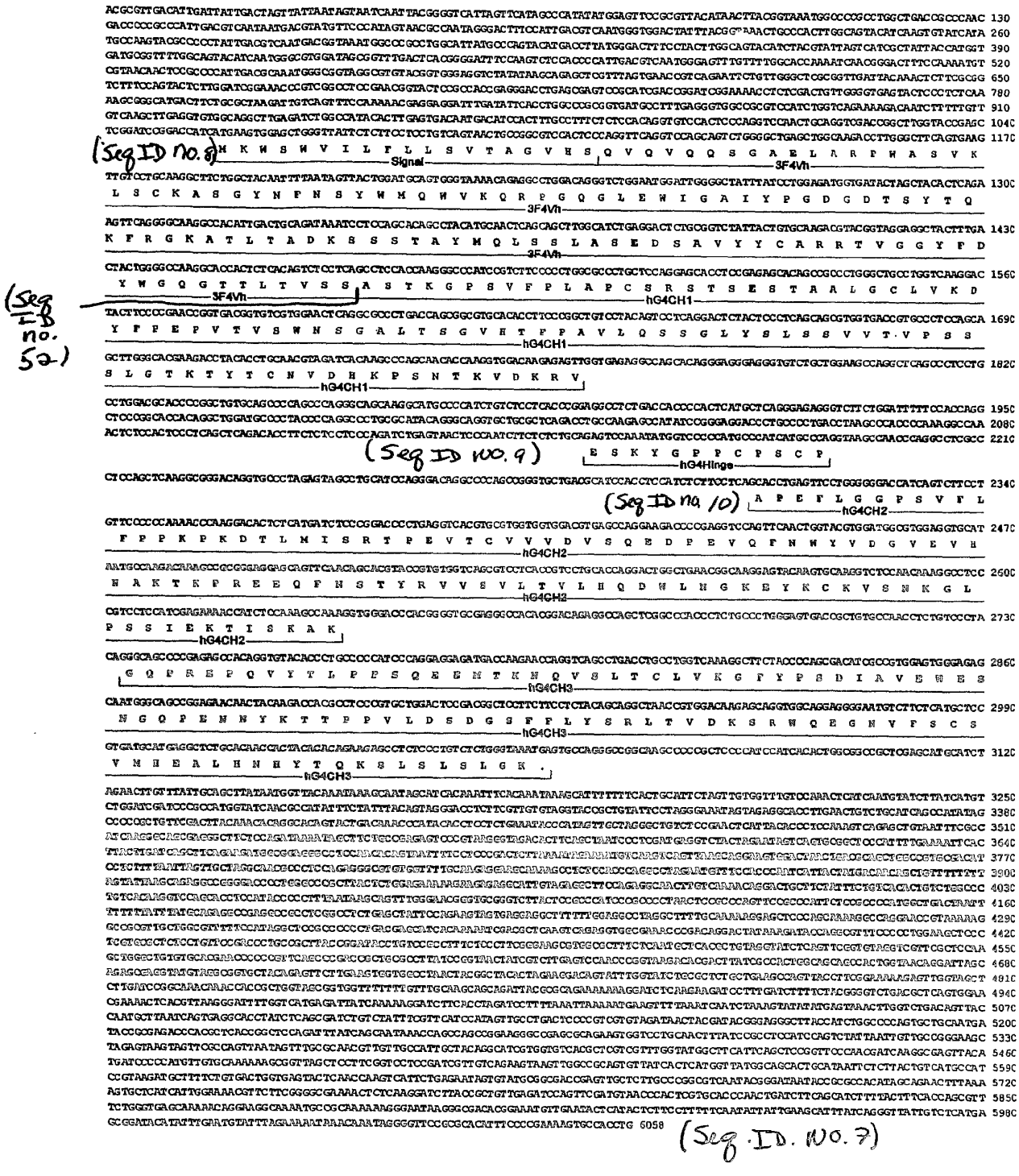

Figure 5A. Schematic map of the vector Apex-1 3F4V_HHuG2/G4.

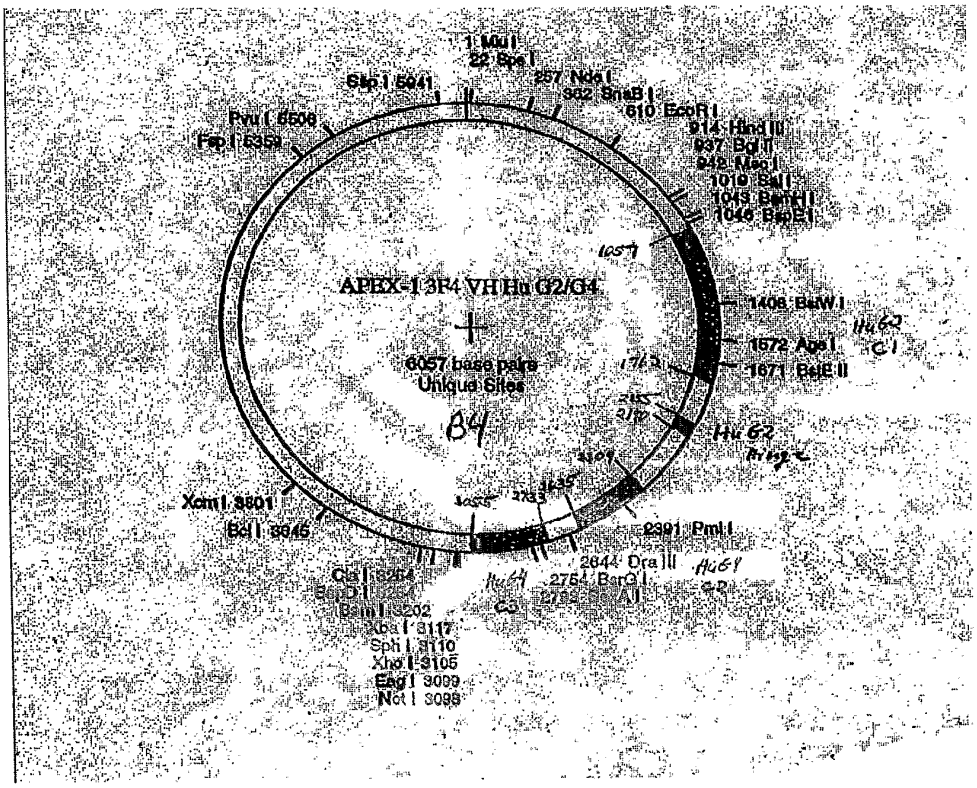

Figure 5B. Vector Sequence (APEX-13F4V$_H$HuG2/G4)

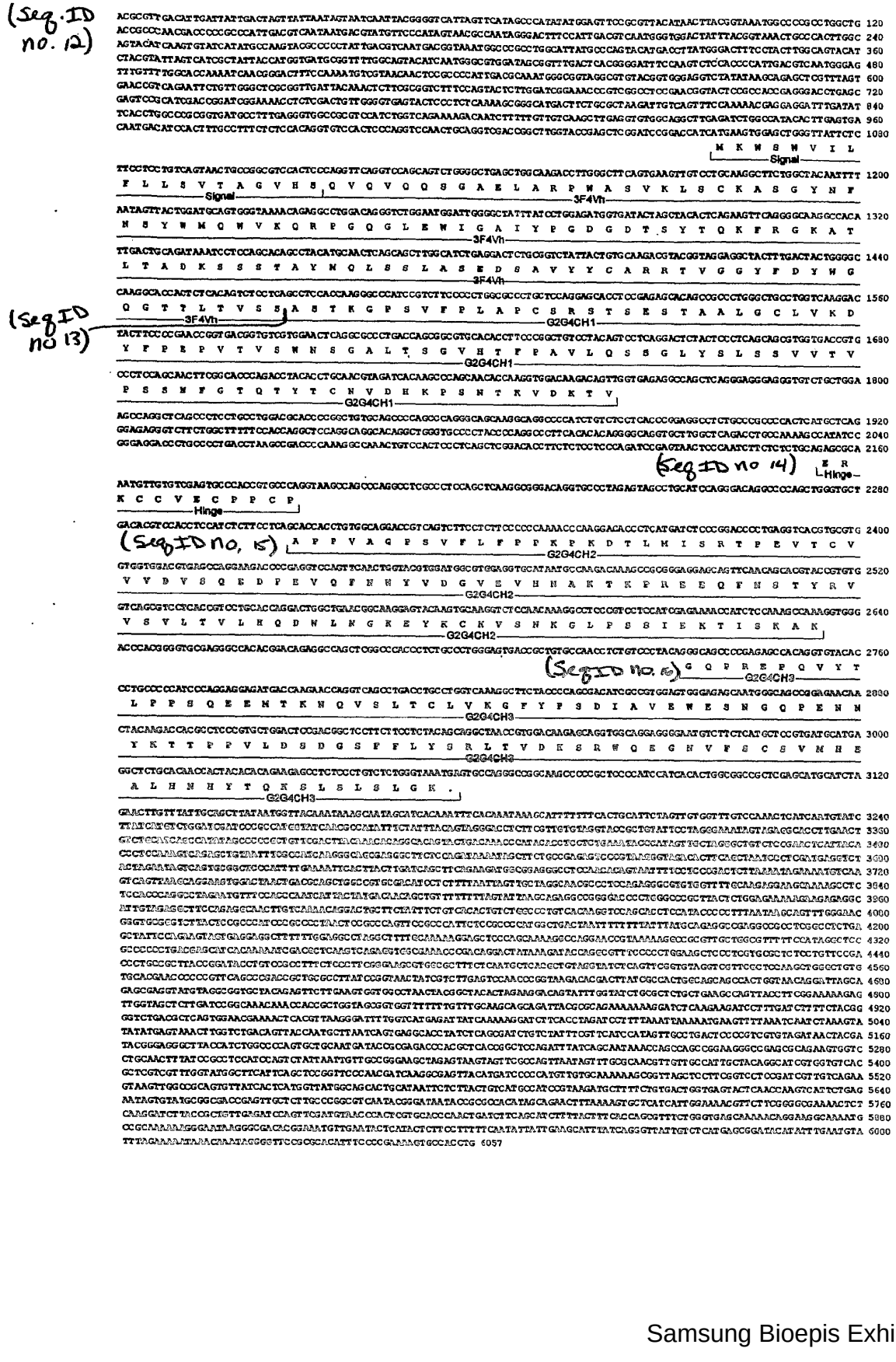

Figure 6. Amino Acid and nucleotide sequence of the murine OKT3 heavy chain variable region (Accession #A22261)

MERHWIFLLLLSVTAGVHSQVQLQQSGAELARPGASVKMSCKASYTFTRYTMHWVKQRPGQGLEWIGYINPSRGYTN
YNQKFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCARYYDDHYCLDYWGQGTTLTVSSAKTTAPSVYPLAPVCGD
TTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAHPASSTKVD
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TQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTL
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RTPGK (Seq. ID. no 17)

ORIGIN

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      121 ggctgaactg gcaagacctg gggcctcagt gaagatgtcc tgcaaggctt ctggctacac
      181 ctttactagg tacacgatgc actgggtaaa acagaggcct ggacagggtc tggaatggat
      241 tggatacatt aatcctagcc gtggttatac taattacaat cagaagttca aggacaaggc
      301 cacattgact acagacaaat cctccagcac agcctacatg caactgagca gcctgacatc
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      601 tgtgcacacc ttcccagctg tcctgcagtc tgacctctac accctcagca gctcagtgac
      661 tgtaacctcg agcacctggc ccagccagtc catcacctgc aatgtggccc acccggcaag
      721 cagcaccaag gtggacaaga aaattgagcc cagagggccc acaatcaagc cctgtcctcc
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     1021 ccccatccag caccaggact ggatgagtgg caaggagttc aaatgcaagg tcaacaacaa
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     1201 ctgcatggtc acagacttca tgcctgaaga catttacgtg gagtggacca acaacgggaa
     1261 aacagagcta aactacaaga acactgaacc agtcctggac tctgatggtt cttacttcat
     1321 gtacagcaag ctgagagtgg aaaagaagaa ctgggtggaa agaaatagct actcctgttc
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     1441 taaatgagct cagcacccac aaaactctca ggtccaaaga gacacccaca ctcatctcca
     1501 tgcttccctt gtataaataa agcacccagc aatgcctggg accatgtaaa aaaaaaaaaa
     1561 aaaggaattc (Seq. ID no. 18)
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Figure 7. Amino acid and nucleotide sequence of the murine OKT3 light chain variable region (Accession #A22259)

MDFQVQIFSFLLISASVIISRGQIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPKRWIYD
TSKLASGVPAHFRGSGSGTSYSLTISGMEAEDAATYYCQQWSSNPFTFGSGTKLEINRADTAPTVSIFPPS
SEQLTSGGASVVCFLNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSY
TCEATHKTSTSPIVKSFNRNEC (Seq ID. NO 19)

ORIGIN

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          acatccaaac
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          tactctctca
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          gatggcagtg
      541 aacgacaaaa tggcgtcctg aacagttgga ctgatcagga cagcaaagac
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          aggaatgagt
      721 gttagagaca aaggtcctga gacgccacca ccagctccca gctccatcct
          atcttccctt
      781 ctaaggtctt ggaggcttcc ccacaagcgc ttaccactgt tgcggtgctc
          taaacctcct
      841 cccacctcct tctcctcctc ctccctttcc ttggctttta tcatgctaat
          atttgcagaa
      901 aatattcaat aaagtgagtc tttgccttga aaaaaaaaaa aaa (Seq ID No. 20)
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Figure 8. Expression System #1: Nucleic Acid and amino acid sequences of murine OKT3 VH gene construct.

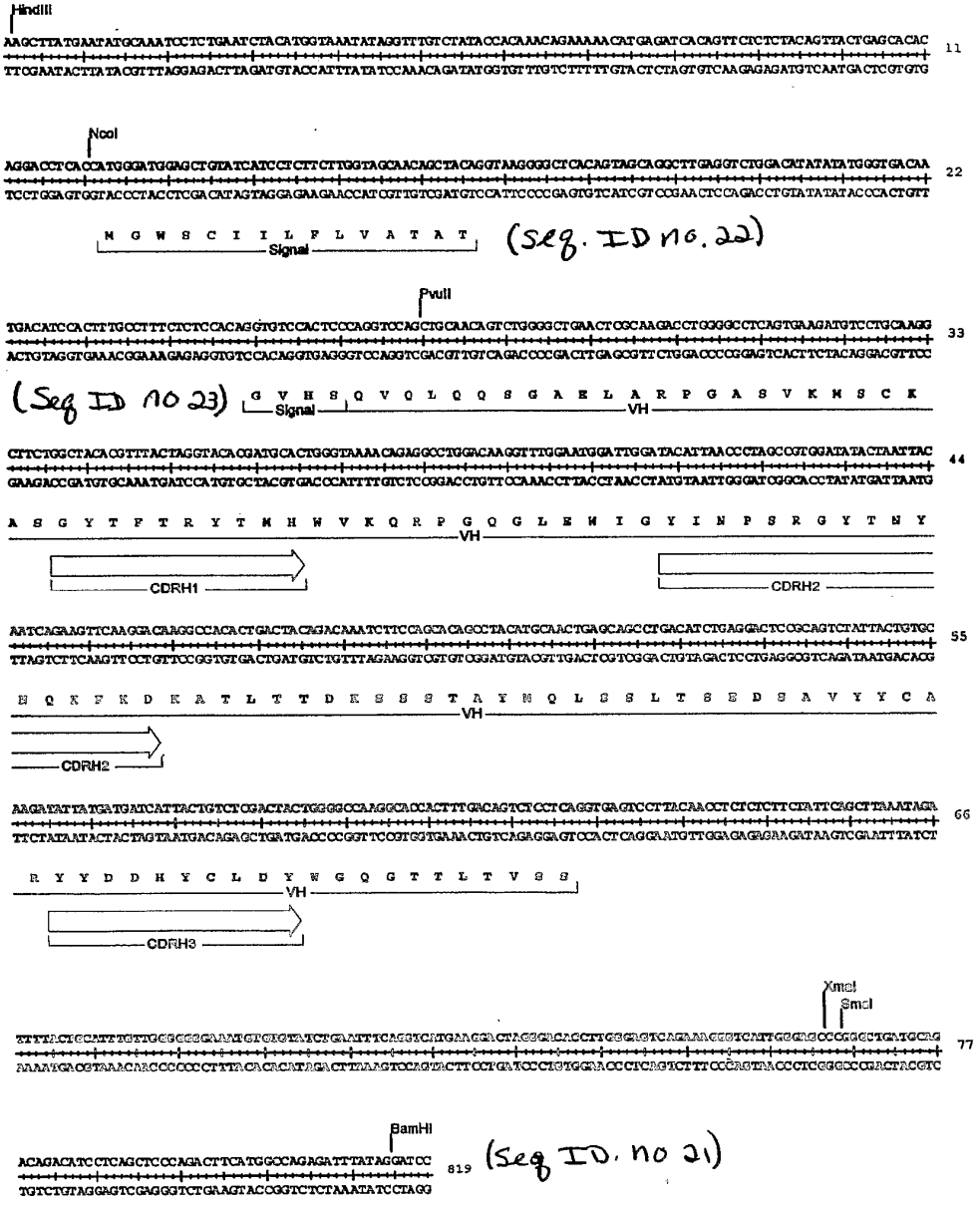


Figure 9. Expression System #1: Nucleic acid and amino acid sequences of murine OKT3 VL gene construct.

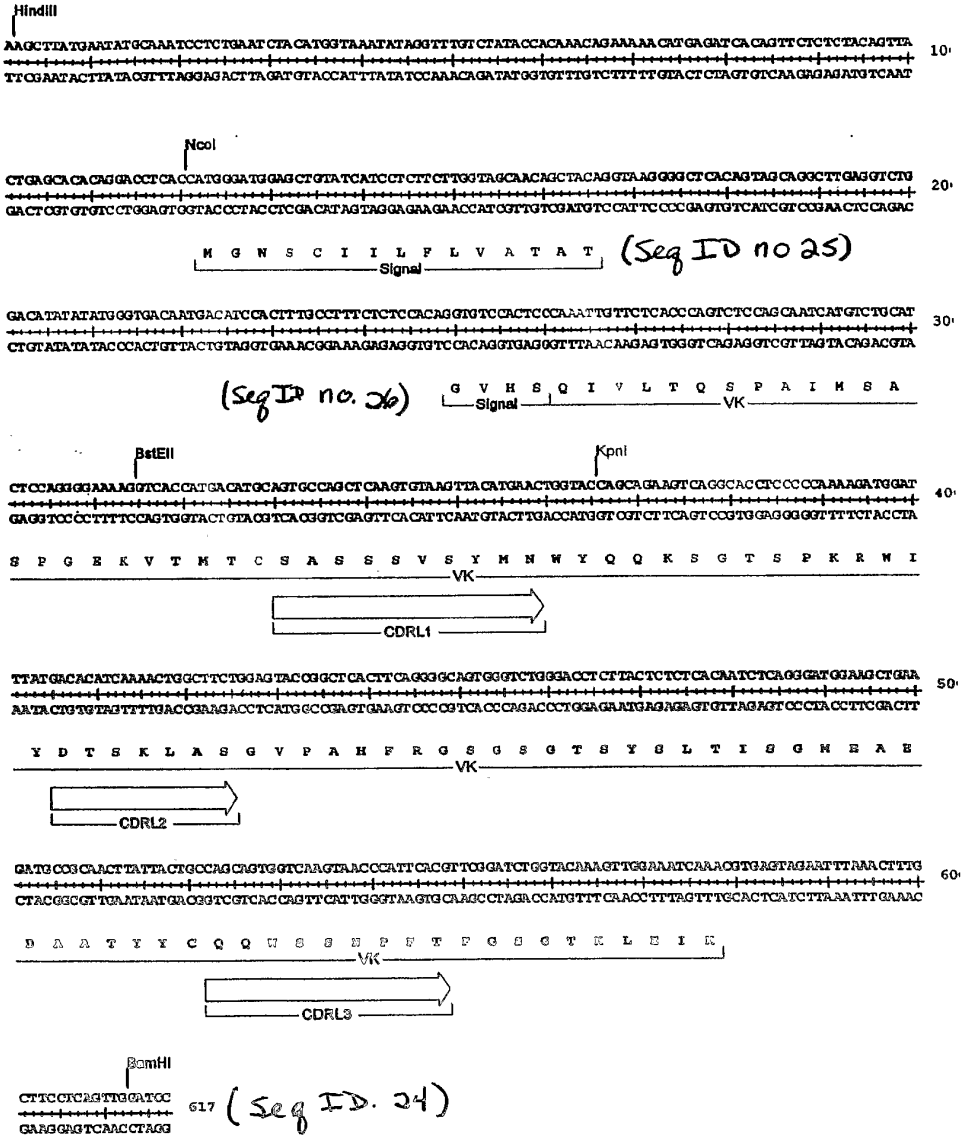


Figure 10. Complete nucleotide sequence of the BamHI-BglII restriction fragment containing the human G2/G4 constant region.

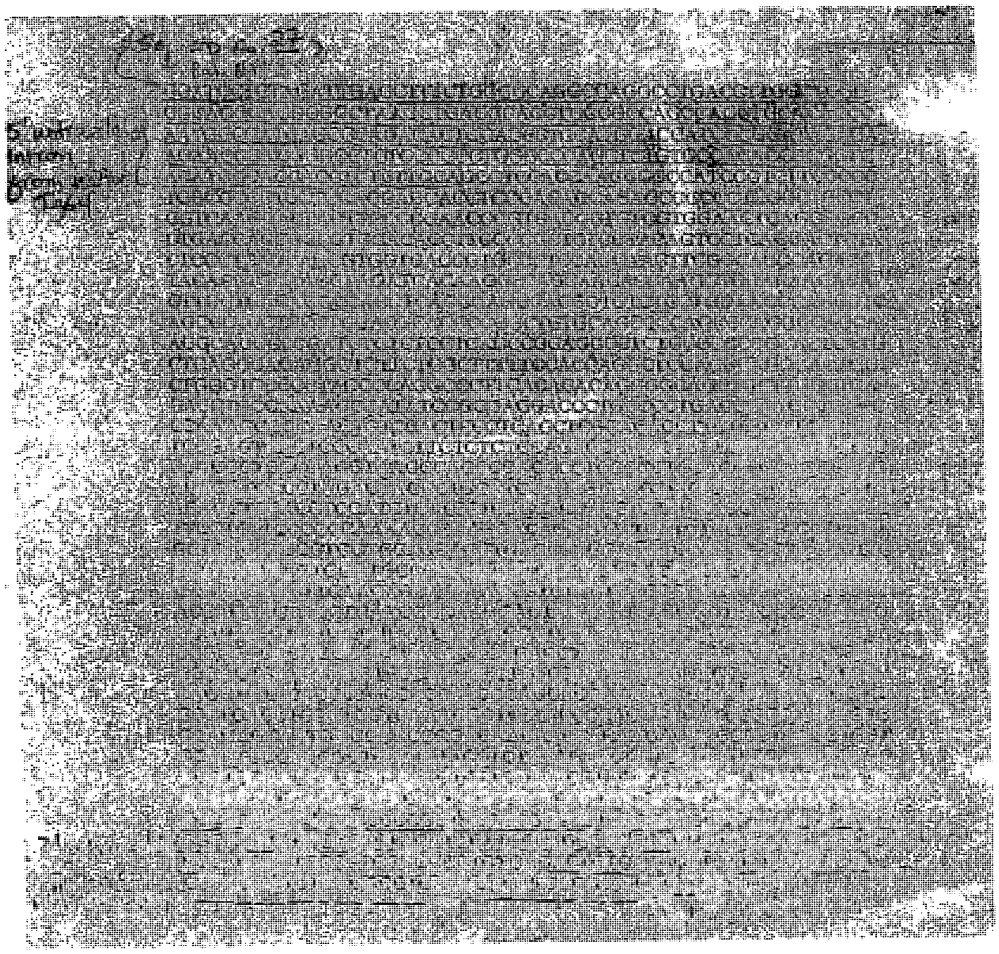


Figure 11. Map of the heavy chain expression vector pSVgptHuG2/G4 used in Expression System #1.

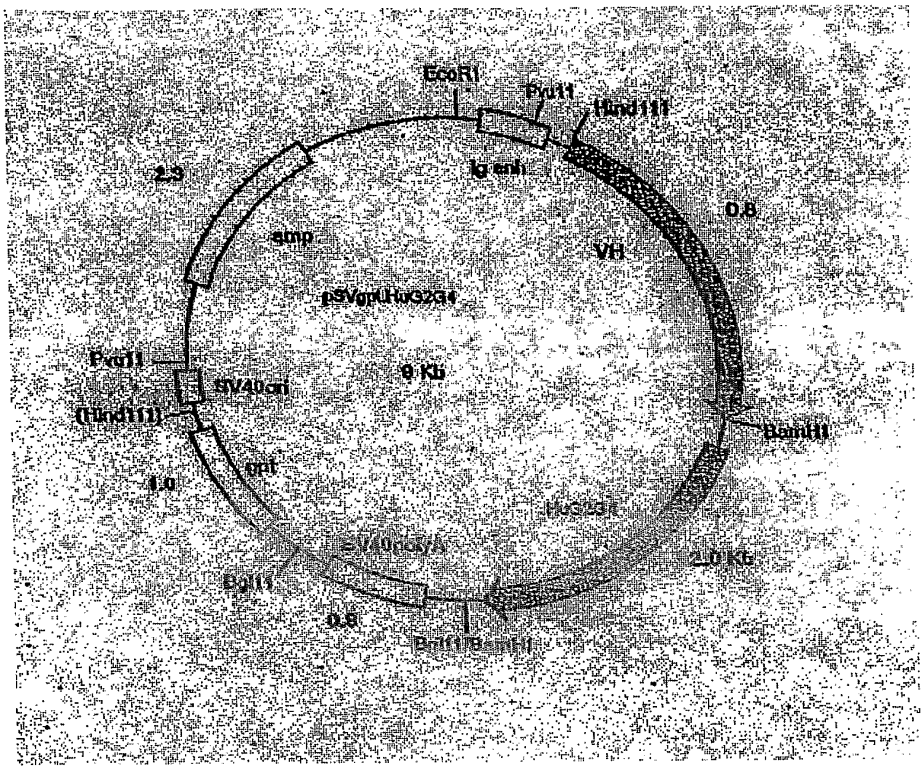


Figure 12. Map of the light chain expression vector pSVgptHuCK used in Expression System #1.

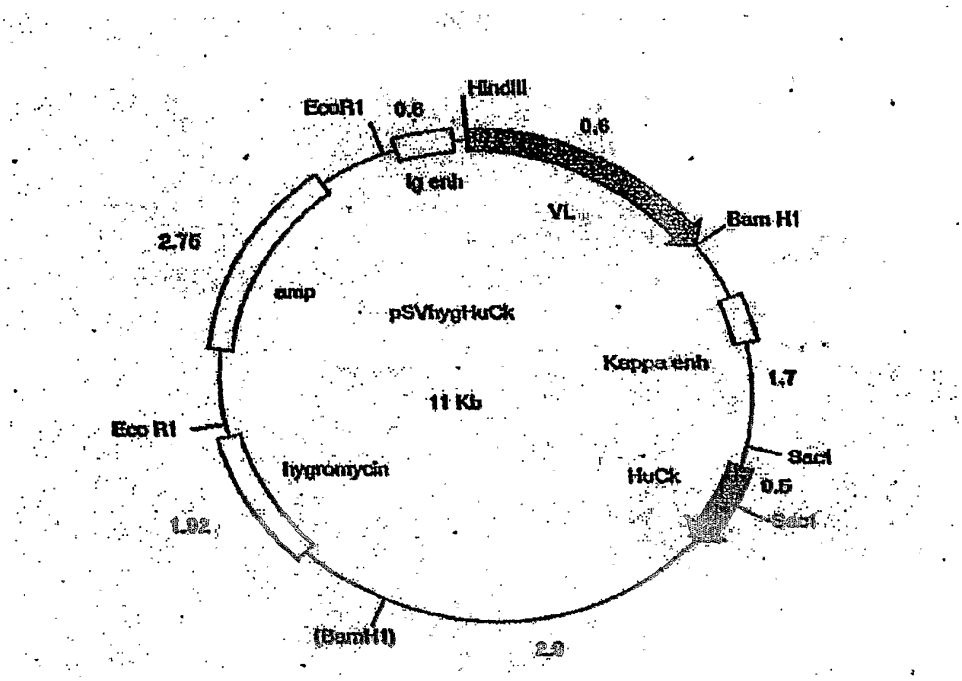


Figure 13. Nucleotide and amino acid sequences of the OKT3 VH human G2/G4 construct used in Expression System #2.

(Seq ID no. 28)

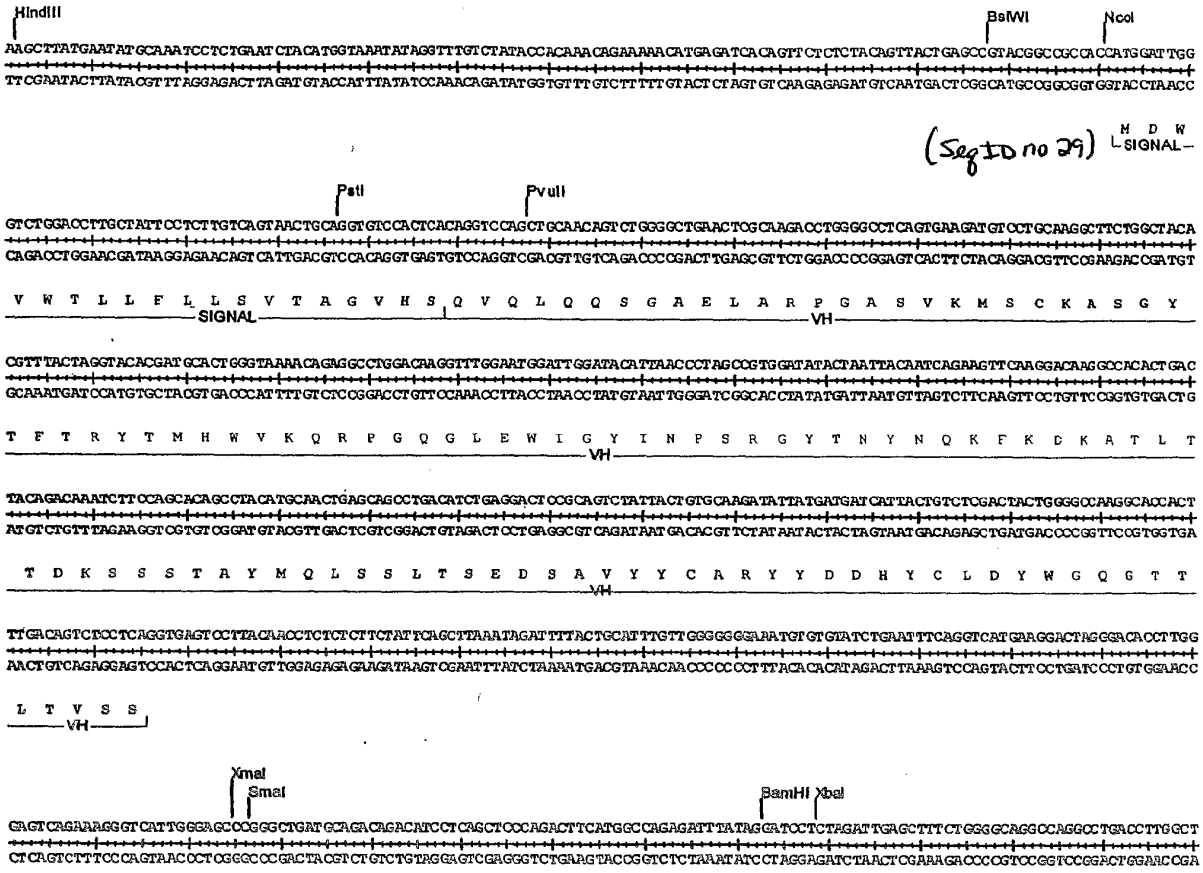


Figure 13 (con't.) B

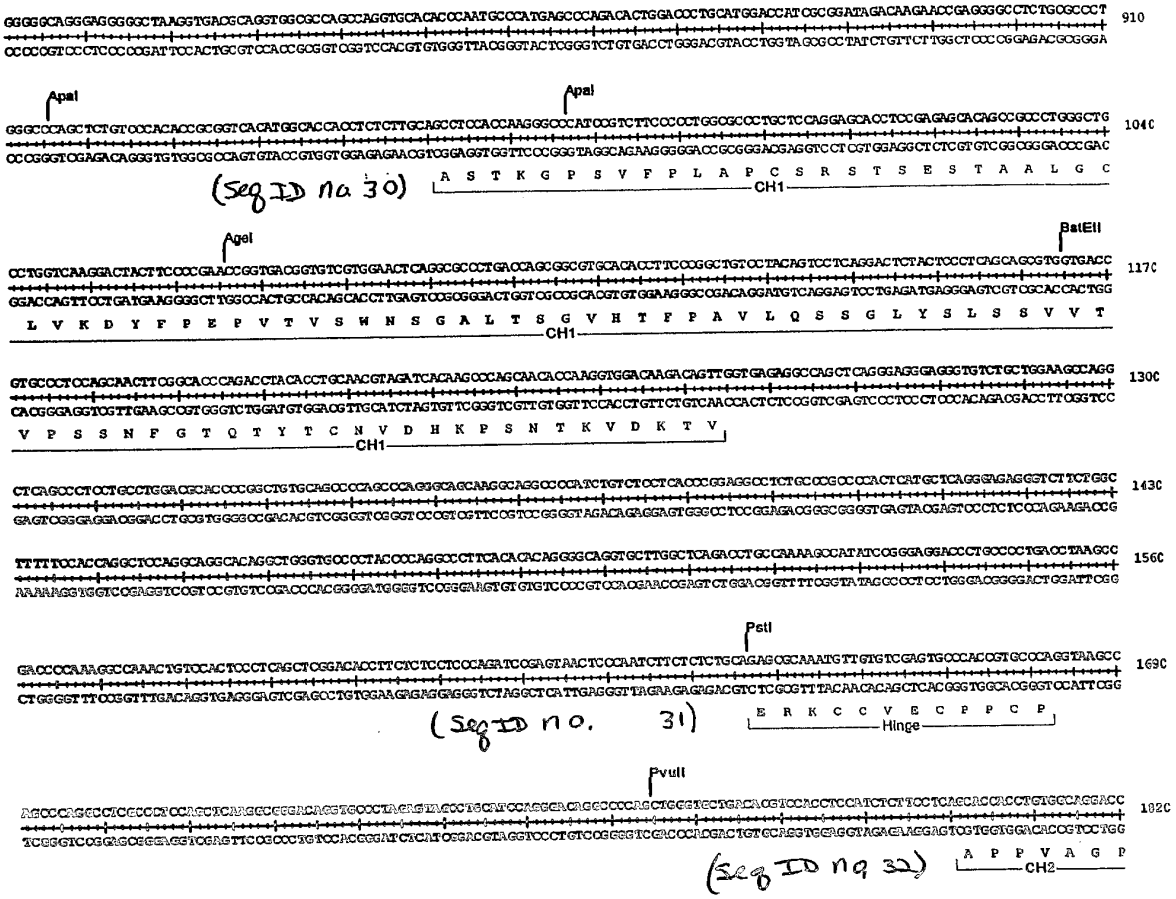


Figure 13 (con't.)C

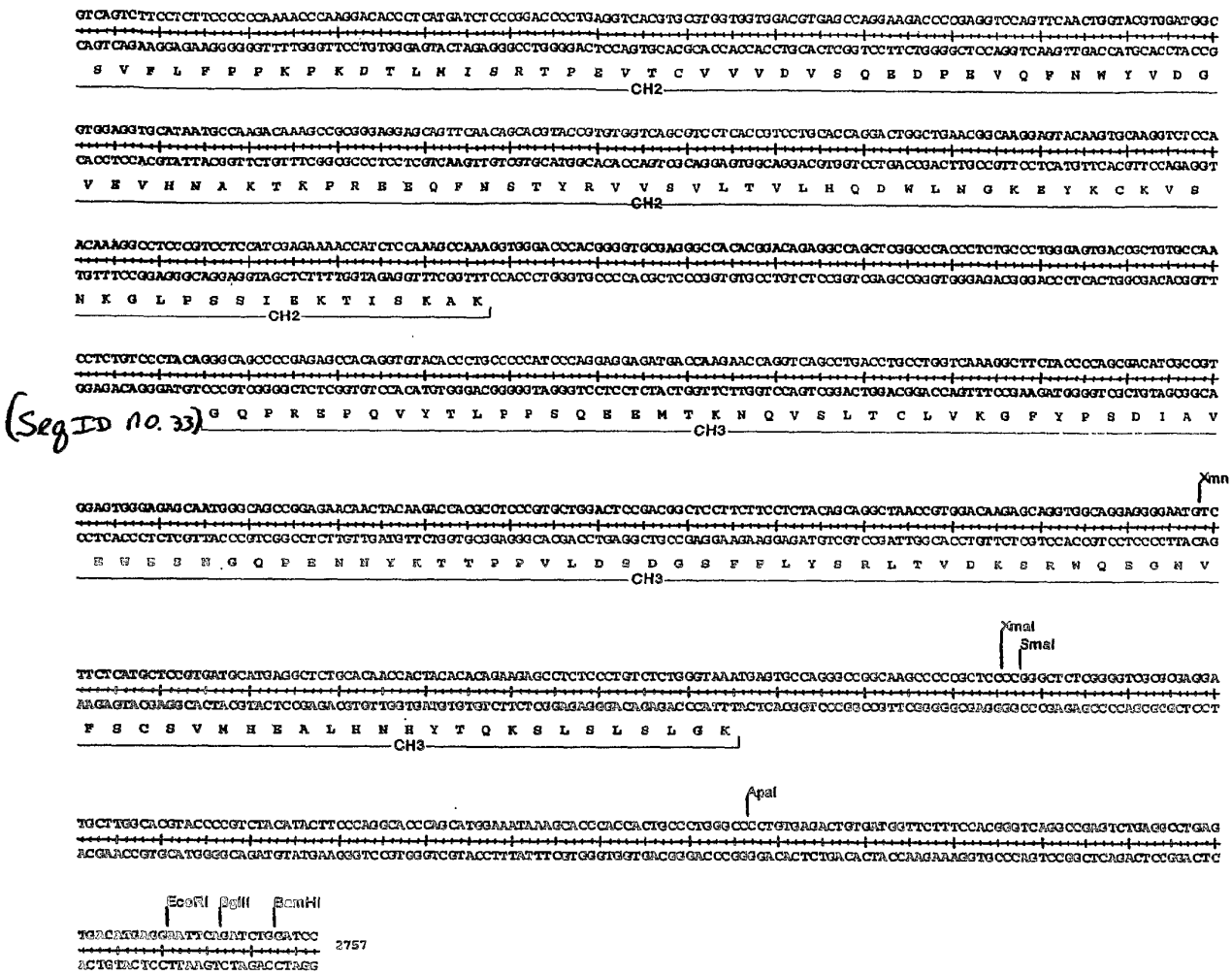


Figure 14. Nucleic acid and amino acid sequences of the APEX-3P G2/G4 expression vector used in Expression System #2

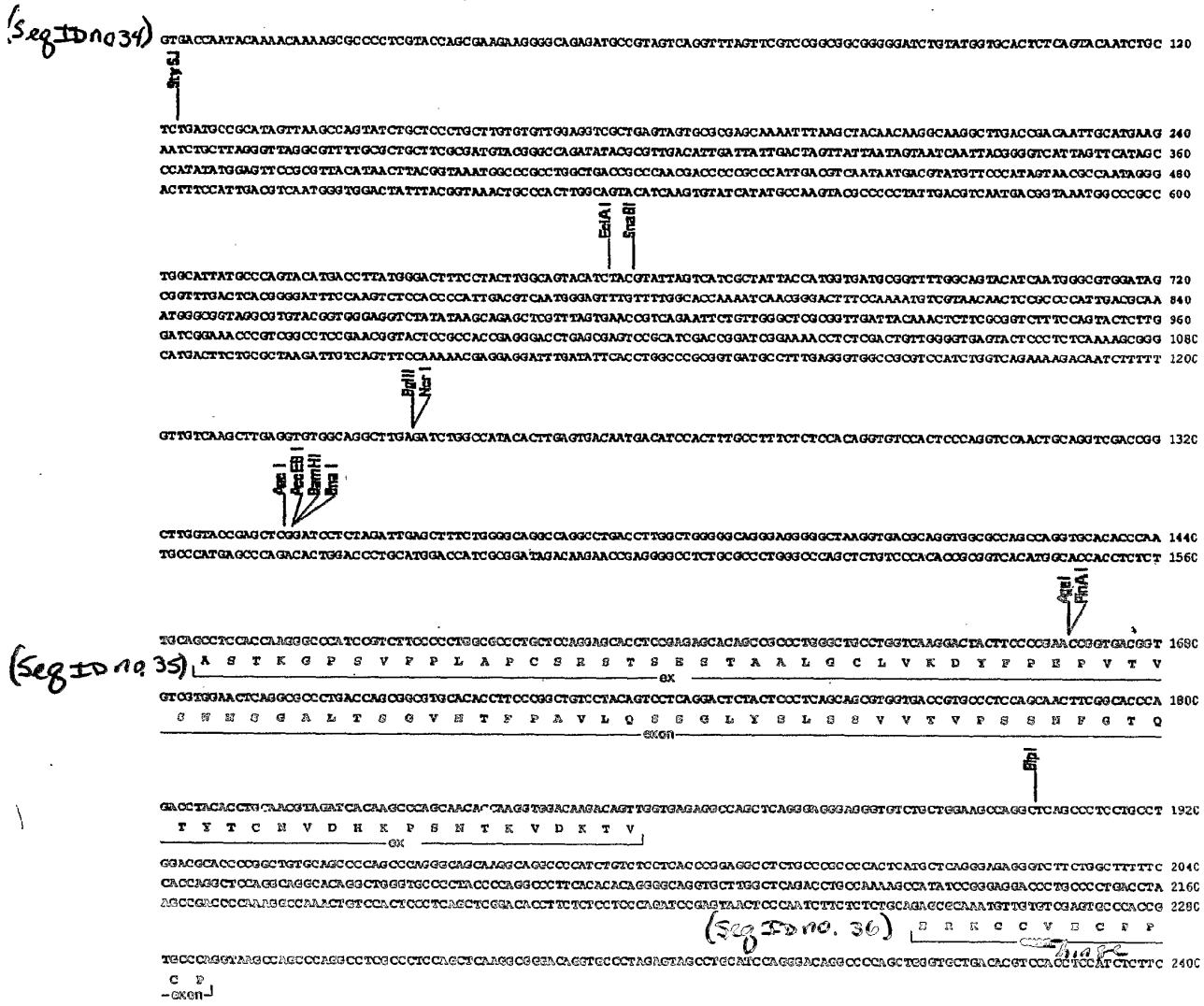


Figure 14 B (con't.)

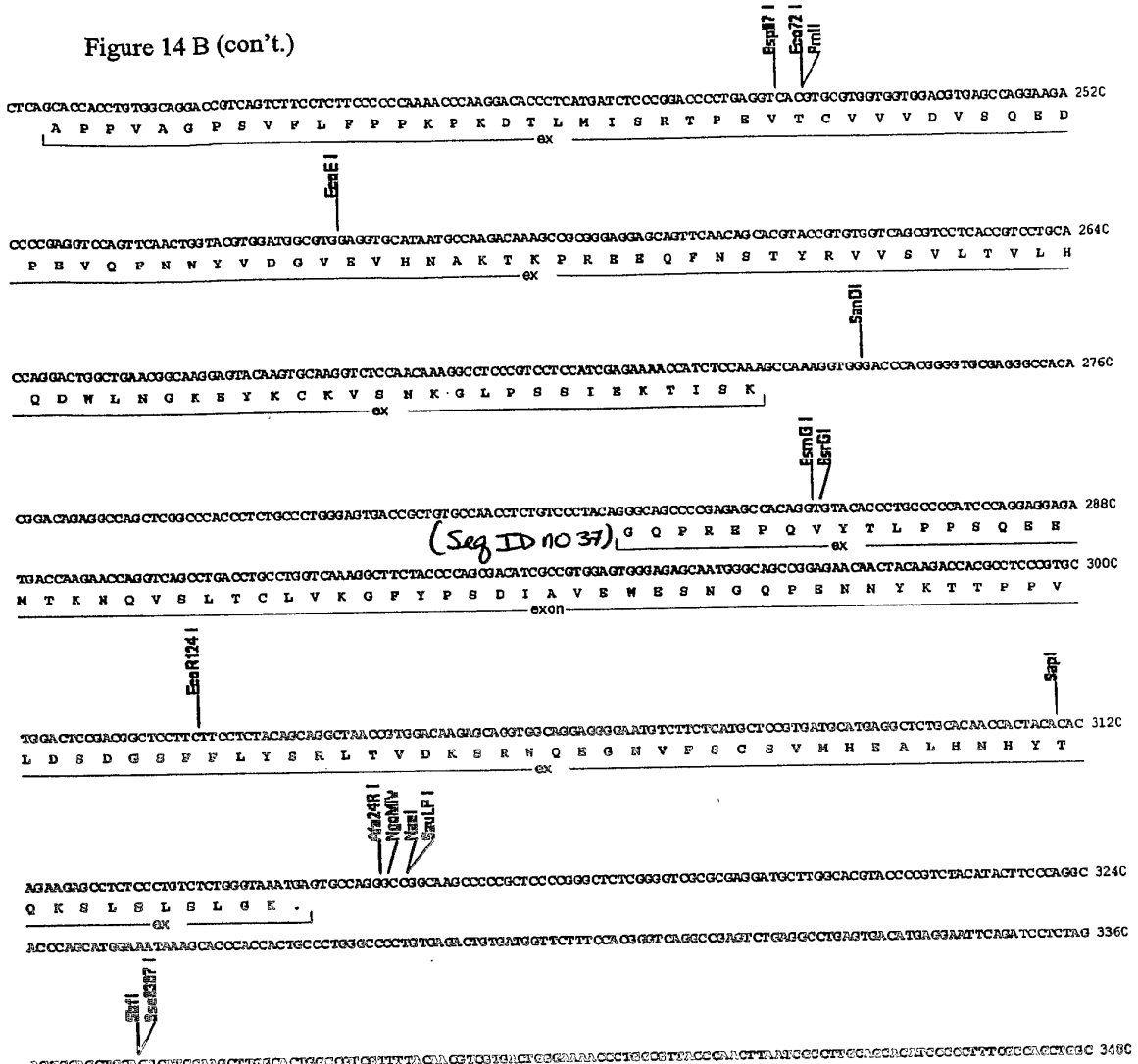


Figure 14 C (con't.)

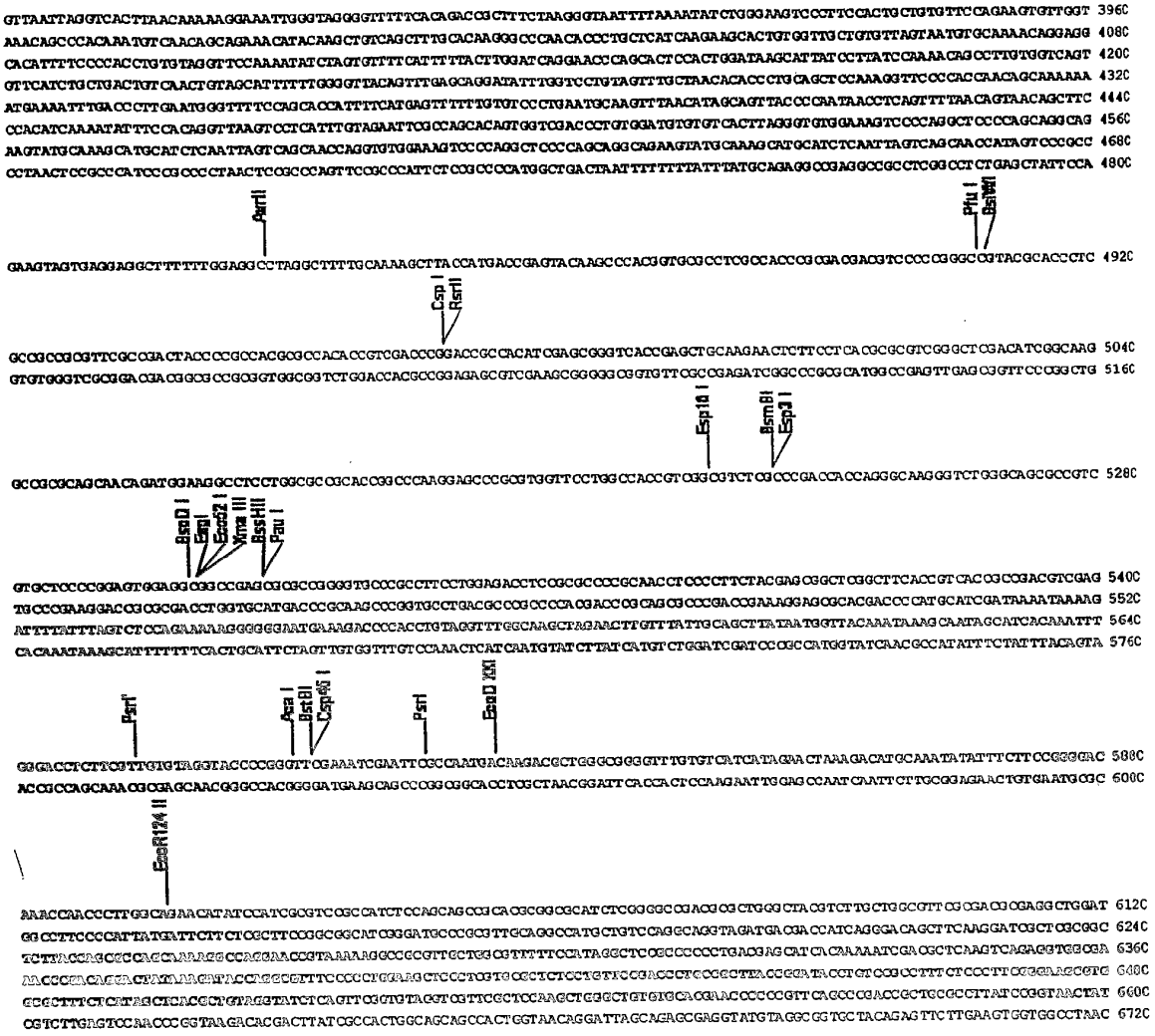


Figure 14 D (con't.)

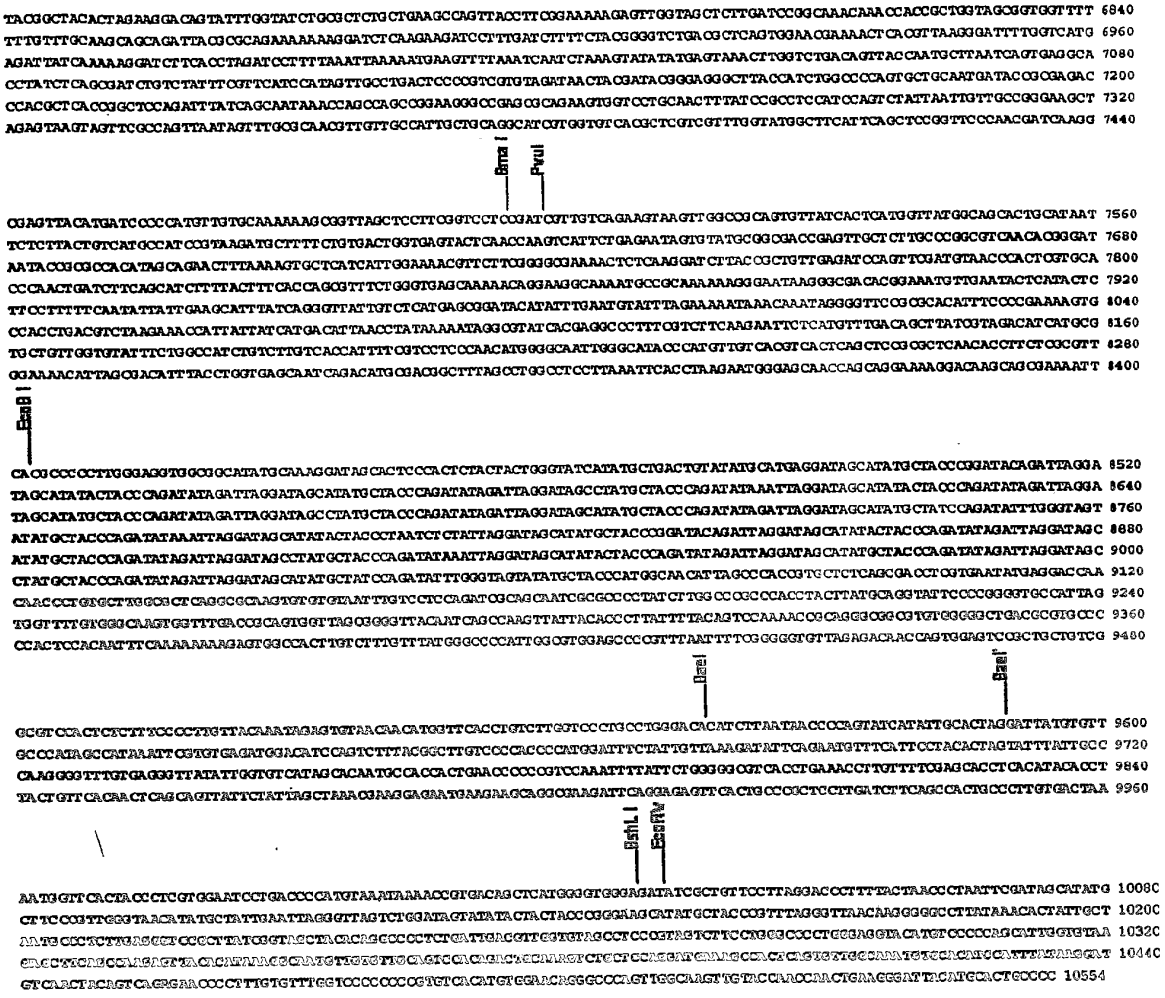


Fig. 15A – Nucleic acid sequence (SEQ. ID No. 38) of vector APEX-3PmOKT3VhG2G4

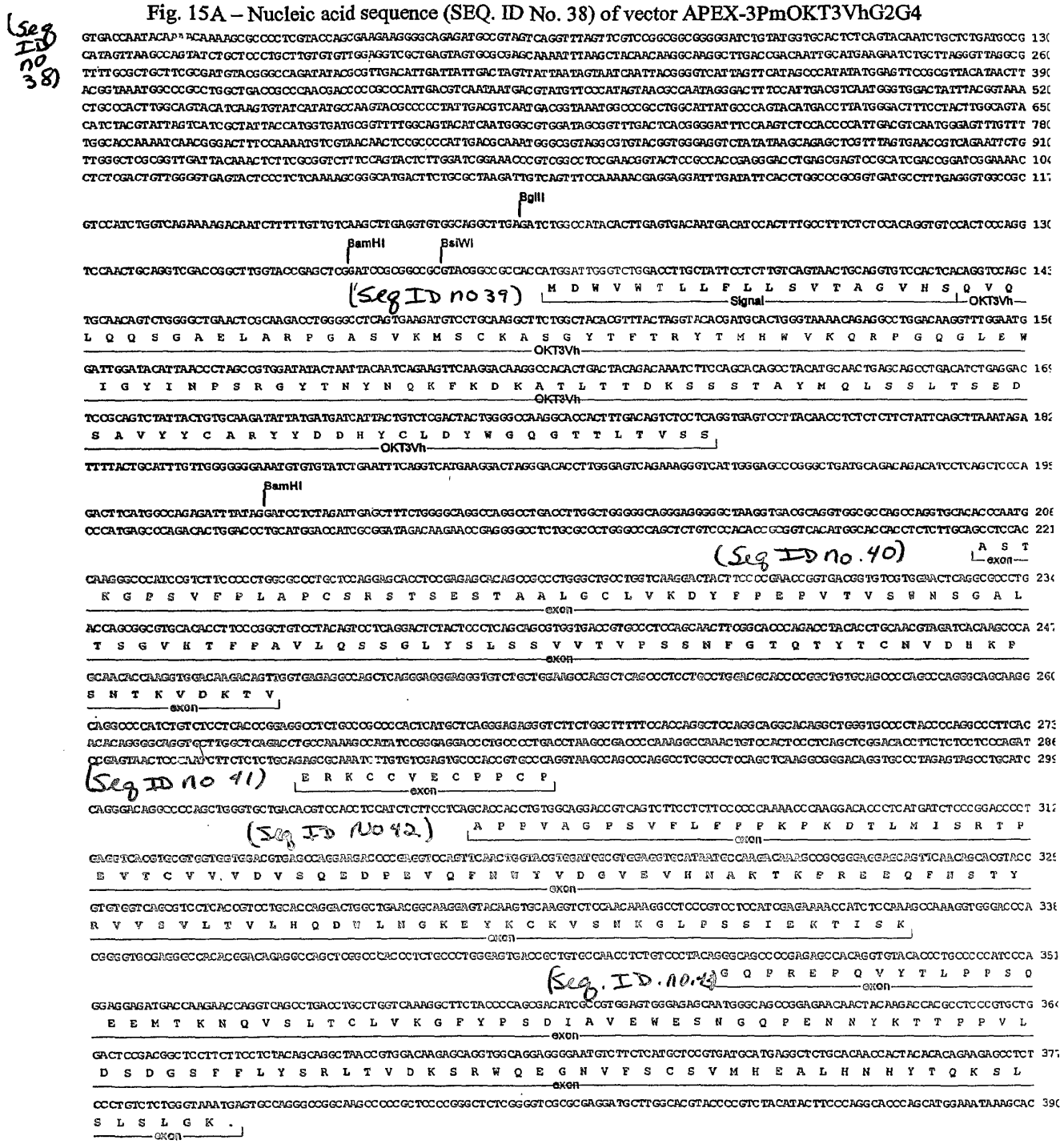


Figure 15 B (con't.)

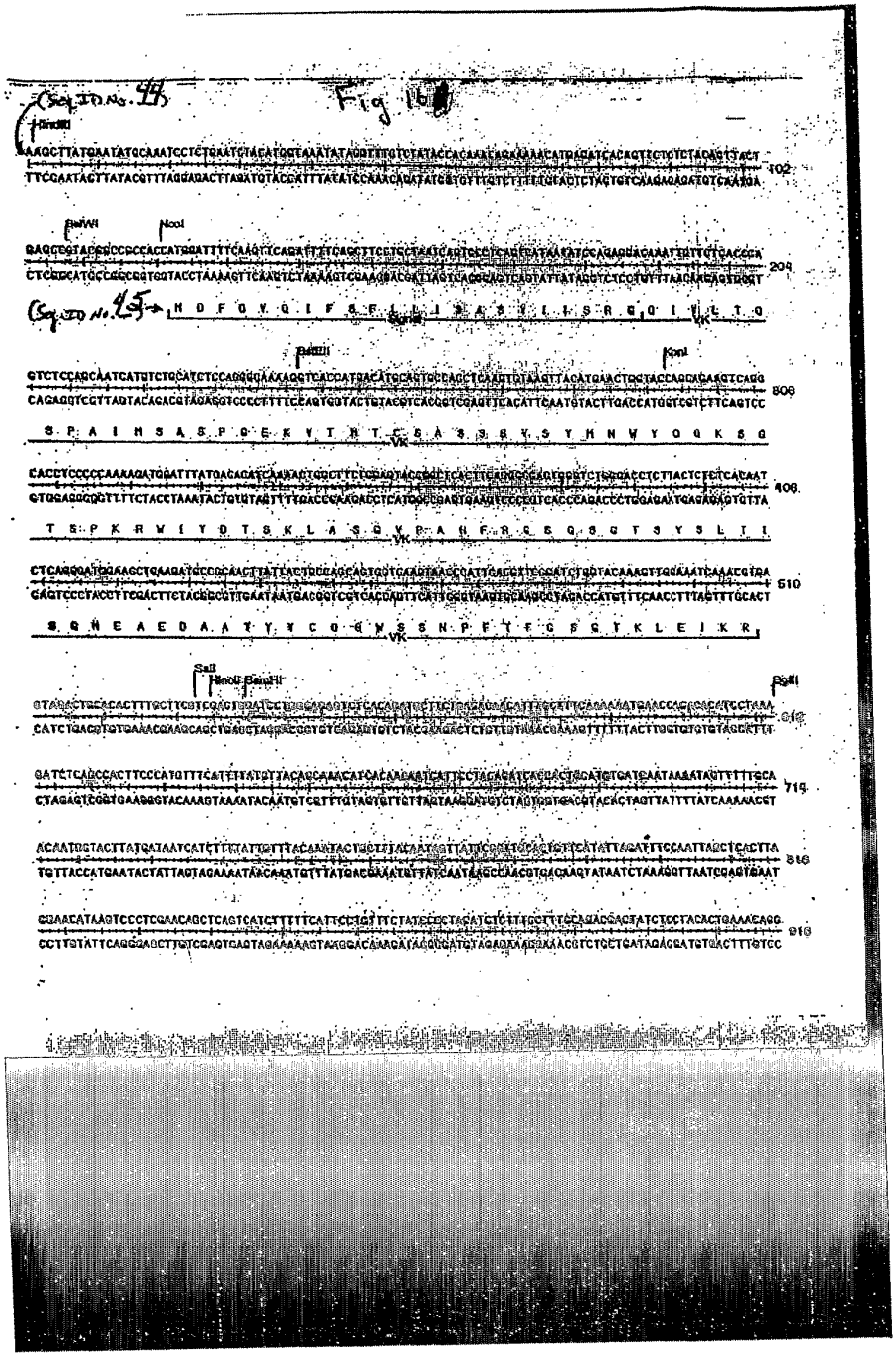


FIG 16B

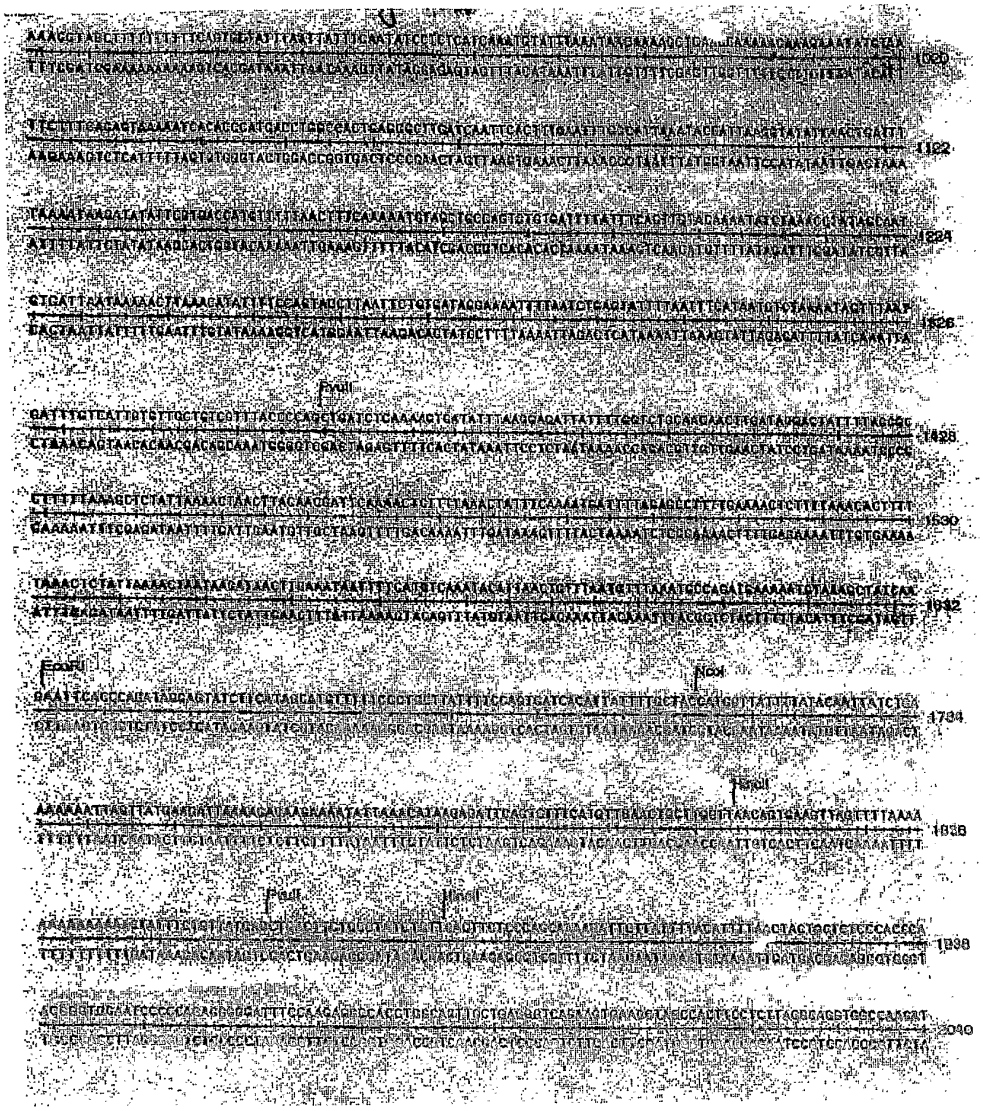


FIG. 16 C

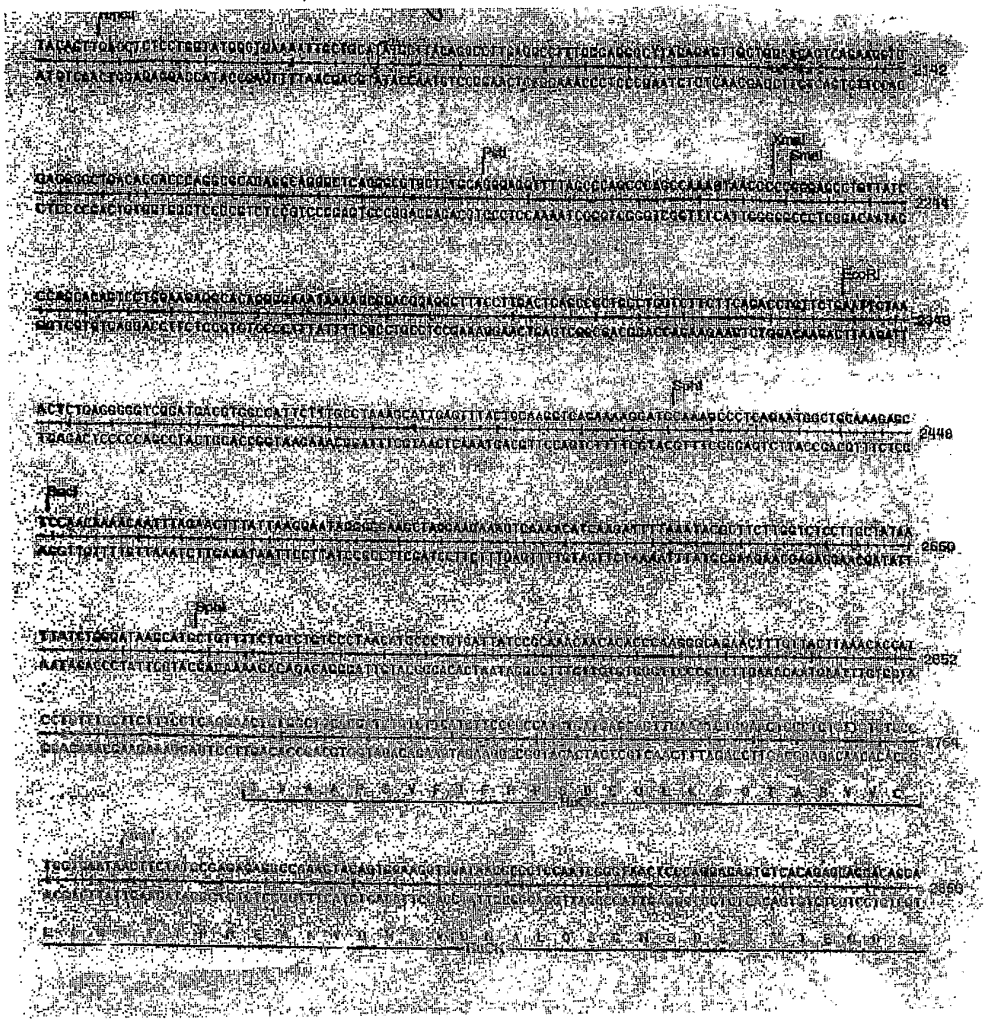


FIG 16D

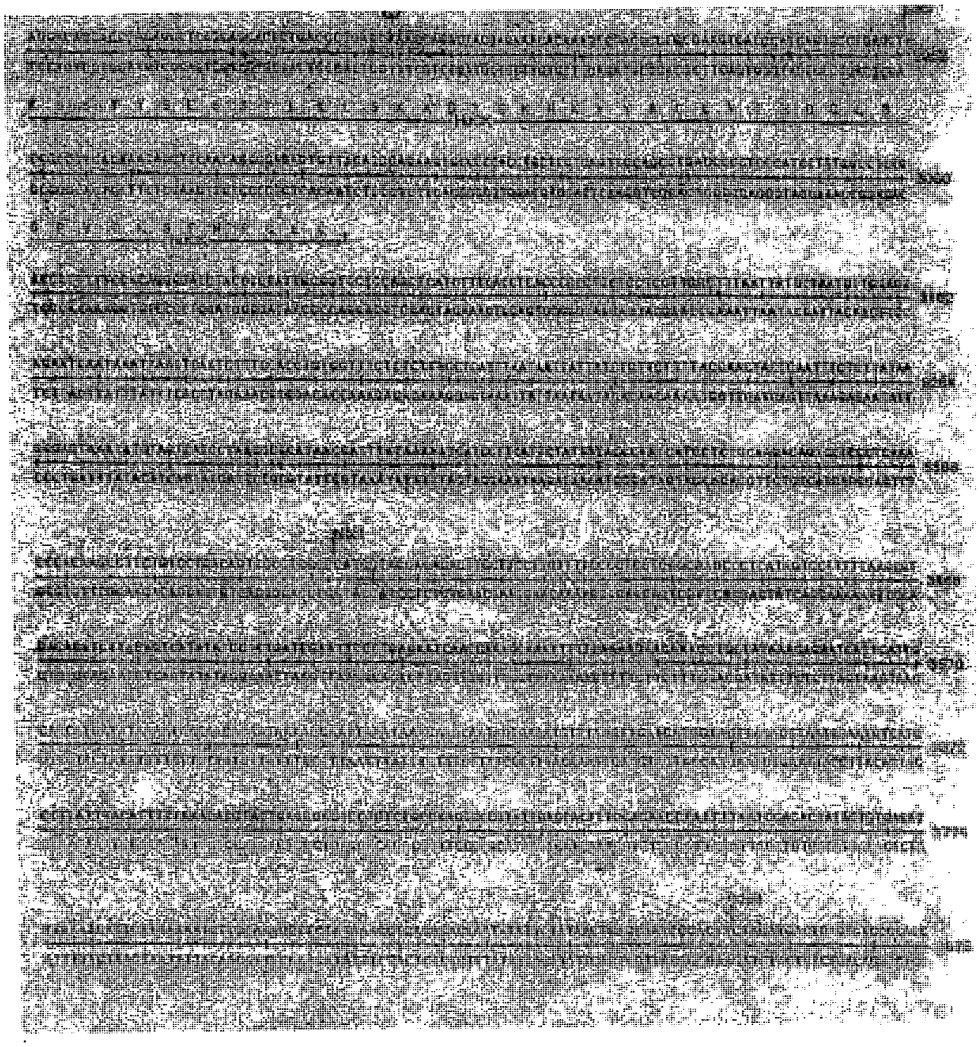


FIG. 16 E

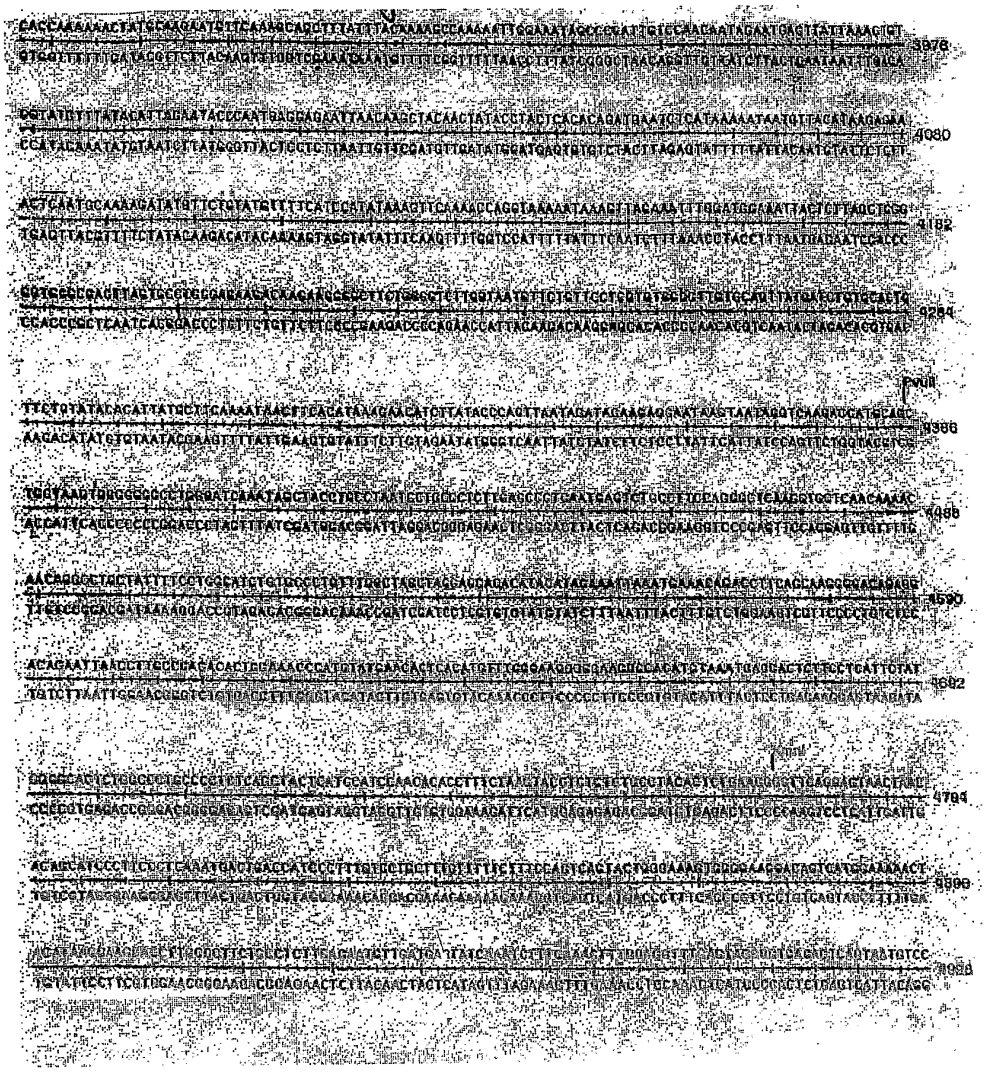


FIG 16 F

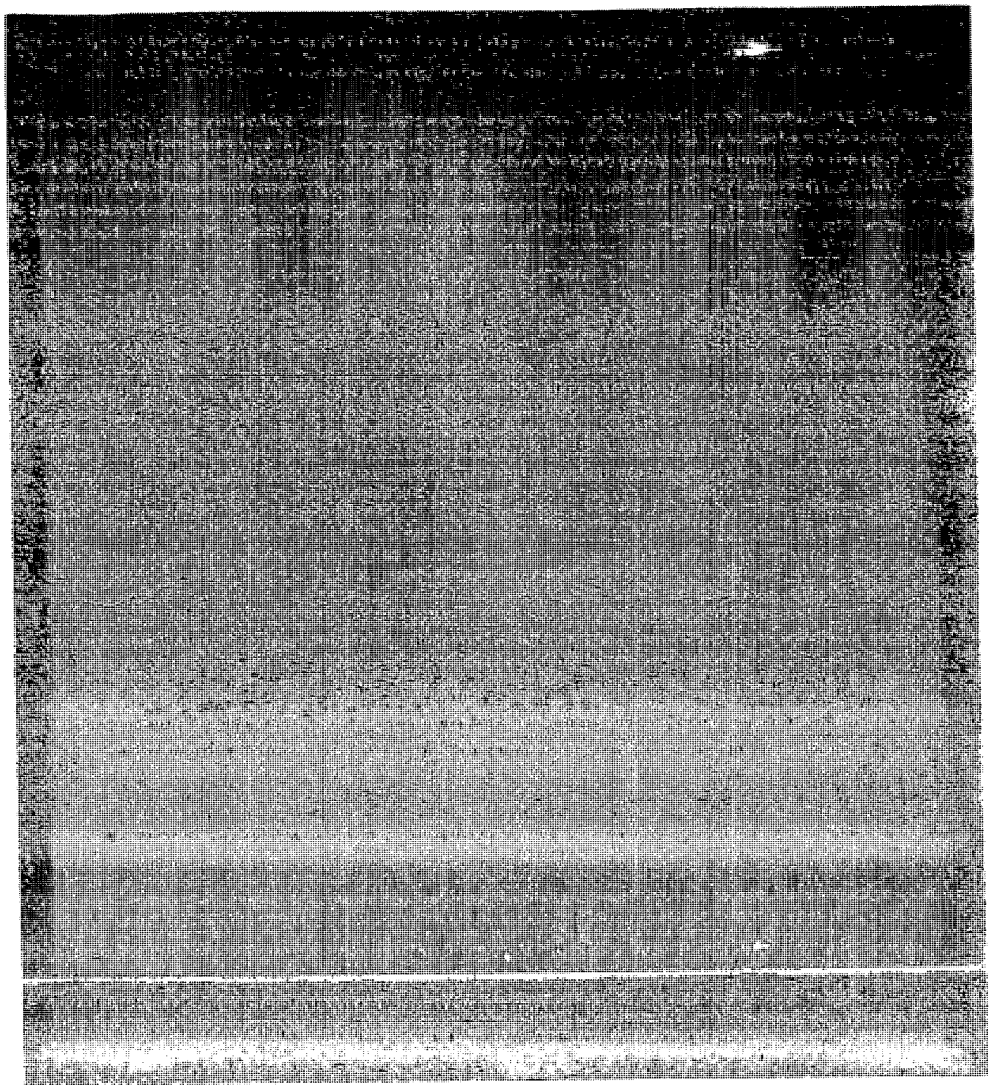


Figure 17. Nucleotide sequence of the LITMUS 28 shuttle vector, indicating the nucleic acid and amino acid sequences of the OKT3VkhCk insert used in Expression System #2.

(Seq ID no 46)

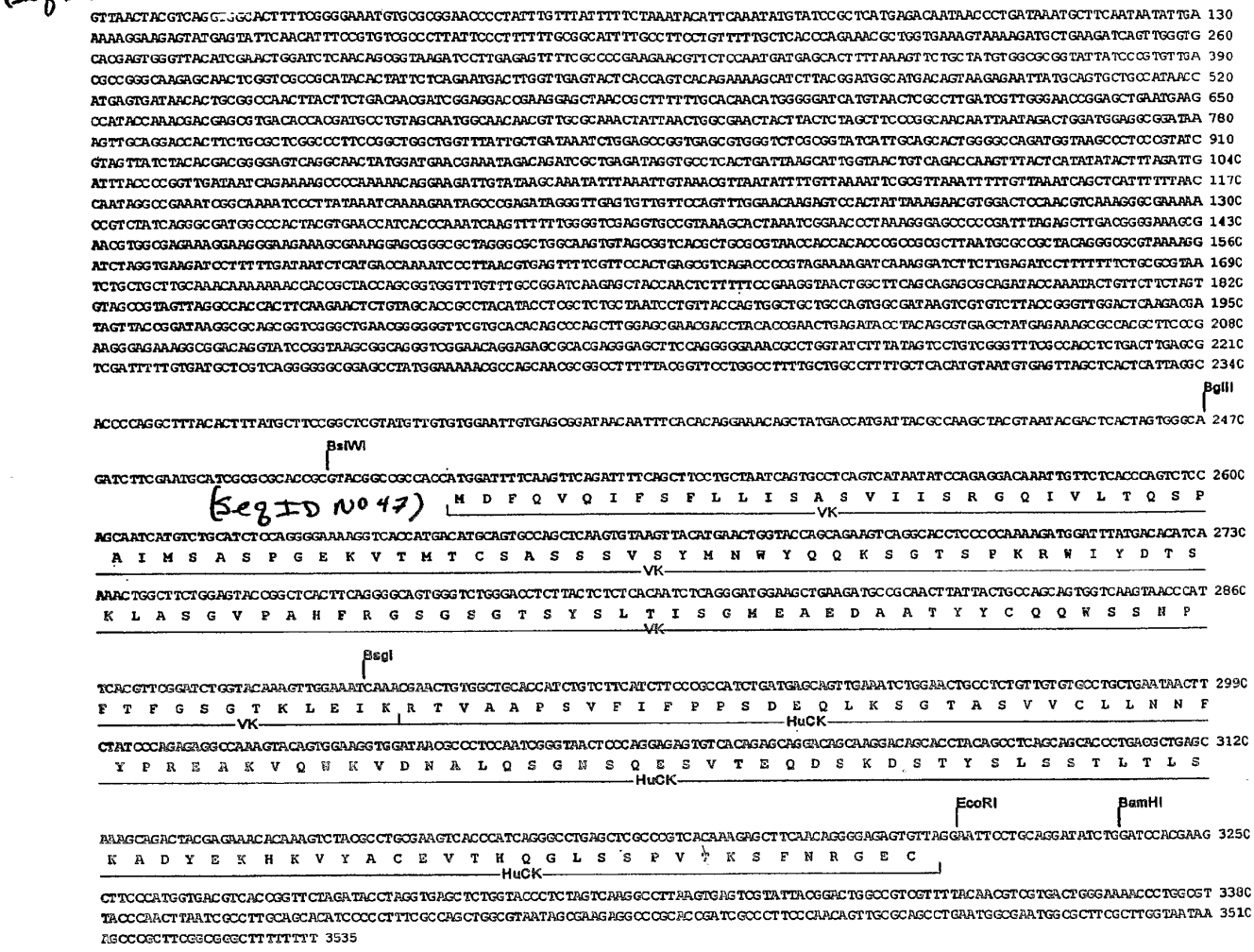


Figure 18. Nucleotide sequence (SEQ. ID No. 48) of the APEX-3 OKT3Vk+Ck vector

(Seq ID no. 48)

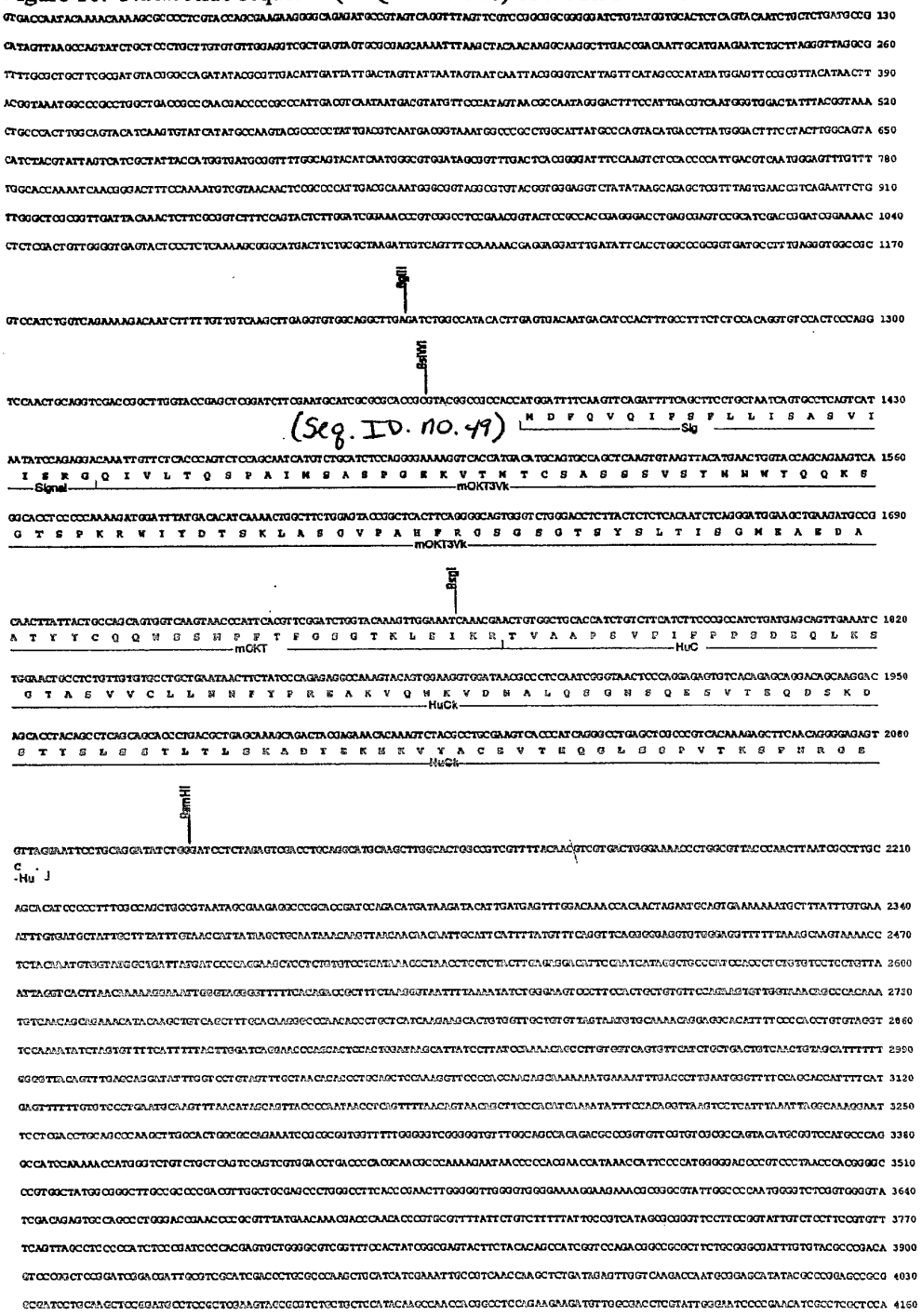


Figure 18 (con't.)

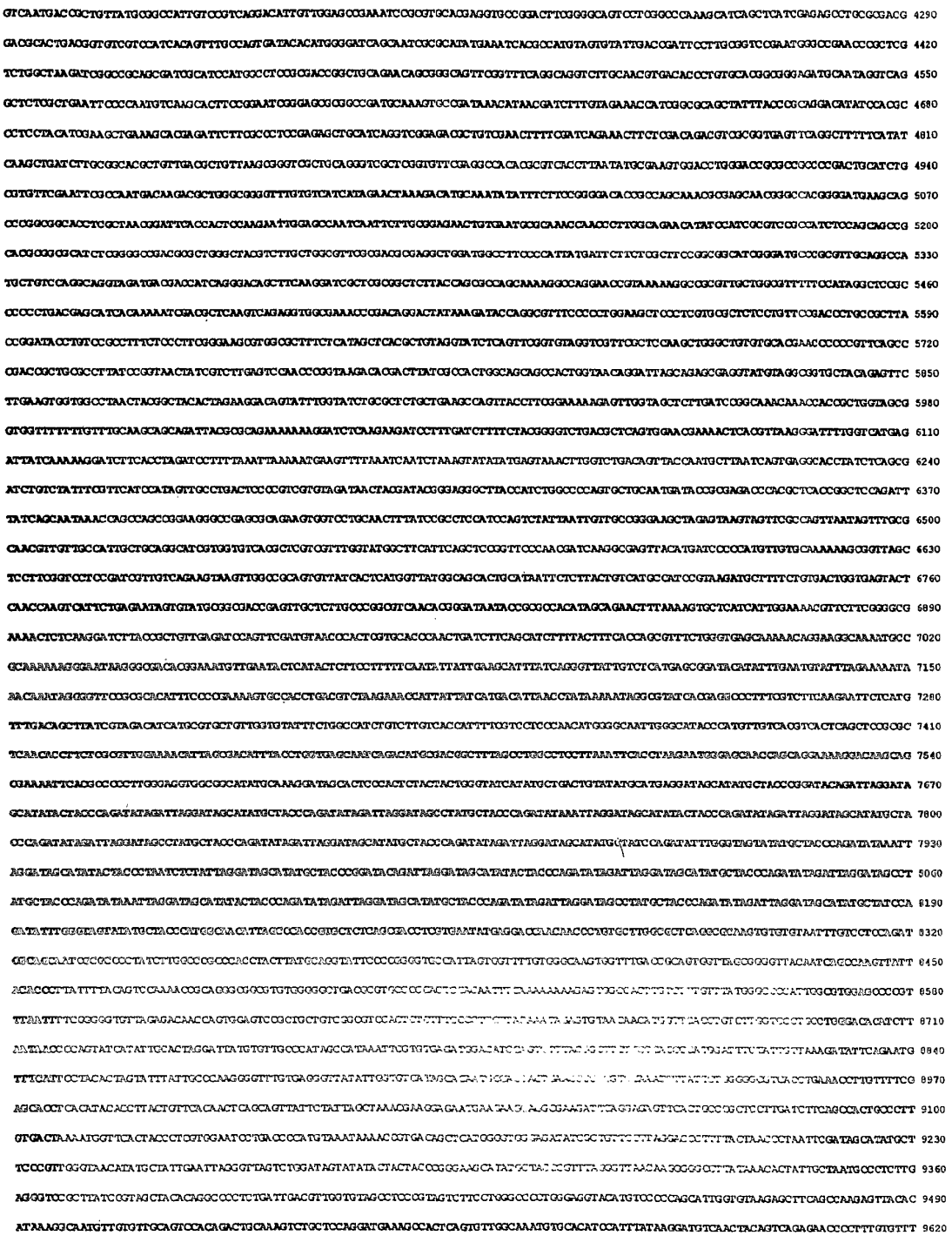


Figure 19. Evaluation of the binding of the OKT3huG2/G4 antibody to the high affinity FcγRI receptors on U937 cells.

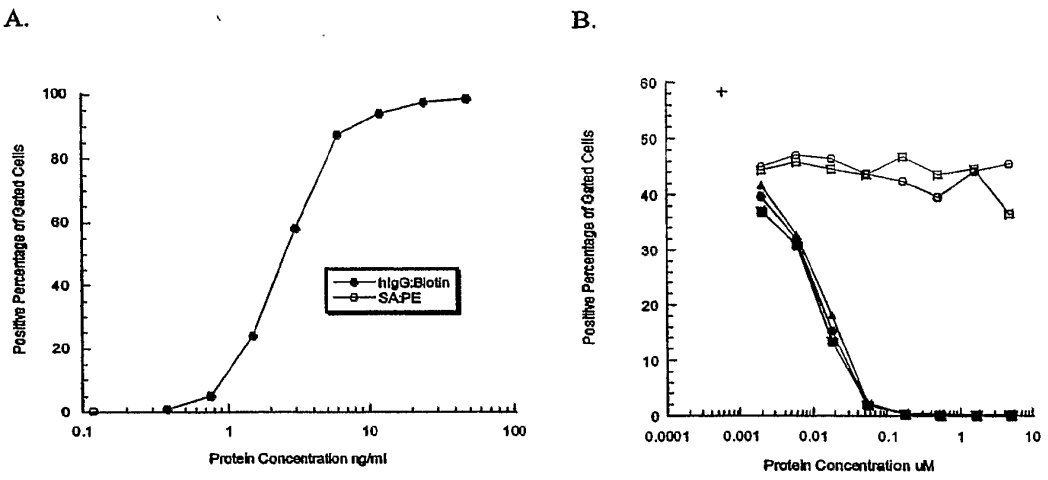


Figure 19. An IgG $_{G2/G4}$ antibody does not bind the human high affinity receptor for IgG (FcγRI). Cells of the U937 line were incubated with the indicated concentrations of biotinylated hIgG (Sigma) for 15 minutes at 4°C, washed, incubated with streptavidin-phycoerythrin (SA-PE) for 15 minutes at 4oC, washed, and then analyzed by flow cytometry using a Becton Dickenson FACS Calibur flow cytometer. The resulting binding curve (A) indicated that a concentration of approximately 2-4ng/mL biotinylated hIgG was appropriate for further competition studies. U937 cell were incubated with 3.0ng/mL biotinylated hIgG together with the indicated concentrations of competing antibodies for 30 minutes on ice, washed, incubated with SA-PE for 15 minutes, washed, and then analyzed by flow cytometry (B). Preparations of mOKT3 (●), $hIgG_1$ (■) and $hIgG_4$ (▲) efficiently blocked binding of the biotinylated hIgGs to the target cells, indicating that they bound the FcγRI receptor. However, $hIgG_2$ antibodies (□), or a recombinant antibody generated using the $hIgG_{G2/G4}$ constant region (OKT3hG2/G4; (○) did not compete for binding to the FcγRI receptor on these cells. Binding of biotinylated hIgG in the absence of competing antibody is indicated (+).

Figure 20. Evaluation of the binding of the OKT3huG2/G4 antibody to the low affinity FcγRII receptors on K562 cells.

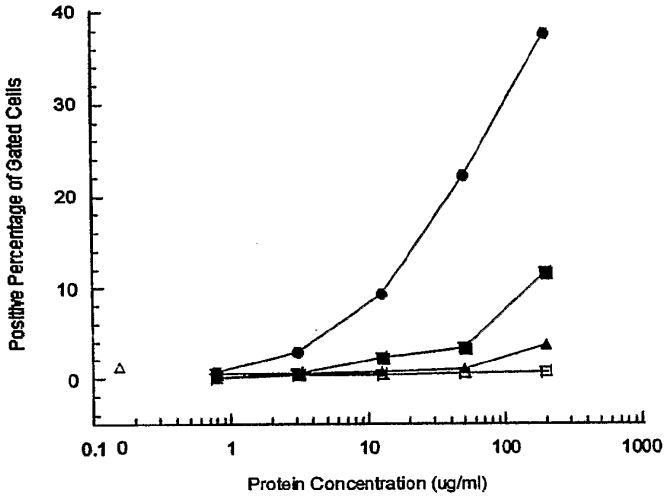


Figure 20. An IgG $_{G2/G4}$ antibody does not bind the human low affinity receptor for IgG (FcγRII). In order to reveal binding to low affinity Fc receptors, antibody preparations were first complexed by incubation with equimolar concentrations of fluorescein isothiocyanate (FITC)-labeled rabbit Fab'2 anti-human Fab'2 antibodies overnight at 4°C. Cells of the K562 line, which bear both allotypes of the human low affinity receptor for IgG (FcγRII), were incubated with the indicated concentrations of antibody complexes for 30 minutes on ice, washed, and analyzed for bound antibodies by flow cytometry using a Becton Dickenson FACS Calibur flow cytometer.. Human IgG_1 antibody complexes (●) demonstrated efficient binding to the K562 cells, while $hIgG_2$ antibody complexes (■) demonstrated much lower levels of binding. Human IgG_4 (▲) and a recombinant antibody bearing an $IgG_{G2/G4}$ constant region (OKT3huG2/G4 (□)) formed antibody complexes that were unable to bind the low affinity FcγRII receptors on these cells. Binding of the FITC- rabbit Fab'2 anti-human Fab'2 antibodies alone is indicated (Δ).

Figure 21. Evaluation of the ability of the OKT3huG2/G4 antibody to induce cytokine production in human PBL.

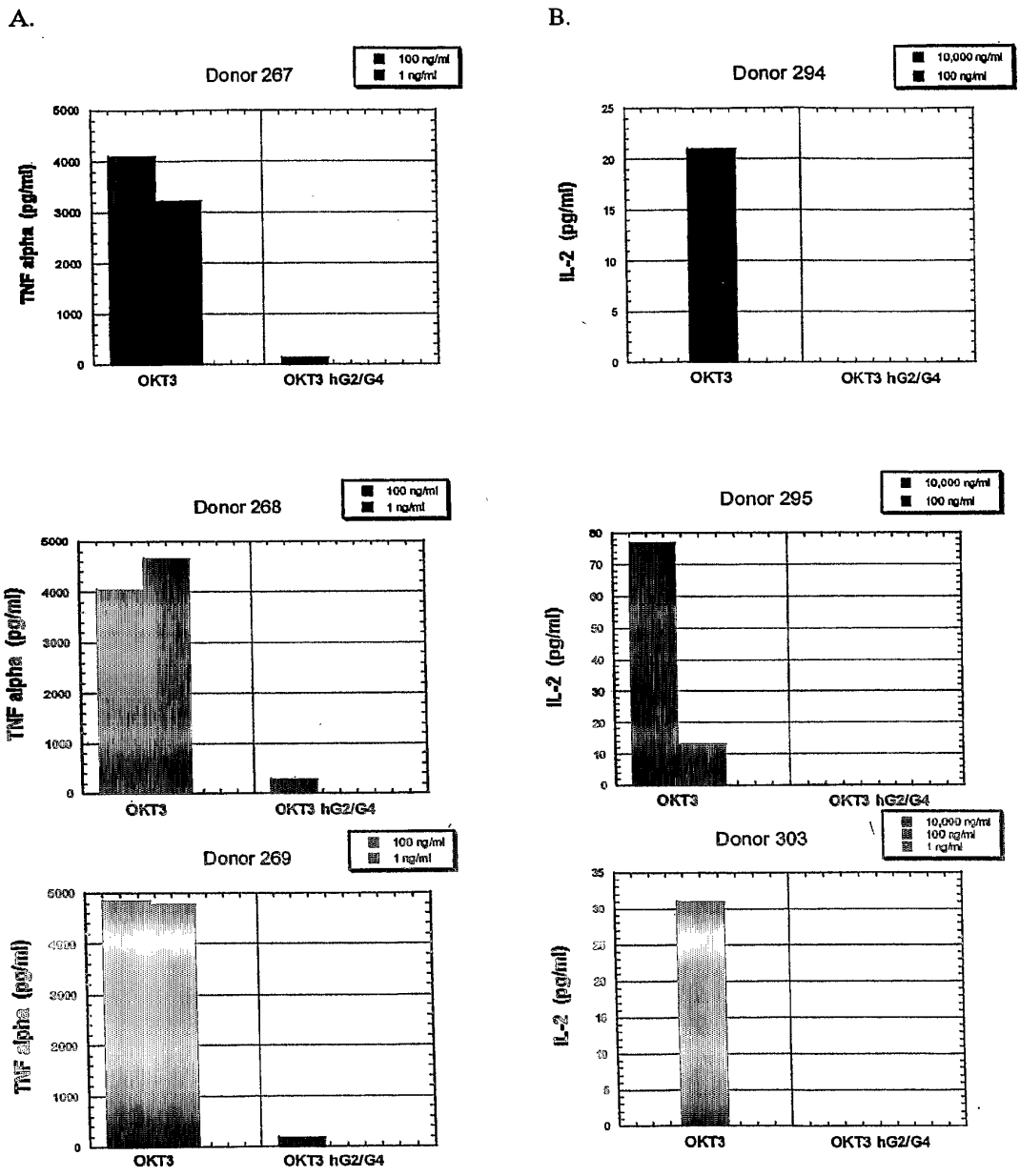
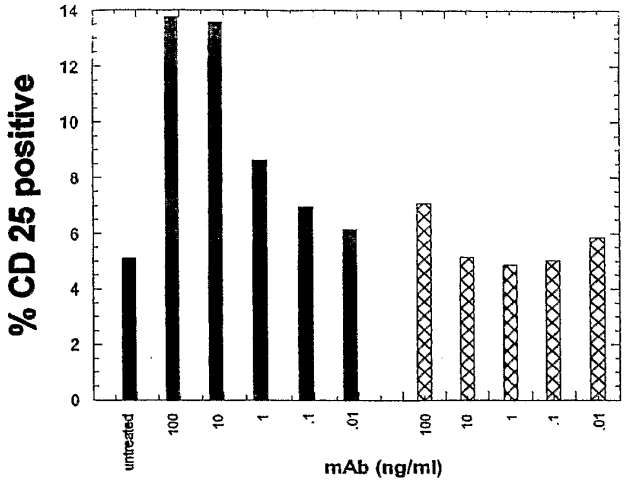


Figure 21. An IgG $_{G2/G4}$ antibody directed against human CD3 demonstrates a reduced ability to induce cytokine production in peripheral blood leukocytes (PBL). Freshly isolated

human peripheral blood from a panel of donors was enriched for the leukocyte fraction by Ficoll-Hypaque density sedimentation. The resulting PBL were incubated with the indicated concentrations of anti-CD3 antibodies bearing either a murine IgG2a constant region (OKT3) or a human $IgG_{G2/G4}$ constant region (OKT3 hG2/G4). Supernatants were collected at 24 and 36 hours and evaluated for the accumulation of TNF-α (A) and IL-2 (B) by sandwich ELISA. The graphs shown represent the timepoint at which peak levels of a given cytokine were observed (e.g. 24 hours for IL-2 and 36 hours for TNF-α). The OKT3 antibody, which crosslinks T cell receptors on T cells through the binding of human FcγRI and FcγRII receptors on accessory cells, induced potent levels of both cytokines. However, the recombinant antibody OKT3 hG2/G4, which has the OKT3 variable regions and so is directed at the identical CD3 epsilon epitope as OKT3, but which has lost its ability to bind Fc receptors, was unable to stimulate the production of significant levels of these cytokines.

Figure 22. Evaluation of the ability of the OKT3huG2/G4 antibody to induce the cell surface expression of CD25 and CD69 on human PBL.

A.



B.

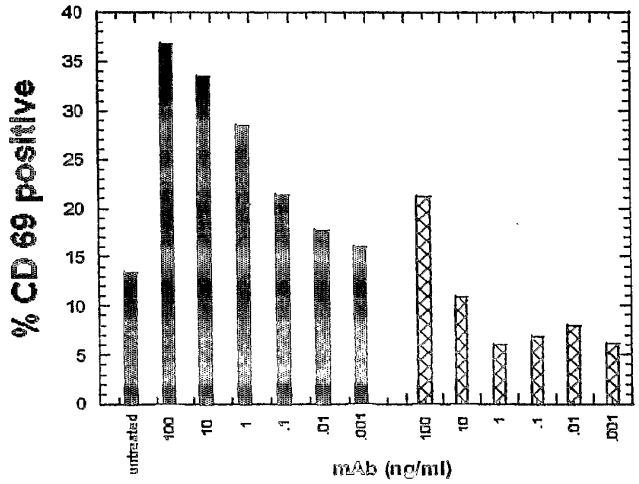


Figure 22. An IgG $_{G2/G4}$ antibody directed against human CD3 demonstrates a reduced ability to activate target T cells from human PBL. CD25 is the receptor for interleukin-2 (IL-2) and its expression is upregulated on the surface of T cells activated through the T cell receptor complex. Similarly, CD69 is also an early T cell activation marker whose levels of expression increase upon T cell receptor engagement. Thus both markers serve as sensitive measures of T cell activation. Freshly isolated human peripheral blood from a panel of donors was enriched for the leukocyte fraction by Ficoll-Hypaque density sedimentation. The resulting PBL were incubated in the absence or presence of the indicated concentrations of anti-CD3 antibodies bearing either a murine IgG2a constant region (OKT3; solid bars) or a human IgG $_{G2/G4}$ constant region (OKT3hG2/G4; hatched bars). Cells were harvested at 24 hours, washed, and incubated with FITC-conjugated monoclonal antibodies specific for human CD25 and

human CD69 on ice for 30 minutes. The cells were washed and analyzed for antibody binding by flow cytometry using a Becton Dickenson FACS Calibur flow cytometer. Data are shown for one representative donor, with the percentage of cells expressing CD25 (A) or CD69 (B) indicated.

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RAPID COMMUNICATION

IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma

By David G. Maloney, Antonio J. Grillo-López, Christine A. White, David Bodkin, Russell J. Schilder, James A. Neidhart, Nalini Janakiraman, Kenneth A. Foon, Tina-Marie Liles, Brian K. Dallaire, Ken Wey, Ivor Royston, Thomas Davis, and Ronald Levy

IDEC-C2B8 is a chimeric monoclonal antibody (MoAb) directed against the B-cell–specific antigen CD20 expressed on non-Hodgkin's lymphomas (NHL). The MoAb mediates complement and antibody-dependent cell-mediated cytotoxicity and has direct antiproliferative effects against malignant B-cell lines in vitro. Phase I trials of single doses up to 500 mg/m² and 4 weekly doses of 375 mg/m² showed clinical responses with no dose-limiting toxicity. We conducted a phase II, multicenter study evaluating four weekly infusions of 375 mg/m² IDEC-C2B8 in patients with relapsed low-grade or follicular NHL (Working Formulation groups A-D). Patients were monitored for adverse events, antibody pharmacokinetics, and clinical response. Thirty-seven patients with a median age of 58 years (range, 29 to 81 years) were treated. All patients had relapsed after chemotherapy (median of 2 prior regimens) and 54% had failed aggressive chemotherapy. Infusional side effects (grade 1-2) consisting of mild fever, chills, respiratory symptoms, and occasionally hypotension were observed mostly with the initial antibody infusion and were rare with subsequent doses. Peripheral blood B-cell depletion occurred rapidly, with recovery beginning 6 months posttreatment. There were no significant changes in mean IgG levels and infections were not increased over what would be expected in this population. Clinical remissions were observed in 17 patients (3 complete remissions and 14 partial remissions), yielding an intent to treat response rate of 46%. The onset of these tumor responses was as soon as 1 month posttreatment and reached a maximum by 4 months posttreatment. In the 17 responders, the median time to progression was 10.2 months (5 patients exceeding 20 months). Likelihood of tumor response was associated with a follicular histology, with the ability to sustain a high serum level of antibody after the first infusion, and with a longer duration of remission to prior chemotherapy. One patient developed a detectable but not quantifiable immune response to the antibody that had no clinical significance. IDEC-C2B8 in a dose of 375 mg/m² weekly for 4 weeks has antitumor activity in patients with relapsed low-grade or follicular NHL. Results with this brief, outpatient treatment compare favorably with results with standard chemotherapy, and IDEC-C2B8 has a better safety profile. Further studies evaluating IDEC-C2B8 in other types of lymphoma either alone or combined with chemotherapy are warranted.
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THE TREATMENT OF cancer with agents specific for the tumor cell with sparing of the host has long been a goal of oncology. Unfortunately, treatment approaches using chemotherapy and radiotherapy have increased host toxicity to obtain antitumor activity. The development of monoclonal antibodies (MoAbs) provided hope that tumor-targeted therapy would one day play a role in the treatment of cancer. Indeed, promising results have been presented in several areas; however, these treatments have often proved technically difficult, produced disappointing efficacy, and were often not broadly applicable to patients with a given malignancy. The treatment of patients with lymphoma is an exception. Patients with advanced stage or relapsed low-grade non-Hodgkin's lymphoma (NHL) are not curable using conventional approaches and are usually treated with combination chemotherapy regimens of increasing intensity as needed to reduce disease and palliate symptoms.[1] Aggressive approaches using high-dose therapy and autologous marrow support may provide maximal tumor reduction; however, there is currently no plateau on the failure-free survival curve.[2] New treatment modalities and approaches that provide tumor reduction with less toxicity are needed.

MoAbs against a variety of tumor surface antigens have shown activity in the treatment of patients with low-grade NHL. Unmodified murine MoAbs have included custom, patient-specific anti-idiotype MoAbs,[3-6] anti-CD20 MoAbs,[7] and antibodies against CD19 and CD22 armed with immunotoxins.[8-10] Anti-CD20 MoAbs radiolabeled with ^{131}I or ^{90}Y in low dose[11-13] and in high dose with stem cell support[14,15] have also demonstrated significant antitumor activity in the treatment of patients with relapsed disease, but have encountered dose-limiting toxicities and are limited by bone marrow involvement.

IDEC-C2B8 is a chimeric anti-CD20 MoAb containing human IgG1 and κ constant regions with murine variable regions.[16] It binds the CD20 antigen with high affinity (5×10^{-9} mol/L). Because of the human constant Ig regions, the chimeric antibody efficiently kills CD20$^+$ cells in vitro by augmented complement-mediated lysis and participates in antibody-dependent cell-mediated cytotoxicity (ADCC) using human complement and immune effector cells.[16] In some

From the Department of Medicine, Division of Oncology, Stanford University, Stanford, CA; Scripps Memorial Hospital, San Diego Regional Cancer Center, San Diego, CA; IDEC Pharmaceuticals, San Diego, CA; Fox Chase Cancer Center, Philadelphia, PA; University of New Mexico Cancer Center, Albuquerque, NM; Henry Ford Hospital, Detroit, MI; and the University of Kentucky Medical Center, Lexington, KY.

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Address reprint requests to David G. Maloney, MD, PhD, Fred Hutchinson Cancer Research Center, M-385, 1124 Columbia St, Seattle, WA 98104.

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NHL cell lines, the binding of the antibody inhibits proliferation and directly induces apoptosis.[17] In patients with lymphoma, the administration of single doses up to 500 mg/m^2 was not associated with any dose limiting toxicity. Rapid binding to and depletion of CD20$^+$ normal B cells and tumor cells in the peripheral blood and bone marrow was observed, and tumor cells in lymph node biopsies obtained 2 weeks after antibody therapy showed that the chimeric MoAb bound to CD20 antigen sites.[18] The treatment was well tolerated, causing only minimal infusion-related symptoms. Tumor responses (2 partial remissions [PR] lasting 8.1 and 8.6 months and 5 minor responses lasting 0.9 to 6 months) were observed in 7 of 9 patients treated with single doses of at least 100 mg/m^2. Repeated weekly infusion for 4 weeks of doses of 125, 250, or 375 mg/m^2 in 20 patients with relapsed lymphoma has also recently been reported.[19] The treatment was well tolerated and 6 of 18 evaluable patients had a PR with no dose-limiting toxicity identified. The 375 mg/m^2 for 4 weeks dose was selected for phase II evaluation. We report here on the clinical results obtained in the treatment of 37 patients with relapsed low-grade or follicular lymphoma.

MATERIALS AND METHODS

Study design. This was a phase II, open-label, single-arm, multicenter trial evaluating four intravenous infusions of the chimeric monoclonal anti-CD20 antibody IDEC-C2B8 at a dose of 375 mg/m^2 in patients with relapsed low-grade NHL. Study objectives included the evaluation of safety, dose-limiting toxicities, pharmacokinetics, immune response, and clinical activity. Patients received a single infusion weekly, and completed the 4 antibody infusions in 22 days.

Antibody. IDEC-C2B8 is a chimeric MoAb containing human IgG1 (κ) heavy and light chain constant regions and murine variable regions from the murine antihuman CD20 MoAb IDEC-2B8 (murine IgG1, κ). The chimeric antibody was produced in vitro from a transfected Chinese hamster ovary (CHO) cell line.[16] The antibody is specific for the human CD20 antigen, a 35-kD phosphoprotein present on normal and malignant B cells, but not on other tissues.[20] The antibody was produced and supplied by IDEC Pharmaceuticals Corp (San Diego, CA).

Patient population and sample size. Adults with histologically confirmed, relapsed B-cell lymphoma expressing the CD20 antigen were eligible, as were nonresponders to first chemotherapy. All patients met the following criteria: expected survival of $\geq$3 months with no serious nonmalignant disease; prestudy performance status of 0, 1, or 2 on the World Health Organization (WHO) scale; seronegative for human immunodeficiency virus (HIV) and hepatitis B surface antigen; serum IgG level of $\geq$600 mg/dL; hemoglobin level of $\geq$8.0 g/dL; white blood cell count of $\geq 3.0 \times 10^3/\mu L$; absolute granulocyte count of $\geq 1.5 \times 10^3/\mu L$; platelet count of $\geq 75 \times 10^3/\mu L$; bilirubin level of less than 1.5 mg/dL; alkaline phosphatase level of less than 2$\times$ normal; aspartata amino transferase (AST) level of less than 2$\times$ normal; and serum creatinine level of less than 2.0 mg/dL. Patients tested negative for human antimurine antibody (HAMA).

The 375 mg/m^2 dose was identified from a phase I dose-escalation trial evaluating 125, 250, and 375 mg/m^2 infusions for 4 weeks.[19] To determine clinical efficacy, a total of 37 patients were treated at the 375 mg/m^2 dose and form the basis of this report.

Study sites. Patients were treated at seven sites in the United States. All patients signed an informed consent approved by the local Institutional Review Boards at Stanford University Medical Center (Palo Alto, CA), San Diego Regional Cancer Center (San Diego, CA), Scripps Memorial Hospitals (La Jolla and Encinitas, CA), Fox Chase Cancer Center (Philadelphia, PA), University of New Mexico Cancer Center (Albuquerque, NM), Henry Ford Hospital (Detroit, MI), or Markey Cancer Center (Lexington, KY). Patients were enrolled and treated between August 12, 1993 and September 13, 1994.

Pharmacokinetic sampling and HAMA/HACA evaluation. Serum samples were obtained pretreatment and at scheduled follow-up evaluations to determine anti-CD20 MoAb levels and to analyze for evidence of human antichimeric antibody (HACA) and HAMA immune response. Extended pharmacokinetic sampling was performed during the treatment course in selected patients whose schedules permitted. This included samples during the weeks 1 and 4 of treatment, including before infusion, postinfusion, and 24, 48, 72, and 96 hours postinfusion, as well as preinfusion and postinfusion samples from weeks 2 and 3. Serum pharmacokinetics were determined using frozen serum samples on microtiter plates coated with polyclonal goat anti–IDEC-2B8 antibody. Serum samples were serially diluted and washed, and bound IDEC-C2B8 was detected using labeled goat antihuman IgG and compared with a standard curve obtained using IDEC-C2B8 diluted into normal human serum. The assay has a lower limit of quantification of 0.5 μg/mL of the chimeric antibody.

HAMA was detected using microtiter plates coated with murine IgG. Serum samples were serially diluted on the plate and washed. Any bound human Ig was then detected using labeled goat antihuman Ig. HACA was detected by incubating serum samples on plates coated with IDEC-C2B8. Human antibody bound to the microtiter wells was then detected using biotin–IDEC-C2B8 followed by avidin-horseradish peroxidase and the substrate 2, 2-azinobis (3-ethylbenzthiazoline sulfonic acid) (ABTS). The minimum quantifiable level for these assays was 100 ng/mL (detectable to 5 ng/mL).

Patient monitoring and efficacy evaluation. Patients were monitored for safety and for clinical antitumor effect with regular medical histories, physical examinations, and laboratory studies including complete blood count and differential, chemistry panel, quantitative serum Igs, serum complement, serum anti-CD20 levels (HACA and HAMA), and urinalysis performed at baseline; at weeks 1, 2, 3, and 4; and at specified intervals to a maximum of 4 years. Toxicity was evaluated using the National Cancer Institute's Adult Toxicity Criteria. Peripheral blood was analyzed by flow cytometry to determine lymphocyte subsets at baseline, week 1, months 1, and 3 and at 3-month intervals for 1 year. Chest x-ray was performed at baseline and at 1 and 3 months after the completion of IDEC-C2B8 therapy. Computed tomography scans of the neck, chest, abdomen, and pelvis, as well as physical examination and measurement of palpable tumor masses or lymph nodes was conducted at baseline, at 1 and 3 months after treatment, and at 3-month intervals for 1 year and then yearly for 4 years. Tumor lesions were serially measured by physical exam and radiologic procedures. PR were defined as a decrease of greater than 50% in the total sum of the products of the bidimensional measurements. Complete remissions (CR) were defined as the disappearance of all disease. Stable disease was defined by no significant change in tumor measurements without progression over the period of observation. Remissions (PR and CR) were confirmed on a second complete evaluation at least 28 days later. Disease progression was determined by a 25% increase in measurable disease or the appearance of any new lesion. Time to progression was measured from date of first antibody infusion to first date when progressive disease was documented.

RESULTS

Patient characteristics. Thirty-seven patients were assigned to receive treatment at the phase II dose level of 375

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Table 1. Patient Characteristics (N = 37)

	No.	% or Range
Age	58	29-81
Sex		
Female	16	43
Male	21	57
Histologic grade*		
Low	34	92
A	4	11
B	21	57
C	9	24
Intermediate	3	8
D	2	5
G	1	3
Stage at diagnosis		
I	5	14
II	2	5
III	10	27
IV	18	49
Unknown	2	5
Prior Therapy		
Chemotherapy	37	100
Median no. of regimens	2	1-5
Time from last Rx median (mo)	10.2	0.9-70.4
Radiotherapy	13	35
ABMT	3	8
All therapy	37	100
Median no.	2	1-8
Time from last Rx, median (mo)	7.2	0.9-67.9
First chemotherapy		
Single agent	9	25
COP or CP	11	31
Aggressive combination	17	44
Response to first chemotherapy		
CR or PR	29	81
Duration, median (mo)	12	
No response	5	14
Unknown	2	5
Response to last therapy		
CP or PR	25	86
Duration, median (mo)	12	
Unknown	2	5

* Histologic group based on Working Formulation.

mg/m^2 for 4 weeks, the highest dose used in the dose escalation phase I portion of the trial. Patient characteristics at diagnosis and prior lymphoma therapy for all 37 patients are detailed in Table 1. The median age was 58 years, with a range of 29 to 81 years. All but 1 patient had an initial diagnosis of a low-grade or follicular histology (Working Formulation [WF] groups A-D), and 76% were diagnosed with stage III or IV disease. At the time of antibody therapy, 17 patients (46%) had bone marrow involvement, 10 patients (27%) had an elevated lactate dehydrogenase (LDH) level, and 10 patients (27%) had at least one lesion greater than or equal to 7 cm. All patients had relapsed after standard chemotherapy with a median of 2 prior regimens (range, 1 to 5). Forty-four percent of patients had failed to respond to an initial aggressive combination chemotherapy regimen such as CHOP, PROMACE-CYTABOM, or MACOP-B. Fifty-six percent of patients were initially treated with a single agent (25%) or combination therapy with an alkylating agent and prednisone. Most patients (81%) had a CR or PR to initial chemotherapy with a median duration of 12 months. Relapsed disease was treated with a variety of agents including radiotherapy, single-agent, and aggressive combination chemotherapy including high-dose therapy supported with autologous stem cells (3 patients). Eighty-six percent of patients had responded to their most recent treatment with a CR (41%) or PR (45%) with a median duration of 12 months (20 patients with duration of <6 months). Treatment was administered at a median of 4.5 years from initial diagnosis (range, 0.8 to 13.3 years) and a median of 10.2 months from last therapy. Two patients had previously been treated in a phase I single-dose study using IDEC-C2B8, one of whom achieved a PR lasting 8 months.

Antibody infusions. IDEC-C2B8 infusions were administered in an outpatient setting, usually through peripheral intravenous catheters. Patients were often premedicated for the first antibody infusion with oral diphenhydramine and acetaminophen. The total dose of antibody was diluted into normal saline (generally 1 mg/mL) and administered intravenously by infusion at an initial rate of 50 mg/h, escalating every 30 minutes in the absence of side effects to a maximum of 200 mg/h.

The average dose of antibody administered during each infusion was 711 mg (range, 562 to 825 mg), with a cumulative dose over 4 infusions of 2,730 mg (maximum cumulative dose of 3,300 mg). The initial antibody infusion duration averaged 5.6 hours (range, 1.5 to 12.7 hours). In the absence of symptoms, subsequent infusions started at 200 mg/h with an average duration of infusion of 4.5, 4.4, and 4.2 hours for doses number 2, 3, and 4, respectively.

Adverse events. The most common adverse events thought to be related to treatment are detailed in Table 2. Thirty-two of the 37 patients experienced adverse events during the course of the trial; 6 patients experienced 12 grade 3 or 4 adverse events (9 reported as related to treatment). The most frequent infusion-related events included grade 1 or 2 fever (73% of patients), chills (38%), nausea (19%), asthenia (16%), headache (16%), and a sensation of tongue or throat swelling (11%). Hypotension occurred in 6 patients and was limited to grade 1 in 3 cases and grade 2 in 3 cases. Treatment-related side effects were seen most frequently with the initial antibody infusion (129 of 192 [67%]) and dramatically decreased during the second, third, and fourth infusions. Adverse events were managed by the administration of diphenhydramine or acetaminophen as indicated and by temporarily halting the antibody infusions until the symptoms abated. The infusions could in general then be restarted with minimal further toxicity. Two patients were withdrawn from study after receiving only the first of 4 planned antibody infusions (described in detail below).

Grade 3 and grade 4 adverse events included thrombocytopenia and anemia in 1 patient, abdominal pain and constipation in 1 patient, transient neutropenia at 4 months and 9 months in 2 patients, myocardial infarction in 1 patient, and malignant pleural effusion with dyspnea and traumatic hip fracture 3 weeks after antibody therapy in 1 patient. Two of the 37 patients did not complete the 4 planned antibody

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Table 2. Observed Adverse Events

	N (%)	Events (%)
Any adverse event	32 (86.5)	192 (100)
Body as a whole		
Fever	27 (73.0)	55 (28.6)
Chills	14 (37.8)	14 (7.3)
Asthenia	6 (16.2)	6 (3.1)
Headache	6 (16.2)	11 (5.7)
Cardiovascular system		
Hypotension	6 (16.2)	6 (3.1)
Digestive system		
Nausea	7 (18.9)	7 (3.6)
Vomiting	4 (10.8)	4 (2.1)
Dyspepsia	2 (5.4)	2 (1.0)
Blood and lymphatics		
Thrombocytopenia	7 (18.9)	7 (3.6)
Neutropenia	3 (8.1)	5 (2.6)
Anemia	2 (5.4)	3 (1.6)
Coagulation disorder	2 (5.4)	2 (1.0)
Leukopenia	1 (2.7)	4 (2.1)
Nervous system		
Vasodilation	1 (2.7)	3 (1.6)
Respiratory system		
Rhinitis	6 (16.2)	6 (3.1)
Laryngismus	4 (10.8)	4 (2.1)
Chest pain	2 (5.4)	2 (1.0)
Skin and appendages		
Rash	5 (13.5)	5 (2.6)
Night sweats	3 (8.1)	3 (1.6)
Urticaria	3 (8.1)	4 (2.1)
Pruritus	2 (5.4)	3 (1.6)
Special senses		
Lacrimation disorder	5 (13.5)	5 (2.6)

Included are events reported as possibly or probably related or of unknown relationship to study treatment.

Abbreviations: N, number of patients; Events, number of events.

infusions. The first patient, who had small lymphocytic lymphoma, had previously been treated with a single infusion of IDEC-C2B8 in an earlier trial and had experienced transient grade 3 thrombocytopenia. Within 24 hours of the first infusion of 375 mg/m^2 antibody, the platelet count again decreased from a baseline value of 93,000/μL to a nadir of 19,000/μL. This was associated with marked elevation in LDH level (629 to 2660 U/L), a decrease in hemoglobin level from 12.6 to 7.8 g/dL, and an elevation in uric acid to 10.5 mg/dL. She received outpatient treatment with allopurinol, prednisone, and a single platelet transfusion. Evaluation for disseminated intravascular coagulation was nondiagnostic and the patient improved (counts returned to above baseline) by day 31. The second patient, a 63-year-old man with follicular small cleaved cell NHL, had a prior history of hypertension, hypercholesterolemia, and atherosclerotic cardiovascular disease, including a prior myocardial infarction (4 months earlier); developed anginal pain within 30 minutes of initiation of his first IDEC-C2B8 infusion; and received nitroglycerin with resolution of symptoms. The antibody infusion was then completed with stable vital signs. However, the patient was hospitalized 5 days later with a myocardial infarction and was removed from study. An occluded right coronary artery was found and the patient underwent a surgical coronary artery bypass procedure.

Hematologic and chemistry laboratory effects. A total of 18 patients had some clinically significant hematologic nadir after antibody therapy and 11 of these patients had bone marrow involvement by their lymphoma. Eleven patients sustained decreases in hemoglobin or hematocrit of greater than 1.5 g or 3%, respectively. Eight patients had decreases in platelet counts to less than 100,000/μL and 10 patients had transient reductions in white blood cell count or absolute granulocyte count of less than 3,000/μL or 1,500/μL, respectively. In general, these effects were mild and patients spontaneously recovered without intervention. Two patients developed late onset isolated neutropenia of unclear etiology at 4 and 10 months after therapy. Both instances were transient and resolved within 1 month.

No clinically significant changes in chemistry laboratory values were noted.

Reported infections. A total of 9 patients (11 infections) were reported to have acquired an infection during the course of the treatment or follow-up. Infections during the first 60 days of antibody therapy included viral upper respiratory infections in 3 patients, localized skin infections in 3 patients, and herpes zoster and otitis media in 1 patient each. Reported late infections, occurring 7 to 12 months after antibody therapy, included pneumonia, impetigo, and sinusitis. All infections were grade 1 or 2 and resolved without complications after appropriate therapy.

Depletion of peripheral blood B cells. Peripheral blood lymphocytes were evaluated by flow cytometry at baseline, 72 hours after the first infusion, and at 1, 2, 6, 9, and 12 months posttreatment. The percentage and absolute number of cells expressing the CD19 and CD20 antigens was determined. Treatment with the chimeric anti-CD20 antibody rapidly and effectively depleted B cells from the peripheral blood circulation as detected by the unrelated anti-CD19 B-cell antibody. In some patients, baseline CD20 cell counts were elevated (due to the presence of circulating lymphoma cells). Most patients had a rapid decrease in the relative percentage and absolute number of CD19$^+$ cells by day 4. This level remained nearly undetectable until approximately 6 months posttreatment, followed by slow gradual recovery.

Serum Ig and complement levels. The CD20 antigen is expressed on early B cells but not upon differentiation to antibody secreting plasma cell. Because of the possibility that the elimination of normal B cells and plasma cell progenitors could affect antibody production, serum Ig (IgG, IgA, and IgM) levels were quantitated at bascline and throughout the study. Mean serum Ig levels remained stable; however, individual patients experienced transient decreases in some subsets. Among these 37 patients, 4, 4, and 5 patients experienced more than a 20% decline in IgG, IgA, or IgM levels, respectively (total of 10 patients with 3 patients having decreases in both IgG and IgA levels).

No clinically significant change in serum complement levels was observed.

Evaluation of immune response (HAMA/HACA). Of the 37 patients evaluated, there were no quantifiable HAMA or HACA titers identified. One patient (with a PR) had a

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Table 3. Summary of Clinical Response

Patient Group	N	CR (%)	PR (%)	CR and PR (%)	95% CI (CR and PR)
Intent to treat	37	3 (8)	14 (38)	17 (46)	30-62%
Evaluable*	34	3 (9)	14 (41)	17 (50)	33-67%

Abbreviation: CI, confidence interval.

* Patients had low-grade or follicular lymphoma and completed four antibody infusions.

detectable, but not a quantifiable (<100 ng/mL) HACA titer 7 months posttreatment. There was no toxicity related to this immune response.

Clinical response. Clinical responses (CR or PR) were observed in 17 of the 37 patients (46%) and are detailed in Table 3. Two patients were withdrawn from the study for adverse events after receiving a single infusion of the antibody and 1 patient had a high-grade B-cell malignancy. Thus, 34 patients completed all four antibody infusions and were considered evaluable for response. All 34 had a low-grade or follicular histology. Three of the 34 patients (9%) had a CR and 14 of 34 (41%) had a PR for an overall response rate for evaluable patients of 50%. An additional 8 patients had some evidence of tumor response (>20% reduction), but did not qualify as responders (PR or CR). Thus, 25 of the 34 evaluable patients (74%) had evidence of antitumor effect. Eleven patients (32%) had stable disease (SD) and 6 patients (18%) were judged to have progressive disease (PD). The median time to onset of clinical response for the 17 responders was 50 days (range, 7 to 112 days). Measured tumor masses continued to regress, with the maximum response in sentinel tumor lesions occurring 3 to 4 months after antibody therapy. The median time to progression for the clinical responders was 10.2 months, with 5 patients exceeding 20 months and 2 patients exceeding 30 months. The median duration of response was 8.6 months. A Kaplan-Meier survival curve for the time to progression is shown in Fig 1 for the clinical responders.

The majority of the patients had follicular histologies. Of 21 patients with follicular small cleaved histology (WF group B), there were 11 PR and 2 CR for a response rate of 62%. Of 9 patients with follicular mixed small and large cell histology (WF group C), there was 1 CR and 3 PR (44%). One of 2 patients with follicular large cell lymphoma (group D) had a PR. The response rate appears similar among the follicular histologies. In contrast, none of 4 patients with small lymphocytic lymphoma (1 with mantle cell histology) had a clinical remission.

There was no clear influence of type of prior therapy on the likelihood of clinical response to antibody treatment. Two of three patients who had been treated previously with high-dose therapy and autologous stem cell rescue achieved a PR to antibody therapy with times to disease progression of 4.2 and 21.7 months. Twenty patients had extranodal disease and two showed a CR and seven showed a PR to antibody therapy. There was a correlation observed between the duration of response to last chemotherapy and response to treatment with IDEC-C2B8 ($P = .05$; Fisher's exact test). Twenty of the 37 patients had a duration of response to last chemotherapy of 6 months or less. Of these 20, 6 (30%) responded to chimeric MoAb therapy. Seventeen of the 37 patients had a duration of response to last chemotherapy of more than 6 months. Of these 17, 11 (65%) responded to IDEC-C2B8.

Antibody pharmacokinetics. At the 375 mg/m^2 dose used in this trial, all studied patients exhibited detectable circulating antibody throughout the treatment period. Preinfusion (doses 2 through 4) antibody concentrations ranged from 0.8 to 517.7 μg/mL and postinfusion levels ranged from 107.8 to 962.7 μg/mL. Five patients consistently had preinfusion antibody levels at or less than 10 μg/mL, suggesting that they did not reach steady state or cleared the antibody at a faster rate. Most patients exhibited increasing preinfusion antibody concentrations with each subsequent infusion.

The Wilcoxon rank sum test was used to examine the relationship between the preinfusion and postinfusion chime-

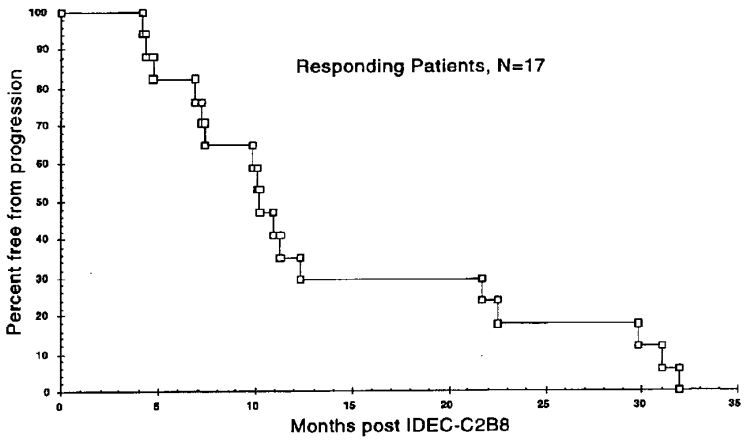

Fig 1. Kaplan-Meier graph of the time to progression from the date of initial treatment with the first dose of IDEC-C2B8 until documented tumor relapse or progression in the 17 clinical responders.

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ric antibody concentrations and the clinical response. A correlation was observed between clinical response and the median values of IDEC-C2B8 serum levels before the second infusion ($P = .029$), with responders having a median of 82.7 μg/mL (range, 1.2 to 125.3 μg/mL) versus nonresponders with a median of 21.9 μg/mL (range, 1.1 to 99.0 μg/mL). Detailed pharmacokinetic sampling was performed on 9 patients, with a mean C_{max} of 500.5 ± 135.2 μg/mL (range, 201.4 to 663.0 μg/mL) and serum antibody half-life values from 12.7 to 370.8 hours (mean $T_{1/2}$ of 225.9 ± 102.7 hours).

DISCUSSION

IDEC-C2B8 represents a new treatment for patients with recurrent low-grade or follicular NHL. This therapy has a response rate in evaluable patients of 50% and a time to progression of 10.2 months. The treatment consists of four intravenous infusions administered over a 22-day period in the outpatient setting with minimal toxicity. This compares favorably with other agents currently in use for the treatment of patients with relapsed disease. These results have recently been confirmed in preliminary reports in a separate phase II/III multicenter trial in more than 150 patients.[21]

The adverse events observed in this trial were predominately infusion related and generally consisted of mild grade 1 or 2 symptoms of fever, chills, rigor, rash, nausea, and, rarely, mild respiratory symptoms or hypotension. All of these side effects were transient and did not interfere with the completion of the planned antibody infusion. Two patients were removed from study after a single dose of the antibody; 1 patient developed thrombocytopenia and an elevated LDH and a second patient with known cardiac disease experienced chest pain and was admitted 1 week later with a myocardial infarction. All other patients completed the planned 4 weekly infusions. The etiology of the observed infusion related symptoms is not completely understood, but may represent the rapid depletion of B cells and lysis in the reticuloendothelial systems of the lung, liver, and spleen. This constellation of symptoms has been seen in other studies using murine MoAbs.[22] The marked decrease in infusional side effects noted with subsequent infusions likely reflects the elimination of most circulating B lymphocytes, the saturation of antigenic sites with the first infusion, and persistent antibody serum levels present at the time of the subsequent antibody infusions.

As expected, normal B cells were rapidly depleted from the peripheral blood of nearly all patients and remained depleted until nearly 6 months posttreatment, followed by a slow recovery. Despite this depletion of B cells, there was minimal change in serum Ig levels and no increase in the frequency or severity of infectious complications. The infections noted in this trial are common to patients with relapsed B-cell lymphoma and are not clearly related to treatment with the antibody. Prolonged B-cell depletion is common to other chemotherapy treatments and after BMT. The type and risk of infection with MoAb treatment appears less than that reported with administration of some of the newer purine analogues (fludarabine and 2-CDA) that are associated with significant depletion of the $CD4^+$ T-cell population.

The patients included in this trial are typical of those represented in the general population and of low-grade patients studied in the Working Formulation Lymphoma Classification Project.[23] The International Prognostic Index (IPI) originally developed for aggressive NHL uses 5 prognostic factors, including age greater than 60 years; stage III/IV disease; performance status greater than 1; elevated LDH level; and extranodal sites greater than 1.[24] It has been applied to patients with low-grade NHL and permits prognostic stratification into risk groups.[25] Using data from presentation, we were able to determine the IPI classification in 32 of the 37 patients included in this trial. As expected, in patients with low-grade NHL, the majority of patients were in the low (41%) and low-intermediate (27%) prognostic groups, followed by those in intermediate/high (16%), high (3%), and unknown (14%) groups. There was no statistically significant correlation (Fisher's exact test, $P = .31$) between the risk groups and response to treatment with IDEC-C2B8. However, there was a correlation observed between the duration of response to last chemotherapy and the response to IDEC-C2B8. Patients with less than a 6-month response to last chemotherapy had a 30% response rate, compared with a 65% response rate for patients with last duration of remission of greater than 6 months. In contrast with the experience with some MoAbs, antitumor activity was observed in patients with bulky disease and in poor prognostic patients who had relapsed after anthracycline-containing regimens or after high-dose therapy with stem cell support. Tumor responses were noted in patients with bulky lymph nodes, splenomegaly, extranodal masses, and lymphoma in blood and bone marrow.

A correlation was also observed between the level of IDEC-C2B8 present in the serum before infusion number 2 and the response to MoAb therapy. Whether this is due to differences in tumor burden or to differences in intrinsic clearance of the MoAb is unknown. All 17 clinical remissions occurred in patients with a follicular histology (WF groups B-D), although the number of patients with other histologies was small. In contrast, none of the 4 patients with small lymphocytic lymphoma (WF group A) responded. These patients had heterogenous disease, including 1 patient with mantle cell histology. Although patients with chronic lymphocytic leukemia (CLL) were excluded from this trial (based on the presence of >5,000 lymphocytes/μL for this histologic subgroup), it is possible that the decreased response rate in this subgroup was due to a lower expression of the CD20 surface antigen that has been observed in cases of CLL.

The method of tumor cell killing by the MoAb is not completely understood and likely involves several mechanisms. The chimeric MoAb was engineered to contain human IgG1 constant regions to augment immune-mediated antitumor activity using human complement and human ADCC effector cells.[16] In vitro, the antibody clearly exhibits much greater activity than the parent murine IgG1 MoAb in these assays. However, in this clinical trial, there were no significant changes in serum complement levels observed after the MoAb treatments. In addition, in earlier phase I trials, tumor biopsies 2 weeks posttreatment showed antibody bound to tumor cells in patients thought to be immunocompetent who

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did not have a clinical remission.[18] The CD20 molecule is thought to aggregate on the cell surface and create or control a Ca^{2+} channel that is important in initiation and progression through the cell cycle.[26] Antibodies binding to CD20 may directly inhibit the cell cycle.[27] Recent data using IDEC-C2B8 have shown that the antibody inhibits proliferation and directly induces apoptosis in some B-cell NHL lines in vitro.[17] The degree to which this additional antitumor mechanism contributes to the observed clinical remissions is unknown and is actively being evaluated in the laboratory.

The optimal treatment for patients with advanced-stage or relapsed low-grade NHL remains unsettled. Diverse options, from watch and wait to treatment with aggressive chemotherapy, are frequently used.[1] Although most patients initially respond to a variety of chemotherapeutic regimens with a PR or CR, all will eventually relapse and require additional treatment with decreasing response rates and decreasing durations of remission. Aggressive combination chemotherapy produces higher CR rates, and high-dose therapy with stem cell or bone marrow support may result in longer durations of remission. Unfortunately, most trials of such aggressive therapies have shown continued risk of relapse without a convincing plateau on the failure-free survival curve.[2] An exception may be allogenic BMT, but this treatment is restricted to younger patients with an appropriate donor and carries a high risk of morbidity and mortality.[28] Most patients undergo a series of treatments with increasing toxicity and decreasing bone marrow reserve until they ultimately become refractory to treatment and die of disease progression or from complications of treatment.

IDEC-C2B8 chimeric anti-CD20 MoAb presents the opportunity to obtain meaningful tumor reductions with minimal toxicity in patients with relapsed low-grade NHL. Retreatment is possible and early experience suggests that a majority of patients with a prior response may respond to retreatment. Fludarabine has also been studied in patients with relapsed disease, with an overall response rate of approximately 40%.[29,30] Time to treatment failure was 4.6 months in one study.[31] Treatment complications from fludarabine included infections or fever of unknown origin in 62% of patients, bone marrow suppression, and opportunistic infections. Similar responses have been observed with cladribine; however, marked immunosuppression and hematologic toxicity was noted.[32,33]

To date, experience using IDEC-C2B8 has been predominately in patients with relapsed measurable disease. A clinical trial combining IDEC-C2B8 with 6 cycles of CHOP chemotherapy in newly diagnosed patients has recently been completed. Early evaluation of this experience suggests that this combination resulted in a PR or CR in all patients and in the clearance of polymerase chain reaction-detectable cells from the peripheral blood and bone marrow in 7 of 8 patients with a positive pretreatment assay.[34] It remains to be determined if this will ultimately decrease the risk of relapse or prolong disease-free survival. Additional areas that should be investigated using this new agent include (1) extended and repeated dosing regimens, (2) combination with or after standard chemotherapy, (3) use as an in vivo B-cell purging agent before collection of bone marrow or stem cells for high-dose therapies, (4) evaluation in other B-cell histologies, and (5) lymphomas arising in association with immunodeficiency such as acquired immunodeficiency syndrome or organ transplantation.

In conclusion, this experience using an engineered chimeric MoAb finally provides practical substance to the promise of antibody therapy of cancer that was envisioned nearly 100 years ago by Ehrlich.[35]

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blood® 1997 90: 2188-2195

IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients With Relapsed Low-Grade Non-Hodgkin's Lymphoma

David G. Maloney, Antonio J. Grillo-López, Christine A. White, David Bodkin, Russell J. Schilder, James A. Neidhart, Nalini Janakiraman, Kenneth A. Foon, Tina-Marie Liles, Brian K. Dallaire, Ken Wey, Ivor Royston, Thomas Davis and Ronald Levy

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ANNEX I: Commercial monoclonal antibodies 2006 (all modes of administration)

Antibody	Trade name	Year	Concentration [mg/ml] *	Concentration range [mg/ml]			
				0.1 - 50	0.5 - 25	2 - 10	10
Gemtuzumab ozogamicin	Mylotarg	2000	0.25	X			
Indium-111 capromab pendetide	ProstaScint	1996	0.5	X	X		
Satumomab pendetide	OncoScint	1992	0.5	X	X		
Muromomab-CD3	Orthoclone OKT	1986	1	X	X		
Acrituomab; Tc-99	CEA-Scan	1996	1.25	X	X		
Ibritumomab-Tiuxetan	Zevalin		1.6	X	X		
Abciximab	ReoPro	1994	2	X	X	X	
Cetuximab	Erbitux	2004	2	X	X	X	
Basiliximab	Simulect	1998	4	X	X	X	
Daclizumab	Zenapax	1997	5	X	X	X	
Alemtuzumab	Campath	2001	10	X	X	X	X
Infliximab	Remicade	1998	10	X	X	X	X
Nofetumomab	Verluma	1996	10	X	X	X	X
Ranibizumab	Lucentis	2006	10	X	X	X	X
Rituximab	Rituxan	1997	10	X	X	X	X
Tositumomab and I-131 Tositumomab	Bexxar	2003	14	X	X		
Natalizumab	Tysabri	2004	20	X	X		
Trastuzumab	Herceptin	1998	21	X	X		
Bevacizumab	Avastin	2004	25	X	X		
Adalimumab	Humira	2002	50	X			
Efalizumab	Raptiva	2003	100				
Palivizumab	Synagis	1998	100				
Omalizumab	Xolair		125				
Number of antibodies (total number: 23)				**20**	**18**	**9**	**5**
Proportion of all antibodies				**87 %**	**78 %**	**39 %**	**22 %**

* Liquid form or after reconstitution

Exhibit no. ANNEX I
of the letter / report / expert opinion / plaint / defense
dated 09.08.2017
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81925 München, Arabellastr. 30

ANNEX II: Commercial monoclonal antibodies 2006 (for intravenous administration)

Antibody	Trade name	Year	Concentration [mg/ml] *	Concentration range [mg/ml]			
				0.1 - 50	0.5 - 25	2 - 10	10
Gemtuzumab ozogamicin	Mylotarg	2000	0.25	X			
Indium-111 capromab pendetide	ProstaScint	1996	0.5	X	X		
Satumomab pendetide	OncoScint	1992	0.5	X	X		
Muromomab-CD3	Orthoclone OKT	1986	1	X	X		
Acrituomab; Tc-99	CEA-Scan	1996	1.25	X	X		
Ibritumomab-Tiuxetan	Zevalin		1.6	X	X		
Abciximab	ReoPro	1994	2	X	X	X	
Cetuximab	Erbitux	2004	2	X	X	X	
Basiliximab	Simulect	1998	4	X	X	X	
Daclizumab	Zenapax	1997	5	X	X	X	
Alemtuzumab	Campath	2001	10	X	X	X	X
Infliximab	Remicade	1998	10	X	X	X	X
Nofetumomab	Verluma	1996	10	X	X	X	X
Rituximab	Rituxan	1997	10	X	X	X	X
Tositumomab and I-131 Tositumomab	Bexxar	2003	14	X	X		
Natalizumab	Tysabri	2004	20	X	X		
Trastuzumab	Herceptin	1998	21	X	X		
Bevacizumab	Avastin	2004	25	X	X		
Number of antibodies (total number: 18)				**18**	**17**	**8**	**4**
Proportion of all antibodies				**100 %**	**94 %**	**44 %**	**22 %**

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Document details: Country/Office: US
Number: 60/783,070
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Date of receipt at the International Bureau: 25 May 2007 (25.05.2007)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

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APPLICATION NUMBER: ***60/783,070***
FILING DATE: ***March 15, 2006***
RELATED PCT APPLICATION NUMBER: ***PCT/US07/06606***

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Express Mail Label No. ED 481024650 US

112987 U.S.PTO 60/783070 031506

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Leonard	Bell	Woodbridge, Connecticut
Russell P.	Rother	Prospect, Connecticut

Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max):

IMPROVEMENT IN QUALITY OF LIFE OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS TREATED WITH AN INHIBITOR OF COMPLEMENT

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ The address corresponding to Customer Number:

OR

☑ Firm or Individual Name Stephen A. Saxe

Address Alexion Pharmaceuticals, Inc.
352 Knotter Drive

City	State	Zip
Cheshire	Connecticut	06410
Country U.S.A.	Telephone 203-271-8289	Email saxes@alxn.com

ENCLOSED APPLICATION PARTS *(check all that apply)*

☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number of CDs _____
☑ Specification *Number of Pages* 32
☐ Other (specify) _____
☑ Drawing(s) *Number of Sheets* 4

Fees Due: Filing Fee of $200 ($100 for small entity). If the specification and drawings exceed 100 sheets of paper, an application size fee is also due, which is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

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SIGNATURE Stephen A. Saxe Date March 15, 2006

TYPED or PRINTED NAME Stephen A. Saxe REGISTRATION NO. 38,609 *(if appropriate)*

TELEPHONE 203-271-8289 Docket Number: 114 CIP2 PRO

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FEE TRANSMITTAL
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☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 100.00

Complete if Known	
Application Number	Not yet assigned
Filing Date	March 15, 2006
First Named Inventor	Leonard Bell
Examiner Name	Not yet assigned
Art Unit	N/A
Attorney Docket No.	114 CIP2 PRO

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Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	100.00

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Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

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HP = highest number of total claims paid for, if greater than 20.

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
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Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	0

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Non-English Specification, $130 fee (no small entity discount)	0
Other (e.g., late filing surcharge): _____	0

SUBMITTED BY

Signature	Stephen A. Saxe	Registration No. (Attorney/Agent) 38,609	Telephone 203-271-8289
Name (Print/Type)	Stephen A. Saxe		Date March 15, 2006

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Application Number	Not yet assigned
Filing Date	March 15, 2006
First Named Inventor	Leonard Bell
Art Unit	N/A
Examiner Name	N/A
Attorney Docket Number	114 CIP2 PRO

ENCLOSURES *(Check all that apply)*

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Remarks

Total pages (41) equals 32 pages of specification, 4 sheets of drawings, 2 pages of Provisional Application for Patent Cover Sheet, 1 page of Fee Transmittal, 1 page of Transmittal Form and 1 page of Certificate of Express Mailing. Additionally, a Return Receipt Postcard is enclosed.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Stephen A. Saxe, Alexion Pharmaceuticals, Inc.		
Signature	Stephen a. Saxe		
Printed name	Stephen A. Saxe		
Date	March 15, 2006	Reg. No.	38,609

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Typed or printed name	Stephen A. Saxe	Date	March 15, 2006

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Docket No.: 114 CIP2 PRO

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Leonard BELL and Russell P. ROTHER		
Serial No.:	Unassigned	Examiner:	Unassigned
Filed:	March 15, 2006	Art Unit:	Unassigned

For: **IMPROVEMENT IN QUALITY OF LIFE OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS TREATED WITH AN INHIBITOR OF COMPLEMENT**

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Stephen A. Saxe

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352 Knotter Drive
Cheshire, CT 06410
Tel. 203-271-8289

IMPROVEMENT IN QUALITY OF LIFE OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS TREATED WITH AN INHIBITOR OF COMPLEMENT

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disease that results from clonal expansion of hematopoietic stem cells with somatic mutations in the X-linked gene called PIG-A.[1,2] Mutations in PIG-A lead to an early block in the synthesis of glycosylphosphatidylinositol (GPI)-anchors, which are required to tether many proteins to the cell surface. Consequently, PNH blood cells have a partial (type II) or complete (type III) deficiency of GPI-anchored proteins.

Intravascular hemolysis is a prominent feature of PNH and a direct result of the absence of the GPI-anchored complement regulatory protein CD59.[3,4] Under normal circumstances, CD59 blocks the formation of the terminal complement complex (also called the membrane attack complex) on the cell surface, thereby preventing erythrocyte lysis and platelet activation.[5-8] Excessive or persistent intravascular hemolysis in PNH patients not only results in anemia (normal ranges of hemoglobin are 14-18 g/dL for men and 12-16 g/dL for women, and persons with lower levels are considered to be anemic), but also hemoglobinuria and clinical sequelae related to the release of the erythrocyte contents into the circulation: fatigue, thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9,10,21,22] Indeed, impaired quality of life in PNH is disproportionate to the degree of anemia. Many PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels. There have been no therapies that effectively reduce intravascular hemolysis and improve the associated clinical morbidities in PNH.

Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5.[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

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SUMMARY

The present pivotal, phase III study, Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH), evaluated the effect of eculizumab on the stabilization of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of 87 transfusion-dependent PNH patients. Measures of intravascular hemolysis and quality of life were also assessed. This is the first placebo controlled study of a PNH patient population to control hemolysis and to differentiate between the effects due to hemolysis and the effects due to anemia.

It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-B show that eculizumab treatment decreases intravascular hemolysis and increases PNH type III erythrocytes. Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels.

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Figure 1B shows the mean proportion of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients.

Figure 2 shows the effect of eculizumab treatment on transfusion requirements in PNH patients. This is a Kaplan-Meier plot of time to first transfusion for eculizumab- and placebo-treated patients from baseline through week 26. The P value is from the log rank analysis.

Figure 3 shows the effect of eculizumab on fatigue assessed by the FACIT-Fatigue Instrument. Quality of Life scores were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. Values for change from baseline to 26 weeks represent least-square means. A positive change indicates an improvement and a negative change indicates deterioration in the FACIT-Fatigue measures of quality of life.

DETAILED DESCRIPTION

The present disclosure relates to a method of treating paroxysmal nocturnal hemoglobinuria ("PNH"), more specifically to improving certain aspects of quality of life which are impaired in PNH patients, and other hemolytic diseases in mammals. Specifically, the methods of treating hemolytic diseases, which are described herein, involve using compounds which bind to or otherwise block the generation and/or activity of one or more complement components. The present methods have been found to provide surprising results. For instance, hemolysis rapidly ceases upon administration of the compound which binds to or otherwise blocks the generation and/or activity of one or more complement components, with hemoglobinuria being significantly reduced after treatment. Also, hemolytic patients can be rendered less dependent on transfusions or transfusion-independent for extended periods (twelve months or more), well beyond the 120 day life cycle of red blood cells. In addition, type III red blood cell count can be increased dramatically in the midst of other mechanisms of red blood cell lysis (non-complement mediated and/or earlier complement component mediated e.g., Cb3). Another example of a surprising result is that symptoms resolved, indicating that NO serum levels were increased enough even in the presence of other mechanisms of red

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blood cell lysis. These and other results reported herein are unexpected and could not be predicted from prior treatments of hemolytic diseases.

Any compound which binds to or otherwise blocks the generation and/or activity of one or more complement components can be used in the present methods. A specific class of such compounds which is particularly useful includes antibodies specific to a human complement component, especially anti-C5 antibodies. The anti-C5 antibody inhibits the complement cascade and, ultimately, prevents red blood cell ("RBC") lysis by the complement protein complex C5b-9. By inhibiting and/or reducing the lysis of RBCs, the effects of PNH and other hemolytic diseases (including symptoms such as hemoglobinuria, anemia, hemoglobinemia, dysphagia, fatigue, erectile dysfunction, recurrent abdominal pain and thrombosis) are eliminated or decreased.

Also useful in the present methods are naturally occurring or soluble forms of complement inhibitory compounds such as CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. Other compounds which may be utilized to bind to or otherwise block the generation and/or activity of any of the human complement components include, but are not limited to, proteins, protein fragments, peptides, small molecules, RNA aptamers including ARC187 (which is commercially available from Archemix Corp., Cambridge, Mass.), L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, molecules which may be utilized in RNA interference (RNAi) such as double stranded RNA including small interfering RNA (siRNA), locked nucleic acid (LNA) inhibitors, peptide nucleic acid (PNA) inhibitors, etc.

The complement system, useful complement inhibitors, and use of these inhibitors to treat PNH and other patients are more fully described in PCT Patent Application PCT/US2005/003225 filed February 3, 2005 and published as International Publication Number WO 2005/074607 A2 on August 18, 2005, the contents of which are incorporated herein by reference in their entirety.

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I. METHODS

Patient Selection

The TRIUMPH trial consisted of a 2-week screening period, an observation period of up to 3 months duration, and a 26-week treatment period.

During the screening period, patients were evaluated with respect to inclusion and exclusion criteria. Men and women, 18 years or older, diagnosed as having PNH with a type III erythrocyte population of ≥10%, and who had received at least 4 transfusions in the previous 12 months were eligible. Concomitant administration of erythropoietin, immunosuppressants, corticosteroids, coumadin, low molecular weight heparin, iron supplements, and folic acid were not reasons for exclusion, provided the doses were steady prior to the first visit and throughout the duration of the study. Because of the increased frequency of neisserial infections in individuals genetically deficient in terminal complement proteins, all patients were vaccinated against *Neisseria meningitides*. Patients were to avoid conception. The protocol was approved by an Investigational Review Board at each clinical site and written informed consent was obtained from all patients enrolled.

Patients transfused with a mean pre-transfusion hemoglobin level >10.5 g/dL over the previous 12 months, and those who showed evidence of having a suppressed immune response, complement deficiency, or active bacterial infection, including any history of meningococcal disease, were excluded from the study. Patients were also not eligible if they had previously received a bone marrow transplant or if they had participated in another trial or received another investigational drug within 30 days of the first visit. An individualized transfusion algorithm was calculated for each patient based on their prior 12-month transfusion history; the written algorithm documented the number of packed red blood cell (PRBC) units transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during observation and treatment periods.

Each patient considered eligible entered an observation period of up to 13 weeks in order to confirm their PBRC transfusion dependence. At least one transfusion --termed the "qualifying" transfusion-- during the 13-week observation period at a hemoglobin value at or below 9 g/dL with symptoms, or at or below 7 g/dL with or without symptoms, in accordance with the transfusion algorithm indicated for each patient, was a

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requirement to proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set point" for that individual for the purpose of the primary efficacy variable. A platelet count ≥100,000/mL and a LDH level ≥1.5 times the upper limit of the normal range were also required either at screening or during the observation period for eligibility.

Study Design

Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Measures of Clinical Efficacy

There were two co-primary endpoints in the study: (1) stabilization of hemoglobin levels, defined as a hemoglobin value maintained above the individual hemoglobin set point in the absence of transfusions for the entire 26-week treatment period, and (2) reduction in units of PRBCs transfused during the 26-week treatment phase of the study. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia and reached their individualized, pre-determined "set point". Pre-specified secondary endpoints included transfusion avoidance, hemolysis as measured by LDH area under the curve from baseline to 26 weeks, and QoL changes as measured from baseline to 26 weeks using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.[13] Pre-specified exploratory analyses included assessment of the EORTC QLQ-C30 instrument,[14] the change in LDH from baseline through week 26, and thrombosis. Other pre-specified measurements included pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. Time to first transfusion during

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the 26-week treatment phase and the proportion of PNH type III blood cells were also assessed.

Safety Assessments

Treatment-emergent adverse events, clinical laboratory tests (e.g., serum chemical analyses and complete blood counts), electrocardiogram data, and vital signs were assessed. Adverse events were defined using the MedDRA preferred terms and tabulated as incidence rates per treatment group.

Statistical Analysis

For co-primary endpoints, analyses were performed according to the intention to treat using the data from all patients who were randomized and received study drug; stabilization of hemoglobin levels was analyzed using the Fisher's exact test and total PRBC units transfused were analyzed with the Wilcoxon's rank sum test. For comparison of treatment effect on transfusion avoidance, the Fisher's exact test was used on the incidence and the log rank test was used for time to first transfusion. For LDH area under the curve the Wilcoxon's rank sum test was used.

Quality of life measure of fatigue was assessed using the scoring guidelines for the FACIT-Fatigue instrument.[15] Assessment of quality of life measures based on the EORTC QLQ-C30 instrument was conducted in accordance with the appropriate scoring guidelines.[16] The changes of FACIT-Fatigue and EORTC QLQ-C30 scores from baseline through 26 weeks were analyzed using a mixed model, with baseline as covariate, treatment and time as fixed effects, and patient as a random effect. Changes in LDH levels and PNH type III erythrocytes from baseline through 26 weeks were analyzed using the same mixed model. Two-sided tests were used for all analyses. The adverse events and long-term safety checklist were tabulated separately and compared between treatments using the Fisher's exact test. A p-value ≤ 0.05 was considered to be statistically significant.

II. RESULTS

Characteristics of Patients

A total of 115 PNH patients were screened. Six patients did not meet the inclusion/exclusion criteria during the screening period. Twenty-one other patients did

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not receive a qualifying transfusion and were not randomized into the treatment phase. One patient who did not meet the inclusion criteria was inadvertently randomized, but did not receive study medication. Thus 87 hemolytic PNH patients (35 men and 52 women) were enrolled and randomized to receive either eculizumab (N=43) or placebo (N=44), exceeding the original target of 75 randomized patients.

Patient characteristics were similar in the eculizumab- and placebo-treated cohorts: median age, 41 (range 20-85) and 35 (range 18-78) years; median duration of PNH, 4.2 (range 0.8 to 29.7) and 9.2 (range 0.4 to 38.3) years; patients with history of aplastic anemia, 4 and 11; history of myelodysplastic syndrome, 1 and 0; and history of thrombosis, 9 (16 events) and 8 (11 events). Stable usage of concomitant medications at baseline in the eculizumab- and placebo-treated groups included the following: erythropoietin, 3 patients and 0 patients; cyclosporine, 1 and 1; anticoagulants (coumarins or heparins) 21 and 11; and steroids (glucocorticoids or androgenic steroids), 12 and 12, respectively.

Of the 87 patients randomized, 85 completed the trial. Two patients who did not complete the trial had been randomized to the eculizumab arm: one patient discontinued due to the inconvenience of travel to the study site and the second patient became pregnant. Ten patients in the placebo-treatment group discontinued infusions, in all cases due to perceived lack of efficacy, but they remained in the study for monitoring purposes.

Pharmacokinetics/Pharmacodynamics

In 42 of the 43 eculizumab-treated patients the levels of drug during the maintenance period (900 mg every 2 weeks±2 days) were sufficient to completely block serum hemolytic activity (mean trough value at week 26 of 101.8 μg/mL). A single patient did not sustain therapeutic trough levels of eculizumab and demonstrated a breakthrough in complement blockade during the last few days of each dosing interval. These breakthroughs were clinically manageable and quickly resolved following the next dose.

Hemolytic Efficacy Variables

The impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an immediate (one week) and sustained decrease in mean levels of LDH (Figure 1A). The median LDH

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area under the curve during the 26-week study period was reduced 85.8% in eculizumab-relative to placebo-treated patients (P<0.001). The mean LDH level decreased from 2199.7±157.7 IU/L at baseline to 327.3±67.6 IU/L by 26 weeks in eculizumab-treated patients while levels in placebo-treated patients remained consistently elevated with values of 2259.0±158.5 IU/L at baseline and 2418.9±140.3 IU/L at 26 weeks (P<0.001, for eculizumab versus placebo). A second biochemical measure of hemolysis, serum aspartate aminotransferase (AST), also showed a statistically significant improvement following eculizumab- versus placebo-treatment (data not shown). Haptoglobin levels were statistically significantly increased in eculizumab- as compared to placebo-treated patients but mean levels of haptoglobin were still below normal levels in eculizumab-treated patients (data not shown).

Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels (±standard error) from baseline (study week 0) to week 26 for both eculizumab- and placebo-treated patient populations. Screening occurred up to 3 months prior to study week 0. The upper limit of the normal range (103-223 IU/L) for LDH is indicated by a dashed line. LDH was reduced to a mean level just above the upper limit of normal at week 26 for eculizumab-treated patients; 15 of 41 patients who completed the study demonstrated LDH levels within the normal range. All placebo-treated patients remained at least 5 times above the upper limit of normal at week 26. The P value is based on a mixed model analysis from baseline through week 26. Figure 1B shows the mean proportion (±standard error) of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients. The screening visit occurred up to 3 months prior to study week 0. The P value is based on a mixed model analysis from baseline through week 26.

A corollary to the reduction in intravascular hemolysis during eculizumab treatment was an observed increase in the PNH type III erythrocyte population (Figure 1B). The mean proportions of type III erythrocytes increased from 28.1±2.0% at baseline to 56.9±3.6% by week 26 for eculizumab-treated patients while proportions in the placebo group remained constant with mean values of 35.7±2.8% before treatment to 35.5±2.8% at 26 weeks (P<0.001, for eculizumab versus placebo). By contrast, the proportions of PNH type III granulocytes and monocytes did not change significantly

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between the treatment groups during the treatment period and were greater than 90% at week 26.

III. CLINICAL EFFICACY

Co-primary endpoints

The co-primary efficacy endpoints in the TRIUMPH trial were stabilization of hemoglobin levels and reduction in PRBC units transfused. At the end of the treatment period, 48.8% of eculizumab-treated patients had maintained levels of hemoglobin above the pre-specified set-point (median set-point value of 7.7 g/dL for both treatment groups) in the absence of transfusions, whereas stabilization of hemoglobin did not occur in any of the patients in the placebo group ($P<0.001$; Table 1). By week 26, the median of PRBC units transfused per patient was 0 in the eculizumab group and 10.0 in the placebo cohort ($P<0.001$), while the mean of PRBC units transfused was 3.0 and 11.0 in the eculizumab and placebo cohorts, respectively. In the 6-month period prior to the study, the median of PRBC units transfused per patient was 9.0 in the eculizumab cohort and 8.5 in placebo patients while the mean of PRBC units transfused was 9.6±0.6 and 9.7±0.7, respectively. Mean hemoglobin levels were similar between the treatment groups at baseline (10.0±1.8 g/dL in eculizumab-treated patients and 9.7±1.8 g/dL in placebo-treated patients) and did not substantially change by week 26 (10.1±2.5 g/dL and 8.9±2.2 g/dL in eculizumab and placebo cohorts, respectively).

The median time to first transfusion was not reached during the study period in eculizumab-treated patients (it was greater than 26 weeks) while the placebo group reached the median time to first transfusion in only 4 weeks ($P<0.001$; Figure 2). Transfusion avoidance was achieved in 51.2% and 0% of the eculizumab and placebo cohorts, respectively ($P<0.001$). By the end of the 26-week treatment period, the total PRBC units transfused were 131 in eculizumab-treated patients versus 482 in the placebo group (Table 1). By contrast, in the 6-month period prior to the study, total PRBC units transfused in the eculizumab- and placebo-cohorts were 413 and 417, respectively.

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Table 1

Stabilization of Hemoglobin Levels and Reduction

in Transfusion Requirements during Eculizumab Treatment

	PRE-TREATMENT HISTORY*		TREATMENT PERIOD		
	Placebo	Eculizumab	Placebo	Eculizumab	P Value
†Stabilization of Hemoglobin Levels in the absence of transfusions (percent of patients)	NA	NA	0	48.8	<0.001‡
†Units Transfused per Patient					
Median	8.5	9.0	10	0	<0.001§
Mean±SE	9.7±0.7	9.6±0.6	11.0±0.83	3.0±0.67	
Total Units Transfused per Group	417	413	482	131	

*Twelve month historical transfusion data normalized to 6 months

†Co-primary endpoints

‡Base on 2-sided Fisher's exact test

§Based on Wilcoxon's rank sum test

NA, not applicable

Improvements in quality of life measures

Assessments of quality of life in PNH patients during eculizumab treatment were performed using two different instruments, FACIT-Fatigue and the EORTC QLQ-C30. Eculizumab-treated patients showed a mean increase (improvement) in the FACIT-Fatigue score of 6.4±1.2 points from baseline to 26-weeks while the mean score in placebo patients decreased by 4.0±1.7 points, a total difference between the treatment groups of 10.4 points (Figure 3). Mixed model analysis of covariance demonstrated a statistically significant difference between treatment groups (P<0.001).

For the EORTC instrument, improvements were observed with eculizumab-treatment in each subscale. Statistically significant improvements with eculizumab-

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compared with placebo-treated groups were observed in the following quality of life subscales (Table 2): global health status (P<0.001), physical functioning (P<0.001), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P<0.001), social functioning (P=0.003), fatigue (P<0.001), pain (P=0.002), dyspnea (P<0.001), appetite loss (P<0.001), and insomnia (P=0.014). The improvements with eculizumab treatment in the other scales, including nausea and vomiting, diarrhea, constipation, and financial difficulties, did not reach statistical significance.

Table 2

Effect of Eculizumab Treatment on

Quality of Life Assessed by the EORTC QLQ-C30 Instrument

	Mean Change from Baseline to Week 26*			
	Placebo	**Eculizumab**	**Absolute Difference**	**P Value†**
Global Health Status	-8.5	10.9	19.4	<0.001
Functional				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.6	=0.003
Cognitive	-6.1	7.9	14.0	=0.002
Physical	-3.5	9.4	13.0	<0.001
Emotional	-3.7	7.5	11.2	=0.008
Symptoms/Single Items				
Fatigue	10.0	-16.9	27.0	<0.001
Pain	5.3	-12.3	17.6	=0.002
Dyspnea	8.9	-7.9	16.9	<0.001
Appetite Loss	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	=0.014

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Financial Difficulties	0.0	-10.3	10.3	=0.186
Constipation	0.0	-6.3	6.3	=0.199
Nausea/vomiting	2.8	-0.4	3.2	=0.056
Diarrhea	5.7	4.8	0.9	=0.147

*A positive change indicates an improvement in global health status and functional scales and a negative change indicates an improvement in symptom and single item scales.

†Based on a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect and baseline as a covariate.

Relationship between FACIT-Fatigue quality of life and intravascular hemolysis

In order to determine if there was a treatment independent relationship between the FACIT-Fatigue quality of life instrument and intravascular hemolysis, an analysis was performed whereby the mean LDH level (through the 26 week study period) for each TRIUMPH patient was analyzed as a function of the patient's respective mean change in FACIT-Fatigue score from baseline (through the 26 week study period) (see Table 3). For this analysis, mean levels of LDH were divided into 4 groups that included: normal levels, 1-2 times the upper limit of normal (ULN), 2-10 times the upper limit of normal, and greater than 10 times the upper limit of normal. The analysis demonstrated that patients who maintained normal LDH levels throughout the study experienced significant improvements in fatigue when compared to patients who had incrementally higher levels of LDH throughout the study ($p=0.0048$). These data establish a clear link between increasing intravascular hemolysis as measured by LDH levels and decreased quality of life as measured by the FACIT-Fatigue quality of life instrument.

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Table 3

Relationship between FACIT-Fatigue and Intravascular Hemolysis

		Change of FACIT from Baseline		
Treatment Group	LDH Category	< 4	>= 4	P Value
Combined	Normal	4 (30.77%)	9 (69.23%)	.0048
	1 - 2 X ULN	16 (61.54%)	10 (38.46%)	
	2 - 10 X ULN	18 (72.00%)	7 (28.00%)	
	> 10 X ULN	16 (80.00%)	4 (20.00%)	

Safety

There were no deaths in the study. Serious adverse events (SAEs) were reported for 13 patients, of which 4 occurred in the eculizumab-treated cohort and 9 were in the placebo-treated cohort (see Table 4). All patients recovered without sequelae.

The most common AEs reported for eculizumab-treated patients were headache, nasopharyngitis, back pain, and upper respiratory tract infection. Headache and back pain occurred more commonly in the eculizumab-treatment group compared with the placebo group. However, the increase in headaches was limited to the first 2 weeks of therapy and was mild to moderate. There were no statistically significant differences in incidents rates between treatment groups for any AEs reported.

One episode of thrombosis (Budd-Chiari) occurred in a placebo-treated patient. There were no thromboses in eculizumab-treated patients.

Only one patient showed a detectable level of anti-eculizumab antibodies in the eculizumab-treated cohort; this response was weak (did not titrate), occurred at only one time point and did not result in a disruption of complement blockade.

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Table 4

Adverse Event Reporting

SERIOUS ADVERSE EVENTS*	Placebo Patients n (percent)	Eculizumab Patients n (percent)
Total	9 (20.5)	4 (9.3)
Eculizumab treatment emergent		
Exacerbation of PNH	3 (6.8)	1 (2.3)
Renal colic	0	1 (2.3)
Lumbar sacral disc prolapse	0	1 (2.3)
Alpha streptococcal bacteremia	0	1 (2.3)
Central line infection and UTI	1 (2.3)	0 (0)
Upper respiratory tract infection	1 (2.3)	0 (0)
Probable viral infection	1 (2.3)	0 (0)
Neutropenia	1 (2.3)	0 (0)
Cellulitis / folliculitis / neutropenia	1 (2.3)	0 (0)
Anemia and pyrexia	1 (2.3)	0 (0)
MOST FREQUENT ADVERSE EVENTS*†		
Headache§	12 (27.3)	19‡ (44.2)
Nasopharyngitis	8 (18.2)	10 (23.3)
Upper respiratory tract infection	10 (22.7)	6 (14)
Back pain	4 (9.1)	8 (18.6)
Nausea	5 (11.4)	7 (16.3)
Cough	4 (9.1)	5 (11.6)
Diarrhea	5 (11.4)	4 (9.3)
Arthralgia	5 (11.4)	3 (7.0)
Abdominal pain	5 (11.4)	2 (4.7)
Dizziness	5 (11.4)	2 (4.7)
Vomiting	5 (11.4)	2 (4.7)

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Fatigue	1 (2.3)	5 (11.6)
Viral infection	5 (11.4)	1 (2.3)

*By preferred terms

†Occurring in 10% or more of patients

‡Sixteen of 19 patients experienced headache within 48 hours of infusion

§Following the first 2 weeks of dosing, 20.9% of eculizumab- and 22.7% of placebo-treated patients experienced headache

IV. DISCUSSION

Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44% reduction in the rate of transfusion (data now shown).

Lactate dehydrogenase, a biochemical marker of hemolysis in PNH,[9] was immediately and consistently decreased in all eculizumab-treated patients, while patients in the placebo cohort continued to hemolyze with levels of LDH exceeding 5 times the upper limit of the normal range in all patients at the study end. Levels of LDH were reduced into the normal range in approximately one-third of eculizumab-treated patients, while the remainder stabilized at a level just above the upper limit of normal suggesting residual low level hemolysis in some patients. Levels of haptoglobin, a more sensitive marker of the presence of cell free hemoglobin in the circulation, were undetectable in most patients. Low level hemolysis in a subset of eculizumab-treated patients is possibly

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due to an inherent decrease in survival of these cells or C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.[17]

Before eculizumab treatment, hemoglobin levels in study patients were artificially maintained by frequent transfusion. Therefore, stabilization of hemoglobin levels with a concomitant cessation of or reduction in transfusions represents a net increase in endogenous hemoglobin levels. Our data suggest that resolution of hemolysis with eculizumab results in a new steady state hemoglobin level determined by a balance between the extent of the underlying bone marrow dysfunction, the number of PNH erythrocytes that are preserved by eculizumab therapy and the new level (if any) of transfusion requirement.

Patients with PNH generally experience markedly impaired quality of life characterized by fatigue, anemia, thrombosis, and pulmonary hypertension as well as smooth muscle dystonia including abdominal pain, dysphagia, and erectile dysfunction.[9,10,18] These symptoms have been attributed to both excessive intravascular hemolysis and downstream scavenging of nitric oxide by cell free hemoglobin in plasma. The reduction of intravascular hemolysis in eculizumab-treated patients in the current study was associated with significant improvements in the fatigue component of quality of life relative to placebo-treated patients as assessed via the FACIT-Fatigue instrument. Further, eculizumab therapy was associated with a median increase of 6.4 points over baseline values established before treatment. It has previously been demonstrated that an increase of 3 or more points from baseline represents a clinically important difference in this quality of life instrument.[19] Patients who received eculizumab also experienced a significant improvement in most domains of the EORTC QLQ-30 relative to the placebo-treated cohort including global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and insomnia. Improvement in the fatigue component of the EORTC QLQ-30 provides support for the improvement demonstrated in the FACIT-Fatigue instrument during eculizumab therapy. Importantly, these improvements in quality of life in the eculizumab-treated patients occurred despite similar levels of erythrocyte hemoglobin in the two treatment groups, further supporting the contribution of hemolysis per se, as opposed to anemia, in mediating the poor quality of life in PNH patients. Clinical

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assessment of additional life quality-related symptoms of PNH, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[20]

Eculizumab was safe and well-tolerated. There were no deaths in the study and only a single thrombotic event which occurred in a placebo patient in a site (the hepatic veins) which is typical of the thrombosis in PNH. The relative brief duration of this study was not sufficient to address the relevant issue of a possible protection from thrombosis by terminal complement inhibition with eculizumab.

Adverse events were generally mild with headache occurring at increased frequency in the eculizumab-treated patients; however, this increased frequency did not persist following the first two doses of therapy. There were 4 SAEs in the eculizumab treatment group and 9 SAEs in the placebo group. There was no evidence of increased infection risk in eculizumab-treated patients during the study period. One eculizumab-treated patient showed a low level of anti-eculizumab antibodies at one time point during the study which did not persist and did not result in a disruption of complement blockade. There were no AEs associated with eculizumab withdrawal in the 2 eculizumab-treated patients who did not complete the trial. Additional safety assessments, as well as efficacy measures, are being examined in an ongoing multi-center, open-label Phase III safety trial of eculizumab (SHEPHERD) in approximately 95 patients with PNH.

Results from the current randomized, double-blind, placebo-controlled, global study show that terminal complement inhibition with eculizumab appears to be a safe and effective therapy for patients with the rare disorder PNH. Treatment with eculizumab reduced intravascular hemolysis, and stabilized hemoglobin levels despite a reduction of transfusions, to the point where most PNH patients were rendered transfusion independent. Substantial and clinically meaningful improvements in fatigue and other key quality of life parameters were also demonstrated. All of the 85 patients who completed the study elected to receive eculizumab in an open-label extension study and all currently remain on drug. The results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency.

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The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

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WHAT IS CLAIMED IS:

1. A method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient a compound which inhibits complement or inhibits formation of C5b-9.

2. The method of claim 1 wherein said quality of life is measured by a FACIT-Fatigue score.

3. The method of claim 2 wherein the FACIT-Fatigue score increases by at least 3 points.

4. The method of claim 2 wherein the FACIT-Fatigue score increases by ≥ 4 points.

5. The method of claim 1 wherein said quality of life is measured by an EORTC QLQ-C30 score.

6. The method of claim 5 wherein said EORTC QLQ-C30 score improves by $\geq 10\%$ of the pretreatment score.

7. The method of claim 5 wherein said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia.

8. The method of claim 7 wherein said aspect of quality of life is fatigue.

9. The method of claim 1 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

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10. The method of claim 1 wherein said compound is a steroid that suppresses complement.

11. The method of claim 1 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

12. The method of claim 11 wherein said compound is an antibody or an active antibody fragment.

13. The method of claim 12 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

14. The method of claim 12 wherein said antibody or active antibody fragment blocks C5 cleavage.

15. The method of claim 12 wherein said antibody or active antibody fragment inhibits the formation of C5b-9.

16. The method of claim 12 wherein said antibody is eculizumab.

17. The method of claim 12 wherein said antibody or active antibody fragment is administered for at least 6 months.

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18. The method of claim 1 wherein said patient has aplastic anemia or myelodysplastic syndrome.

19. A method to improve at least one aspect of the quality of life of an anemic patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient a compound which inhibits complement or inhibits formation of C5b-9, wherein said patient remains anemic.

20. The method of claim 19 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

21. The method of claim 19 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

22. The method of claim 19 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

23. The method of claim 19 wherein said quality of life is measured by a FACIT-Fatigue score.

24. The method of claim 23 wherein the FACIT-Fatigue score increases by at least 3 points.

25. The method of claim 23 wherein the FACIT-Fatigue score increases by $\geq$ 4 points.

26. The method of claim 19 wherein said quality of life is measured by an EORTC QLQ-C30 score.

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27. The method of claim 26 wherein said EORTC QLQ-C30 score improves by ≥ 10% of the pretreatment score.

28. The method of claim 26 wherein said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia.

29. The method of claim 28 wherein said aspect of quality of life is fatigue.

30. The method of claim 19 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

31. The method of claim 19 wherein said compound is a steroid that suppresses complement.

32. The method of claim 19 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

33. The method of claim 32 wherein said compound is an antibody or an active antibody fragment.

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34. The method of claim 33 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2s$, i) Fvs, j) diabodies, and k) human antibodies.

35. The method of claim 33 wherein said antibody or active antibody fragment blocks C5 cleavage.

36. The method of claim 33 wherein said antibody or active antibody fragment inhibits the formation of C5b-9.

37. The method of claim 33 wherein said antibody is eculizumab.

38. The method of claim 33 wherein said antibody or active antibody fragment is administered for at least 6 months.

39. The method of claim 19 wherein said patient has aplastic anemia or myelodysplastic syndrome.

40. A method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient a compound which inhibits intravascular hemolysis.

41. The method of claim 40 wherein said method results in a greater than 30% reduction in LDH in said patient.

42. The method of claim 40 wherein said quality of life is measured by a FACIT-Fatigue score.

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43. The method of claim 42 wherein the FACIT-Fatigue score increases by at least 3 points.

44. The method of claim 42 wherein the FACIT-Fatigue score increases by ≥ 4 points.

45. The method of claim 40 wherein said quality of life is measured by an EORTC QLQ-C30 score.

46. The method of claim 45 wherein said EORTC QLQ-C30 score improves by ≥ 10% of the pretreatment score.

47. The method of claim 45 wherein said aspect of the quality of life as measured by the EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia.

48. The method of claim 47 wherein said aspect of quality of life is fatigue.

49. The method of claim 40 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

50. The method of claim 40 wherein said compound is a steroid that suppresses complement.

51. The method of claim 40 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA

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aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

52. The method of claim 51 wherein said compound is an antibody or an active antibody fragment.

53. The method of claim 52 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

54. The method of claim 52 wherein said antibody or active antibody fragment blocks C5 cleavage.

55. The method of claim 52 wherein said antibody or active antibody fragment is administered for at least 6 months.

56. The method of claim 40 wherein said compound inhibits complement or inhibits the formation of C5b-9.

57. The method of claim 56 wherein said compound is an antibody or active antibody fragment.

58. The method of claim 57 wherein said antibody is eculizumab.

59. The method of claim 40 wherein said patient has aplastic anemia or myelodysplastic syndrome.

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60. A method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient a compound which inhibits intravascular hemolysis, wherein said patient remains anemic.

61. The method of claim 60 wherein said method results in a greater than 30% reduction in LDH in said patient.

62. The method of claim 60 wherein said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman.

63. The method of claim 60 wherein said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman.

64. The method of claim 60 wherein said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

65. The method of claim 60 wherein said patient suffers from paroxysmal nocturnal hemoglobinuria.

66. The method of claim 60 wherein said quality of life is measured by a FACIT-Fatigue score.

67. The method of claim 66 wherein the FACIT-Fatigue score increases by at least 3 points.

68. The method of claim 66 wherein the FACIT-Fatigue score increases by ≥ 4 points.

69. The method of claim 60 wherein said quality of life is measured by an EORTC QLQ-C30 score.

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70. The method of claim 69 wherein said EORTC QLQ-C30 score improves by ≥ 10% of the pretreatment score.

71. The method of claim 69 wherein said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia.

72. The method of claim 71 wherein said aspect of quality of life is fatigue.

73. The method of claim 60 wherein said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH.

74. The method of claim 60 wherein said compound is a steroid that suppresses complement.

75. The method of claim 60 wherein said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors.

76. The method of claim 75 wherein said compound is an antibody or an active antibody fragment.

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77. The method of claim 76 wherein said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

78. The method of claim 76 wherein said antibody or active antibody fragment blocks C5 cleavage.

79. The method of claim 76 wherein said antibody or active antibody fragment is administered for at least 6 months.

80. The method of claim 60 wherein said compound inhibits complement or inhibits the formation of C5b-9.

81. The method of claim 80 wherein said compound is an antibody or an active antibody fragment.

82. The method of claim 81 wherein said antibody is eculizumab.

83. The method of claim 60 wherein said patient has aplastic anemia or myelodysplastic syndrome.

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ABSTRACT

Eculizumab, a humanized monoclonal antibody against C5 that inhibits terminal complement activation, showed activity in a preliminary 12-week open-label trial in a small cohort of patients with paroxysmal nocturnal hemoglobinuria (PNH). The present study examined whether chronic eculizumab therapy could reduce intravascular hemolysis, stabilize hemoglobin levels, reduce transfusion requirements, and improve quality of life in a double-blind, randomized, placebo-controlled, multi-center global Phase III trial. It has been found that eculizumab stabilized hemoglobin levels, decreased the need for transfusions,, and improved quality of life in PNH patients via reduced intravascular hemolysis. Chronic eculizumab treatment appears to be a safe and effective therapy for PNH.

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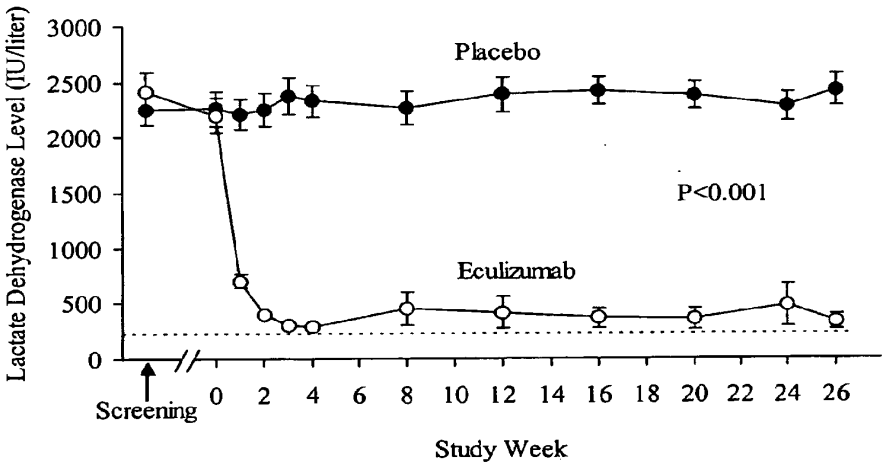
Lactate Dehydrogenase Level (IU/liter)
3000
2500
2000
1500
1000
500
0
Placebo
P<0.001
Eculizumab
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1A

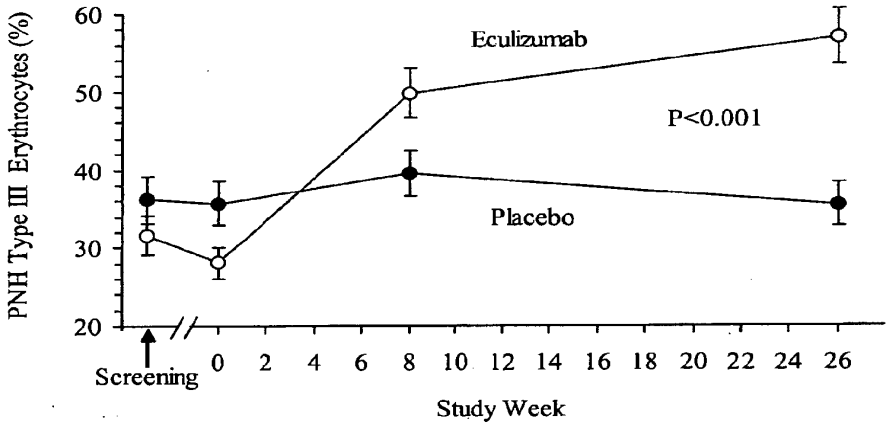
PNH Type III Erythrocytes (%)
60
50
40
30
20
Eculizumab
P<0.001
Placebo
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1B

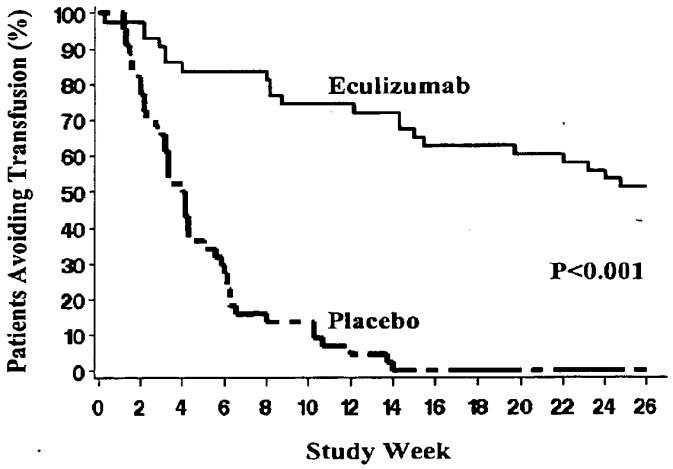
Patients Avoiding Transfusion (%)
100
90
80
70
60
50
40
30
20
10
0
Eculizumab
P<0.001
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 2

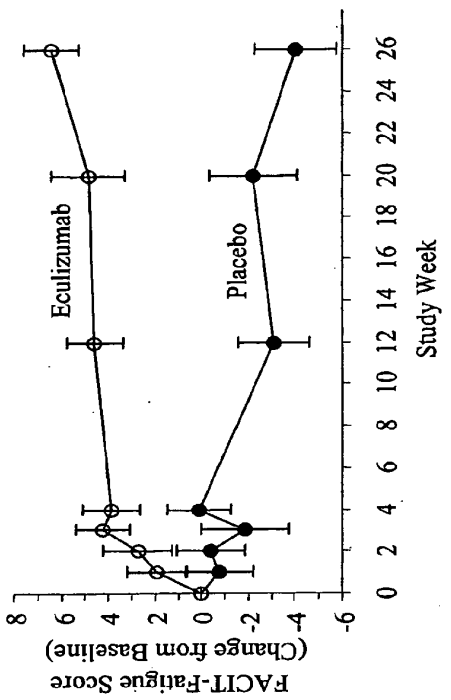
FACIT-Fatigue Score
(Change from Baseline)
8
6
4
2
0
-2
-4
-6
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Eculizumab
Placebo

FIGURE 3

Exhibit no. D 10
of the letter / report / expert opinion / plaint / defense
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Patent- und Rechtsanwälte
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MINIREVIEW

Antibody Structure, Instability, and Formulation

WEI WANG, SATISH SINGH, DAVID L. ZENG, KEVIN KING, SANDEEP NEMA

Pfizer, Inc., Global Biologics, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017

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ABSTRACT: The number of therapeutic monoclonal antibody in development has increased tremendously over the last several years and this trend continues. At present there are more than 23 approved antibodies on the US market and an estimated 200 or more are in development. Although antibodies share certain structural similarities, development of commercially viable antibody pharmaceuticals has not been straightforward because of their unique and somewhat unpredictable solution behavior. This article reviews the structure and function of antibodies and the mechanisms of physical and chemical instabilities. Various aspects of formulation development have been examined to identify the critical attributes for the stabilization of antibodies. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:1–26, 2007

Keywords: biotechnology; stabilization; protein formulation; protein aggregation; freeze drying/lyophilization

INTRODUCTION

Protein therapies are entering a new era with the influx of a significant number of antibody pharmaceuticals. Generally, protein drugs are effective at low concentrations with less side effects relative to small molecule drugs, even though, in rare cases, protein-induced antibody formation could be serious.[1] Therefore, this category of therapeutics is gaining tremendous momentum and widespread recognition both in small and large drug firms. Among protein drug therapies, antibodies play a major role in controlling many types of diseases such as cancer, infectious diseases, allergy, autoimmune diseases, and inflammation. Since the approval of the first monoclonal antibody (MAb) product -OKT-3 in 1986, more than 23 MAb drug products have entered the market (Tab. 1). The estimated number of antibodies and antibody derivatives constitute 20% of biopharmaceutical products currently in development (about 200).[2] The global therapeutic antibody market was predicted to reach $16.7 billion in 2008.[3]

There are several reasons for the increasing popularity of antibodies for commercial development. First, their action is specific, generally leading to fewer side effects. Second, antibodies may be conjugated to another therapeutic entity for efficient delivery of this entity to a target site, thus reducing potential side effects. For instance, Mylotarg is an approved chemotherapy agent composed of calicheamicin conjugated to humanized IgG4, which binds specifically to CD33 for the treatment of CD33-positive acute myeloid leukemia. Another example is the conjugation of immunotoxic barnase with the light chain of the anti-human ferritin monoclonal antibody F11 as potential targeting agents for cancer immunotherapy.[4] Third, antibodies may be conjugated to radioisotopes for specific diagnostic purposes. Examples include CEA-Scan for detection of colorectal cancer and ProstaScint for detection of prostate cancer. Lastly, technology advancement has made complete human MAb available, which are less immunogenic.

Correspondence to: Wei Wang (Telephone: (636)-247-2111; Fax: (636)-247-5030; E-mail: wei.2.wang@pfizer.com)

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Table 1. Commercial Monoclonal Antibody Products

#	Brand name	Molecule	MAb	Year	Company	Route	Indication	MAb Conc	Buffer	Excipients	Surfactant	pH
1	Avastin	Bevacizumab	Humanized IgG1, 149 kDa	2004	Genetech and BioOncology	IV infusion	Metastatic carcinoma of colon or rectum, binds VEGF	100 mg and 400 mg/vial (25 mg/mL) solution	5.8 mg/mL monobasic NaPhos H_2O; 1.2 mg/mL dibasic NaPhos anhydrous (4 mL, 16 mL fill in vial)	60 mg/mL α-Trehalose dihydrate (4 mL, 16 mL fill in vial)	0.4 mg/mL PS20 (4 mL, 16 mL fill in vial)	6.2
2	Bexxar	Tositumomab and I-131Tositumab	Murine IgG2λ	2003	Corixa and GSK	IV Infusion	CD20 positive follicular nonHodgkins lymphoma	Kit: 14 mg/mL MAb solution in 35 mg and 225 mg vials; *I131-MAb* 1.1 mg/mL *I131-MAb* solution	10 mM phosphate (MAb vial)	145 mM NaCl, 10 % w/v Maltose; *I131-MAb*; 5–6% Povidone, 1–2, 9–15 mg/mL Maltose, 0.9 mg/mL NaCl, 0.9–1.3 mg/mL Ascorbic acid		7.2
3	Campath	Alemtuzumab	Humanized, IgG1k, 150 kDa	2001	Ilex Oncology; Millenium and Berlex	IV infusion	B-cell chronic lymphocytic leukemia, CD52-antigen	30 mg/3 mL solution	3.5 mg/3 mL dibasic NaPhos, 0.6 mg/3 mL monobasic KPhos	24 mg/3 mL NaCl, 0.6 mg/3 mL KCl, 0.056 mg/3 mL Na2EDTA	0.3 mg/3 mL PS80	6.8–7.4
4	CEA-Scan (lyo)	Arcitumomab; Tc-99	Murine Fab, 50 kDa	1996	Immunomedics	IV injection or infusion	Imaging agent for colorectal cancer	1.25 mg/vial Lyophilized MAb. Reconstitute w 1 mL Saline w Tc99m	0.29 mg/vial Stannous chloride, potassium sodium tartrate tetrahydrate, NaAcetate.$3H_2O$, NaCl, glacial acetic acid, HCl	Sucrose		5.7
5	Erbitux	Cetuximab	Chimeric human/ mouse IgG1k, 152 kDa	2004	ImClone and BMS	IV infusion	Treatment of EGFR-expressing colorectal carcinoma	100 mg MAb in 50 mL, 2 mg/ mL solution	1.88 mg/mL DibasicNaPhos·$7H_2O$, 0.42 mg/mL MonobasicNaPhos·H_2O	8.48 mg/mL NaCl		7.0–7.4
6	Herceptin (lyo)	Trastuzumab	Humanized IgG1k	1998	Genetech	IV infusion	Metastatic breast cancer whose tumor overexpress HER2 protein	440 mg /vial, 21 mg/mL after reconstitution	9.9 mg/20 mL L-HistidineHCl, 6.4 mg/20 mL L-Histidine	400 mg/20 mL α-Trehalose Dihydrate	1.8 mg/20 mL PS20	6
7	Humira	Adalimumab	Human IgG1k, 148 kDa	2002	CAT and Abbott	SC	RA patients not responding to DMARDs. Blocks TNF-alpha	40 mg/0.8 mL solution (50 mg/mL)	0.69 mg/0.8 mL Monobasic NaPhos·$2H_2O$; 1.22 mg/0.8 mL DibasicNaPhos·$2H_2O$; 0.24 mg/0.8 mL NaCitrate, 1.04 mg/ 0.8 mL Citric acid·H_2O	4.93 mg/0.8 mL NaCl; 9.6 mg/0.8 mL Mannitol	0.8 mg/0.8 mL PS80	5.2
8	Lucentis	Ranibizumab	Humanized IgG1k fragment	2006	Genentech	Intravitreal injection	Age-related macular degeneration (wet)	10 mg/mL solution	10 mM HistidineHCl	10% α-Trehalose-Dihydrate	0.01% PS20	5.5

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9	Mylotarg (lyo)	Gemtuzumab ozogamicin	Humanized IgG4k conjugated with calicheamicin	2000	Celltech and Wyeth	IV infusion	Humanized Ab linked to calicheamicin for treatment of CD33 positive acute myeloid leukemia	5 mg protein-equivalent lyophilized powder/20-mL vial	Monobasic and dibasic NaPhosphate	Dextran 40, Sucrose, NaCl				
10	OncoScint	Satumomab pendetide	Murine IgG1k conjugated to GYK-DTPA	1992	Cytogen	IV injection	Imaging agent for colorectal and ovarian cancer	0.5 mg conjugate/mL solution (2 mL per vial)	Phosphate buffer saline				6.0	
11	Orthoclone OKT	Muromomab-CD3	Murine, IgG2a, 170 kDa	1986	Ortho Biotech	IV injection	Reversal of acute kidney transplant rejection (anti CD3-antigen)	1 mg/mL solution	2.25 mg/5 mL monobasic NaPhos, 9.0 mg/5 mL dibasic NaPhos	43 mg/5 mL NaCl	1 mg/mL PS80	7 ± 0.5		
12	ProstaScint	Indium-111 capromab pendetide	Murine IgG1k-conjugated to GYK-DTPA	1996	Cytogen	IV injection	Imaging agent for prostate cancer	0.5 mg conjugate/mL solution (1 mL per vial)	Phosphate buffer saline				5–7	
13	Raptiva (lyo)	Efalizumab	Humanized IgG1k	2003	Xoma and Genentech	SC	Chronic moderate to severe plaque psoriasis, binds to CD11a subunit of LFA-1	150 mg MAb/vial; 125 mg/ 1.25 mL (100 mg/mL) after reconstitution with 1.3 mL SWFI	6.8 mg/vial L-HistidineHCl·H_2O, 4.3 mg/vial L-Histidine	123.2 mg/vial Sucrose	3 mg/vial PS20	6.2		
14	Remicade (lyo)	Infliximab	Chimeric human/ murine MAb against TNFalpha (app. 30% murine, 70% corresponds to human IgG1 heavy chain and human kappa light chain constant regions)	1998	Centocor	IV infusion	RA and Crohn's disease (anti TNFalpha)	100 mg / 20-mL Vial, 10 mg/mL on reconstitution	2.2 mg/10 mL MonobasicNaPhos H_2O, 6.1 mg/10 mL DibasicNaPhos $\cdot 2H_2O$	500 mg/10 mL Sucrose	0.5 mg/10 mL PS80	7.2		
15	ReoPro	Abciximab	Fab. Chimeric human-murine, 48 kDa	1994	Centocor / Lilly	IV injection and infusion	Reduction of acute blood clot related complications	2 mg/mL solution	0.01 M NaPhosphate	0.15 M NaCl	0.001% (0.01 mg/mL) PS80	7.2		
16	Rituxan	Rituximab	Chimeric mouse/ human IgG1k with murine light and heavy chain variable region (Fab domain), 145 kDa	1997	IDEC and Genentech	IV infusion	NonHodgkin's lymphoma. (anti CD20-antigen)	10 mg/mL solution	7.35 mg/mL NaCitrate $\cdot 2H_2O$	9 mg/mL NaCl	0.7 mg/mL PS80	6.5		

(Continued)

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Table 1. *(Continued)*

#	Brand name	Molecule	MAb	Year	Company	Route	Indication	MAb Conc	Buffer	Excipients	Surfactant	pH
17	Simulect (lyo)	Basiliximab	Chimeric IgG1k, 144 kDa	1998	Novartis	IV injection and infusion	Prevention of acute kidney transplant rejection, IL-2 receptor antagonist	10 mg and 20 mg/ vial, 4 mg/mL on reconstitution	3.61 mg, 7.21 mg Monobasic KPhos, 0.50 mg, 0.99 mg Na_2HPO_4	0.8 mg, 1.61 mg NaCl; 10 mg, 20 mg Sucrose; 40 mg, 80 mg Mannitol; 20 mg 40 mg Glycine		
18	Synagis (lyo)	Palivizumab	Humanized IgG1k, CDR of murine MAb 1129, 148 kDa	1998	MedImmune	IM injection	Prevent replication of the Respiratory syncytial virus (RSV)	50 mg and 100 mg / vial, 100 mg/mL on reconstitution	47 mM Histidine, 3.0 mM Glycine	5.6 % Mannitol		
19	Tysabri	Natalizumab	Humanized IgG4k	2004	Biogen IDEC	IV Infusion	MS relapse	300 mg/15 mL solution	17.0 mg MonobasicNa Phos · H_2O, 7.24 mg diBasicNaPhos · $7H_2O$ for 15 mL	123 mg/15 mL NaCl	3.0 mg/15 mL PS80	6.1
20	Verluma	Nofetumomab	Murine Fab	1996	Boehringer Ingelheim and DuPont Merck	IV injection	Imaging agent for lung cancer	10 mg/mL solution	Phosphate buffer saline			?
21	Xolair (lyo)	Omalizumab	Humanized IgG1k, 149 kDa		Genentech w Novartis and Tanox	SC	Asthma, inhibits binding of IgE to IgE receptor FCeRI	202.5 mg/vial, Deliver 150 mg/ 1.2 mL on reconstitution with 1.4 mL SWFI	2.8 mg LHistidineHCl · H_2O; 1.8 mg LHistidine	145.5 mg Sucrose	0.5 mg PS20	
22	Zenapax	Daclizumab	Humanized IgG1, 144 kDa	1997	Roche	IV infusion	Prophylaxis of acute organ rejection in patients receiving renal transplants. Inhibits IL-2 binding to the Tac subunit of IL-2 receptor complex	25 mg/5 mL MAb Solution	3.6 mg/mL MonobasicNa Phos · H_2O; 11 mg/mL DibasicNaPhos · $7H_2O$	4.6 mg/mL NaCl	0.2 mg/mL PS80	6.9
23	Zevalin	Ibritumomab-Tiuxetan	Murine IgG1k-thiourea covalent linkage to Tiuxetan	IDEC		IV infusion	CD20 antigen. (Kit with Yttrium-90 induces cellular damage by beta emission)	3.2 mg/2 mL solution		09% NaCl		7.1

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Development of commercially viable antibody pharmaceuticals has, however, not been straightforward. This is because the behavior of antibodies seems to vary, even though they have similar structures. In attempting to address some of the challenges in developing antibody therapeutics, Harris et al.[5] reviewed the commercial-scale formulation and characterization of therapeutic recombinant antibodies. In a different review, antibody production and purification have been discussed.[2] Nevertheless, the overall instability and stabilization of antibody drug candidates have not been carefully examined in the literature. This article, not meant to be exhaustive, intends to review the structure and functions of antibodies, discuss their instabilities, and summarize the methods for stabilizing/formulating antibodies.

ANTIBODY STRUCTURE

Antibodies (immunoglobulins) are roughly Y-shaped molecules or combination of such molecules (Fig. 1). Their structures are divided into two regions—the variable (V) region (top of the Y) defining antigen-binding properties and the constant (C) region (stem of the Y), interacting with effector cells and molecules. Immunoglobulins can be divided into five different classes –IgA, IgD, IgE, IgM, and IgG based on their C regions, respectively designated as α, δ, ε, μ, and γ (five main heavy-chain classes).[6] Most IgGs are monomers, but IgA and IgM are respectively, dimmers and pentamers linked by J chains. IgGs are the most abundant, widely used for therapeutic purposes, and their structures will be discussed as antibody examples in detail.

Primary Structure

The structure of IgGs have been thoroughly reviewed.[6] The features of the primary structure of antibodies include heavy and light chains, glycosylation, disulfide bond, and heterogeneity.

Heavy and Light Chains

IgGs contain two identical heavy (H, 50 kDa) and two identical light (L, 25 kDa) chains (Fig. 1). Therefore, the total molecular weight is approximately 150 kDa. There are several disulfide bonds linking the two heavy chains, linking the heavy and light chains, and residing inside the chains (also see next section). IgGs are further divided

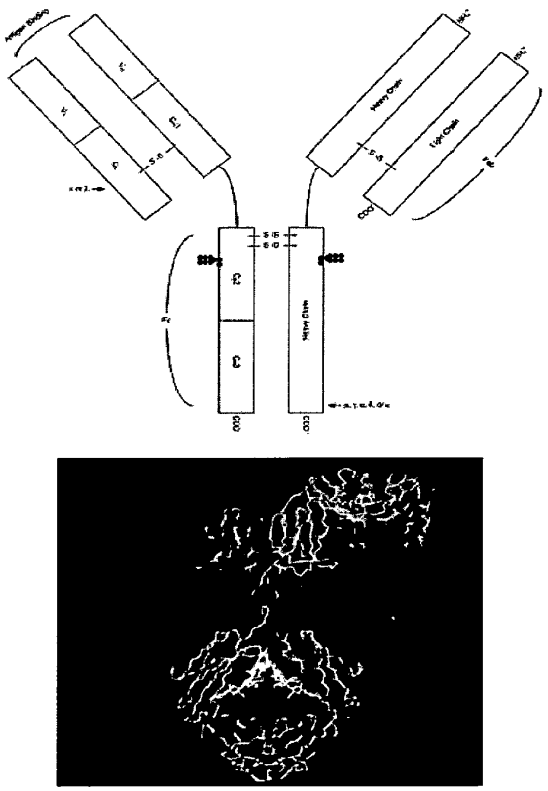

Figure 1. Linear (upper panel) and steric (lower panel) structures of immunoglobulins (IgG).

into several subclasses—IgG1, IgG2, IgG3, and IgG4 (in order of relative abundance in human plasma), with different heavy chains, named γ1, γ2, γ3, and γ4, respectively. The structural differences among these subtypes are the number and location of interchain disulfide bonds and the length of the hinge region. The light chains consist of two types—lambda (λ) and kappa (κ). In mice, the average of κ to λ ratio is 20:1, whereas it is 2:1 in humans.[6] The variable (V) regions of both chains cover approximately the first 110 amino acids, forming the antigen-binding (Fab) regions, whereas the remaining sequences are constant (C) regions, forming Fc (fragment crystallizable) regions for effector recognition and binding.[6] The N-terminal sequences of both the heavy and light chains vary greatly between different antibodies. It was suggested that the conserved sequences in human IgG1 antibodies

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are approximately 95% and the remaining 5% is variable and creates their antigen-binding specificity.[5]

The V regions are further divided into three hypervariable sequences (HV1, HV2, and HV3) on both H and L chains. In the light chains, these are roughly from residues 28 to 35, from 49 to 59, and from 92 to 103, respectively.[6] Other regions are the framework regions (FR1, FR2, FR3, and FR4). The HV regions are also called the complementarity determining regions (CDR1, CDR2, and CDR3). While the framework regions form the β-sheets, the HV sequences form three loops at the outer edge of the β barrel (also see Section 2.2).

Disulfide Bonds

Most IgGs have four interchain disulfide bonds—two connecting the two H chains at the hinge region and the other two connecting the two L chains to the H chains.[6] Exceptions do exist. Two disulfide bonds were found in IgG1 and IgG4 linking the two heavy chain in the hinge region but four in IgG2.[7] In IgG1 MAb, HC is linked to the LC between the fifth Cys (C217) of HC and C213 on the LC. In IgG2 and IgG4 MAbs, it is the third Cys of HC (C123) linking to the LC.[7] A disulfide bond between HC C128 and LC C214 was found for mouse catalytic monoclonal antibodies (IgG2a).[8]

IgGs have four intrachain disulfide bonds, residing in each domain of the H and L chains, stabilizing these domains. The intrachain disulfide bonds in V_H and V_L are required in functional antigen binding.[9] Native IgG MAbs should not have any free sulfhydryl groups.[7] However, detailed examination of the free sulfhydryl groups in recombinant MAbs (one IgG1, two IgG2, and one IgG4) suggests presence of a small portion of free sulfhydryl group (approximately 0.02 mol per mole of IgG2 or IgG4 MAb and 0.03 for IgG1.[7] In rare cases, a free cysteine is found. A nondisulfide-bonded Cys at residue 105 was found on the heavy chain of a mouse monoclonal antibody, OKT3 (IgG2a).[10]

Oligosaccharides

There is one oligosaccharide chain in IgGs.[6] This N-linked biantennary sugar chain resides mostly on the conserved Asn 297, which is buried between the C_H2 domains.[5,11] For example, the oligosaccharide resides on Asn-297 of the C_H2 domain of chimeric IgG1 and IgG3 molecules[12] but on Asn 299 in a monoclonal antibody, OKT3 (IgG2a).[10] The oligosaccharide, often microheterogeneous, is typically fucosylated in antibodies produced in CHO or myeloma cell lines[5] and may differ in other cell lines.[2,11] There are many factors that dictate the nature of the glycan microheterogenity on IgGs. These include cell line, the bioreactor conditions and the nature of the downstream processing. An additional oligosaccharide can be found in rare cases. A human IgG produced by a human-human-mouse heterohybridoma contains an additional oligosaccharide on Asn 75 in the variable region of its heavy chain.[13] In addition, O-linked carbohydrates could also exist in this antibody.

Proper glycosylation is critical for correct functioning of antibodies.[11] It was demonstrated that removal of the oligosaccharide in IgGs (IgG1 and IgG3) made them ineffective in binding to C1q, in binding to the human FcγRI and activating C; and generally more sensitive to most proteases than their corresponding wild-type IgGs (one exception).[12] This is because the binding site on IgG for C1q, the first component of the complement cascade, is localized in the C_H2 domains.[11] Furthermore, the glycosylation can affect the antibody conformation.[12]

Oligosaccharides in other regions can also play a critical role. Removal of an oligosaccharide in a Fv region of the CBGA1 antibody resulted in a decreased antigen-binding activity in several ELISA systems.[13] In addition, this oligosaccharide might play critical role in reducing the antigenicity of the protein.[14]

The sugar composition of the oligosaccharide is also critical in antibody functions. It has been shown that a low fucose (Fuc) content in the complex-type oligosaccharide in a humanized chimeric IgG1 is responsible for a 50-fold higher antibody-dependent cellular cytotoxicity (ADCC) compared with a high Fuc counterpart.[15]

Heterogeneity

Purified antibodies are heterogeneous in structure. This is true for all monoclonal antibodies (MAbs) due to differences in glycosylation patterns, instability during production, and terminal processing.[5] For example, five charged isoforms were found in recombinant humanized monoclonal antibody HER2 as found by capillary isoelectric focusing (cIEF) and sodium dodecyl sulfate–capillary gel electrophoresis (SDS–CGE).[16] Six separate bands were focused under

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IEF for two mouse monoclonal antibodies IgG2a (κ) and IgG1 (κ).[17] A mature monoclonal antibody, OKT3 (IgG2a), contain cyclized N-terminus (pyroglutamic acid, −17 D) in both H and L chains, processed C-terminus (no Lys, −128 D) of the H chains, and a small amount of deamidated form.[10] Similar observation was also reported for a humanized IgG1 (κ).[18] In rare cases, gene cross-over may lead to formation of abnormal heavy chains. For example, a purified monoclonal anti-IgE antibody contains a small amount of a variant H chain, which had 16 fewer amino acid residues than the normal H chain (position is between Arg108 of the L chain and Ala124 of the H chain).[19]

Secondary and Higher-Order Structure

The basic secondary and higher-order structural features of IgGs have been reviewed.[6] Only a small portion of the three-dimensional structures of IgGs has been solved.[20] The antibody's secondary structure is formed as the polypeptide chains form anti-parallel β-sheets. The major type of secondary structure in IgGs is these β-sheets and its content is roughly 70% as measured by FTIR.[21] The light chain consists of two and the heavy chain contains four domains, each about 110 amino acid long.[6,20] All these domains have similar folded structures—β barrel, also called immunoglobulin fold, which is stabilized by a disulfide bond and hydrophobic interaction (primary). These individual domains (~12 kDa in size) interact with one another (V_H and V_L; C_H1 and C_L; and between two C_H3 domains except the carbohydrate-containing C_H2 domain) and fold into three equal-sized spherical shape linked by a flexible hinge region. These three spheres form a Y shape (mostly) and/or a T shape.[22]

The less globular shape of IgGs is maintained both by disulfide bonds and by strong noncovalent interactions between the two heavy chains and between each of the heavy-chain/light-chain pairs.[23] Through noncovalent interactions, a less stable domain becomes more stable, and thus, the whole molecule can be stabilized.[24] A detailed study indicates that the interaction between two CH3 domains are dominated by six contact residues, five of these residues (T366, L368, F405, Y407, and K409) forming a patch at the center of the interface.[25] These noncovalent interactions are spatially oriented such that variable domain exchange (switching V_H and V_L; inside-out IgG; ioIgG) induces noncovalent multimerization.[26]

The six hypervariable regions in CDR (L1, L2, L3, H1, H2, and H3) form loops of a few predictable main-chain conformations (or canonical forms), except H3 loop, which has too many variations in conformation to be predicted accurately.[27,28] There is a slight difference in the loop composition and shape between the two types of light chains.[20] However, no functional difference was found in antibodies having λ or κ chain.[6]

Basic Functions of Antibodies

The basic functions of antibodies have been reviewed.[6] There are two functional areas in IgGs—the V and C regions. The V regions of the two heavy and light chains offer two identical antigen-binding sites. The binding of the two sites (bivalent) can be independent of each other and does not seem to depend on the C region.[29] The exact antigen-binding sites are the CDR regions with participation of the frame work regions.[30] Binding of antigens seems through the induced-fit mechanism.[31,32] The induced-fit mechanism allows multispecificity and polyreactivity. It has been suggested that about 5–10 residues usually contribute significantly to the binding energy.[32]

The C regions of antibodies have three main effector functions (1) being recognized by receptors on immune effector cells, initiating antibody-dependent cell cytotoxicities (ADCC), (2) binding to complement, helping to recruit activated phagocytes, and (3) being transported to a variety of places, such as tears and milk.[6] In addition, C domains also modulate *in vivo* stability.[23,29,33] The function of Fc is affected by the structure of Fab. Variable domain exchange (switching V_H and V_L; inside-out IgG; ioIgG) affected Fc-associated functions such as serum half-life and binding to protein G and FcγRI.[26]

The hinge region provides flexibility in bivalent antigen binding and activation of Fc effector functions.[26] Two chimeric IgG3 antibodies lacking a genetic hinge but with Cys residues in CH2 regions was found to be deficient in their intermolecular assembly, and both IgG3 ΔH + Cys and IgG3 ΔH + 2Cys lost greatly their ability to bind FcγRI and failed to bind C1q and activate the complement cascade.[34]

Alternative Forms of Antibodies

In addition to species-specific antibodies, other antibody forms are generated to meet various needs. In the early development of antibody therapies, antibodies were made from murine

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sources. However, these antibodies easily elicit formation of human anti-mouse antibody (HAMA). Therefore, humanized chimeric antibodies were generated. Chimeric monoclonal antibodies (60–70% human) are made of mouse variable regions and human constant regions.[2] Such antibodies can still induce formation of human anti-chimeric antibody (HACA). Highly humanized antibodies, CDR-grafted antibodies, are made by replacing only the human CDR with mouse CDR regions (90–95% human).[2] These antibodies are almost the same in immunogenicity potential as completely human antibodies, which may illicit formation of human anti-human antibody (HAHA).

Other alternative forms of antibodies have also been generated and these different forms have been reviewed.[35] Treatment with papain would cleave the N-terminal side of the disulfide bonds and generate two identical Fab fragments and one Fc fragment. Fab's are 50 kDa $(V_H + C_H1)/(V_L + C_L)$ heterodimers linked by a single disulfide bond. Treatment with pepsin cleaves the C-terminal side of the disulfide bonds and produces a $F(ab)'_2$ fragment. The remaining H chains were cut into several small fragments.[6] Cleavage by papain occurs at the C-terminal side of His-H228[36] or His-H227.[37] Reduction of $F(ab')_2$ will produce two Fab'.[23]

Fv fragments are noncovalent heterodimers of V_H and V_L. Stabilization of the fragment by a hydrophilic flexible peptide linker generates single-chain Fv (scFvs).[2] Fragments without constant domains can also be made into domain antibodies (dAbs). These scFvs are 25–30 kDa variable domain $(V_H + V_L)$ dimers joined by polypeptide linkers of at least 12 residues. Shorter linkers (5–10 residues) do not allow pairing of the variable domains but allow association with another scFv form a bivalent dimer (diabody) (about 60 kDa, or trimer: triabody about 90 kDa).[38] Two diabodies can be further linked together to generate bispecific tandem diabody (tandab).[39] Disulfide-free scFv molecules are relatively stable and useful for intracellular applications of antibodies—"intrabodies."[38] The smallest of the antibody fragments is the minimal recognition unit (MRU) that can be derived from the peptide sequences of a single CDR.[2]

ANTIBODY INSTABILITY

Antibodies, like other proteins, are prone to a variety of physical and chemical degradation pathways, although antibodies, on the average, seem to be more stable than other proteins. Antibody instabilities can be observed in liquid, frozen, and lyophilized states. The glycosylation state of an antibody can significantly affect its degradation rate.[40] In many cases, multiple degradation pathways can occur at the same time and the degradation mechanism may change depending on the stress conditions.[41] These degradation pathways are divided into two major categories—physical and chemical instabilities. This section will explore the possible degradation pathways of antibodies and their influencing factors.

Physical Instability

Antibodies can show physical instability via two major pathways—denaturation and aggregation.

Denaturation

Antibodies can denature under a variety of conditions. These conditions include temperature change, shear, and various processing steps. Compared with other proteins, antibodies seem to be more resistant to thermal stress. They may not melt completely until temperature is raised above 70°C,[21,42,43] while most other mesophilic proteins seem to melt below 70°C.[44] Shear may cause antibody denaturation. For example, the antigen-binding activity of a recombinant scFv antibody fragment was reduced with a first-order rate constant of 0.83/h in a buffer solution at a shear of approximately 20,000/s.[45]

Lyophilization can denature a protein to various extents. An anti-idiotypic antibody (MMA 383) in a formulation containing mannitol, saccharose, NaCl, and phosphate was found to loose its *in vivo* immunogenic properties (only 10–20% of normal response rate) upon lyophilization.[46] Since the protein showed no evidence of degradation after lyophilization, no change in secondary structure by CD (29% β-sheet, 14% α-helix, and 57% "other"), the loss of activity was attributed to the conformational change. Indeed, tryptophan fluorescence properties were different between the lyophilized and unlyophilized antibodies.[46]

Aggregation

Antibody aggregation is a more common manifestation of physical instability. The concentration-dependent antibody aggregation was considered the greatest challenge to developing protein formulations at higher concentrations.[47] This is

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because protein aggregates generally have reduced activity and more importantly, greater immunogenicity potential because of the multiplicity of epitopes and/or conformational changes.[14,48] Immunoglobulin aggregates have been shown to cause serious renal failure[49] and anaphylactoid reactions such as headache, fever, and chills.[50] Therefore, the aggregate level in commercial intravenous immunoglobulin products is limited to less than 5% based on the WHO standards.

Aggregates can form easily both in liquid and solid states under a variety of conditions (Tab. 2). Since protein aggregation is often the consequence of protein–protein interactions, a process influenced by diffusion rate and geometric constraints of the interaction sites, such factors would influence significantly the aggregation rate, including protein concentration change, viscosity, ionic strength, pH, and temperature.[51] Other conditions may also affect protein aggregation, including shaking, long-term storage, freeze-thaw process, lyophilization process, etc.

Increasing the concentration of antibodies often increases the aggregation tendency of the protein. It was demonstrated that increasing the IgG1 concentration (in 10 mM citric acid, 100 mM NaCl pH 5.5) from 2.7 mg/mL to 50 mg/mL almost linearly increased the Nephelometric Unit (NU) from 2 to 40.[52] Since EP defines a clear solution as having equal or less than three NU, most antibody solutions in the study are opalescent except those at 5 mg/mL or less. However, as the weight average molecular weight was found to be 0.9–1.3 times that expected of a monomer (about 149 kDa), minimal protein–protein association (and readily reversible) is suggested.[52] Shaking can accelerate antibody precipitation and the shape of the precipitates may depend on the sample volume in a container.[53] It appears that protein solutions exhibiting lower surface tension are more susceptible to protein denaturation and precipitation.[53]

Low-temperature treatment may induce aggregation of antibodies. The reversible low-temperature-induced aggregation (below 37°C) of serum cryoglobulins is well known.[54] Human IgM cryoglobulin preparations easily precipitate or gel at temperatures below 10–12°C and the process is reversible at a higher temperature.[20] In a recent study, aggregation of IgG1 at low temperature at above 18 mg/mL was reversible as measured by light scattering.[52] The low-temperature-induced aggregation of cryoglobulins is poorly understood and was thought to involve sites within both Fab and Fc.[20] The authors of this article believe that low temperature reduces the hydrophobic interaction, which is the major force in protein folding. Without enough hydrophobic interaction at low temperature, hydrophobic regions of antibodies become more exposed to solvent and lead to increased intermolecular hydrophobic interaction, leading to aggregation.

In close relation to the low-temperature effect, freeze-thaw process often induces protein aggregation. However, freeze-thaw-induced antibody aggregation does not seem to be a major issue, partly due to the reversibility of antibody aggregates. Freeze-thawing of a chimeric (L6) antibody solution at pH 7.2 for as many as 35 times led to formation of dimers (not larger aggregates).[41] Maximum amount of dimers (about 20%) was observed at pH 6.5 and minimum was below 5.5 or above 8.5 (less than 2%). The freeze-thaw-induced aggregation is apparently reversible after treatment at 37°C for a few hours.[41] Freeze-thawing of rhuMAb anti-CD20 three times (freezing to either −20 or −70°C, thawing to 5°C) did not lead to significant change in aggregation, no significant loss of monomer by RP-HPLC or SEC-HPLC.[55] On the other hand, isolated Fabs seems to be more prone to freeze-thaw-induced aggregation relative to full-length antibodies. For example, Lee[56] found that freeze-thawing of a scF_v (MW 27,000 d) at 1.45 mg/mL in sodium phosphate buffered saline (PBS) at pH 7.3 dropped the %monomer content (due to aggregation) from 95% to 84%, 59%, 44%, and 37%, respectively after 1–4 cycles.

Lyophilization may induce antibody aggregation to a variable degree. It was demonstrated that lyophilization of a recombinant humanized monoclonal antibody (rhuMAb HER2), in the absence of sugars, led to a slight increase in aggregate (less than 1.2%).[57] Lyophilization caused detectable aggregation of a human monoclonal antibody in PBS or physiological saline as measured by OD600,[58] and aggregation of a mouse monoclonal antibody (MN12) [IgG2a (κ)] in the absence or presence of 5% sucrose, dextran, or hydroxypropyl-beta-cyclodextrin (HP-β-CD), as measured by visual examination.[59] In a different study, lyophilization of a monoclonal antibody-vinca conjugate in PBS at pH 7.4 caused 6.2% aggregation.[60] The lyophilization-induced aggregates could be non-covalent-linked monomers and/or even disulfide-linked.[61,62]

Antibody aggregation can easily occur during storage in a liquid state. Storing of a fully human anti-IL8 monoclonal antibody (ABX-IL8; IgG2)

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Table 2. Instabilities of Antibodies

Instability	Antibody	Formulation	Condition	Effect	References
Denaturation	scFv	3 μg/mL in 10 mM phosphate-buffered saline containing 0.02% sodium azide	Shaking at a mean velocity gradient approximately 20,000/s	Loss of activity at a first-order rate of 0.83/h	45
Aggregation	Chimeric mouse/human IgG1	2 mg/mL in PBS at pH 7.2	Stirring for 48 h with Teflon bar at 600 RPM	Increased turbidity Formation of >15 k particles (>10 μ)	91
	Human Anti-IL-8 (IgG2)	55 mg/mL, 5 mM His, pH 6	Freeze/thaw three times (room/−70°C)	About 0.6% aggregates (by SEC-HPLC)	21
	Anti-IL-8 (IgG2)	100 mg/mL, 200 mM Sucrose, 15 mM Arg, 15 mM His, pH 6	Incubation at 40°C for 6 months	About 11% aggregates (by SEC-HPLC)	21
	rhuMAbE25	10 mg/mL in excipient-free solution	Spray drying Tin = 105°C, Tout = 50–55°C	5–6% aggregate (by SEC-HPLC)	65
	MAb (type not specified)	MAb at 40 mg/mL, 85 mM sucrose, 5 mM His at pH 6, 0.01% Tween 20	Lyophilization	Cloudy (OD350 > 0.2)	1
	Human Anti-IL-8 (IgG2)	50 mg/mL, 20 mM Gly, 4 mM His, 0.2% mannitol, 16 mM Glu, 0.03% Tween 20 pH 5.7	Incubation of lyophilized form at 37°C for 1 month	4.8% aggregates (by SEC-HPLC)	21
	RhuMAb HER2	50 mg/mL in 100 mM trehalose, 5 mM His at pH 6.0	Incubation of lyophilized form at 40°C for 23 months	9.7% aggregates (by SEC-HPLC)	57
Deamidation	OKT3 (IgG2a)	1 mg/mL, PBS at pH 7.0 + Tween80	Incubation at 37°C for 2 months	90% deamidation of Asn386	10
	LA298 (IgG1)	0.5 mg/mL in 10 mM citrate at pH 7	Incubation at 25°C for 6 weeks	~12% increase in deamidation at Asn55	78
Isomerization	MAb	Lyophilized at 40 mg/mL, 85 mM sucrose, 5 mM His, 0.01% Tween 20, pH 6.0, containing 8.4% moisture	Incubation at 5°C	First-order rate constant $\sim 0.33 \times 10^{-4}$/day	1
Oxidation	rhuMAb HER2	5 mg/mL, 147 mM NaCl, 0.01% polysorbate 20, 5 mM sodium acetate at pH 5.0	5, 30, and 40°C for 2 weeks	10, 17, and 52% (total peak area)	81

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in aqueous solutions at 2–8°C or 25°C led to formation of high-molecular-weight (HMW) species.[21] Incubation of two mouse monoclonal antibodies IgG2a (κ) and IgG1 (κ) at 37°C for 32 days caused precipitation in pH 3 and 4 solutions for both antibodies.[17] Aggregation can also occur to an antibody conjugate. Storing a monoclonal antibody-vinca alkaloid conjugate (murine IgG2a) in phosphate-buffered saline solutions at 5°C between pH 4.5 and 7.4 for 1.5 months caused precipitation regardless of solution pH and aggregation was accelerated at 30°C throughout the pH range.[63]

Antibody aggregation is a common phenomenon during storage in a lyophilized state. Aggregation (OD350 > 0.2) was observed of a high concentration, lyophilized, monoclonal antibody (type not specified) by SEC under accelerated conditions.[1] So did a lyophilized chimeric monoclonal antibody during storage at 5°C (0.4% after 2 months).[64] In the absence of sugars, the extent of rhuMAb HER2 aggregation increased from about 1% to >10% after 3 months at 40°C and the rate of aggregation for these formulations was about 0.2% per month at 40°C.[57]

Antibody aggregation can readily occur in other solid forms during storage.[5] It was found that the primary degradation upon storage of a spray-dried anti-IgE (protein:mannitol = 80:20) is aggregation, and the amount of aggregates increased with increasing temperature and relative humidity (Maa et al., 1998a).[65] As much as 52% aggregate was observed by SEC-HPLC of a spray-dried anti-IgE (protein:mannitol = 80:20) after 1 year at 40°C and 38% RH (Maa et al., 1998b).[66]

Antibody aggregation is usually accelerated upon thermal treatment. In the study of chimeric (human/mouse) monoclonal antibody (BR96), Alexander and Hughes demonstrated that thermal treatment at 60°C for 166 h generated noncovalently linked aggregates.[67] In the evaluation of the relative stability of murine IgG2a (κ), chimeric IgG1(κ), trioma IgG1 (λ), and murine IgG1 (κ), Hartmann et al. demonstrated that IgG2a (κ) aggregated and precipitated after heating at 55°C for 8 h and the half-life for the loss of monomer for those four IgGs is 1, 18.1, 3.4, and 8.2 h with different aggregate species (dimer, trimer...) by SEC-HPLC.[68]

Surface Adsorption

Antibodies, like other proteins, can easily adsorb to a variety of surfaces. Surface adsorption can significantly reduce the antibody concentration in a solution. For example, a mouse monoclonal IgG1 has been shown to be adsorbed on the surface of glass shake flasks, causing a loss of protein in plant culture media.[69] Such a loss was minimized by coating the glass vessels or by addition of Pluronic F127.

Chemical Instability

A variety of chemical degradation pathways have been observed. These chemical degradants may or may not loose protein activity depending on the site of changes. For examples, deamidation of a monoclonal antibody, OKT3 (IgG2a) as measured by change in IEF pattern does not correlate with loss of antigen binding potency (90% deamidation of Asn386 vs. 80% activity in the potency assay).[10] In comparison, the activity of light chain deamidated recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb) at Asn30 (to aspartate) is only 70% of the main species and that of the isomerized (heavy chain) asp102 species is only 9–21% of major species.[37] The major chemical degradation pathways in an antibody include cross-linking, deamidation, isomerization, oxidation, and fragmentation.

Disulfide Formation/Exchange

Disulfide bond formation/exchange is probably the most common cross-linking pathway, leading to chemical aggregation. This degradation pathway can occur readily in various processing steps. For example, lyophilization of a murine monoclonal antibody (IgG2a) without additives reduced the average number of –SH groups per molecule from 6.65 to 6.28, suggesting disulfide formation.[70] Since the thiolate ions are often the initiating species for this chemical degradation, increasing formulation pH usually leads to increased formation of disulfide formation. This is the case for an antifebrin T2G1s Fab′ (IgG1 (κ)), containing free –SH groups, where the percentage of dimers increased with increasing the pH from 5.8 to 9.5.[61]

Storage often leads to disulfide-based aggregation. Storage of a lyophilized excipient-free antibody (IgG1, containing 12 intra and 4 interchain disulfides) formulation for 1 year at 30°C resulted in formation of reducible dimer and trimers.[62] Similarly, reducible aggregates of a monoclonal antibody (type not specified) were detectable

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by SDS–PAGE after storage of the lyophilized formulation at 50°C for 6 months.[1] Such disulfide-linked covalent dimers and trimers were also observed during storage of spray-dried anti-IgE humanized monoclonal antibody.[71]

Nonreducible Cross-Linking

Nonreducible cross-linking was observed in several studies. Incubation of a human monoclonal antibody (C23) in solution at a basic pH at 37°C for 14 days resulted in formation of nonreducible bands above the light chains at pH 4 and 10.[72] Incubation of two mouse monoclonal antibodies—IgG2a (κ) and IgG1 (κ), between pH 3.0 and 10 at 37°C for 32 days led to formation of a nonreducible 88 kDa species by SDS–PAGE.[17] A species with the same molecular weight was observed after incubation of another monoclonal antibody, OKT3 (IgG2a), at 37°C for 2 months.[10,73] Further examination suggests that this species is a cross-linked product of H and L chains between the L46-52 and H99-121 regions. Although the exact chemical nature was not determined, an oxidative step is apparently involved as inhibition of oxidation delayed the formation of this species.[10,73]

A recent study shows that a nonreducible thioether bond can be formed between C223 of the heavy chain and the C-terminal Cys residue of the light chain in humanized IgG1 antibodies. This cross-linked product has a molecular weight of 75 kDa by MS but shows an apparent molecular weight of 92 kDa by SDS–PAGE.[74]

Nonreducible cross-linked products were also observed in solid dosage forms. Incubation of a lyophilized mouse monoclonal antibody [IgG2a (κ)] without lyoprotectant or in the presence of 5% sucrose, dextran, or hydroxypropyl-beta-cyclodextrin (HP-β-CD) at 56°C for 18 days led to formation of 100-kDa band under reduced conditions by SDS–PAGE.[59]

Deamidation

Antibody deamidation has been extensively reported in the literature. This common protein degradation pathway is so prevalent that purified antibody preparations may contain many deamidated forms. For example, several deamidated forms of recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb) were found by cation-exchange chromatography, including (1) deamidated Asn30 (to aspartate) on one light chain, (2) deamidated Asn30 (to aspartate) on two light chains, and (3) deamidated Asn55 on the heavy chain (to isoaspartate).[37] The sole conversion of Asn30 to aspartate (not isoaspartate) suggests that the deamidation mechanism in cell culture may be different from that during storage.

Storage can easily generate large amounts of deamidated products. Incubation of a monoclonal antibody, OKT3 (IgG2a) in a PBS solution at pH 7 containing Tween 80 at 37°C for 2 months led to more than 90% deamidation at Asn H386.[10] By monitoring the ammonia generation, Poborji et al.[41] estimated that 4% of the total number of Asn and Gln residues in a chimeric antibody (L6) was deamidated after storing the solution at pH 7.2 at 50°C for 3 weeks.

Deamidation also occurs in solid state. In the evaluation of storage stability of a model recombinant humanized monoclonal antibody (rhuMAb HER2), Cleland et al. reported that incubation of a high-moisture formulation (8.4% moisture) for 12 months at 40°C resulted in a 19% drop in the main peak by IEX due to deamidation.[57]

Deamidation in proteins goes mostly through the intermediate of succinimide at Asn (more readily) and Gln (see reviews[75,76]).This seems to be the case for antibodies, even though alternative mechanisms were reported, such as deamidation of Asn30 on the light chain of recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb).[37] A method has been developed to detect the formation of succinimide.[77]

The rate of deamidation via succinimidation in proteins can be affected by a variety of factors, such as pH, sequence, and steric effect (see review[44]). A recent report demonstrated a strong pH-dependency of deamidation at Asn55 (pH 7 > pH 6 > pH 5 > pH 4) in a fully human IgG1 in the pH range of 4–7 during storage at 25°C.[78] Using small peptide as a model, Tyler-Cross and Schirch[79] found that deamidation of Asn residues depends on the amino acid residue on the carboxyl side of Asn in neutral and alkaline solutions. Increasing the size and branching of these amino acids decreased the rate of deamidation by as much as 70-fold compared with the N–G sequence (greatest rate of deamidation) but under acidic conditions, these amino acids lost their protective effect.

Isomerization

The most common isomerization in antibodies is iso-aspartic acid formation, which results not only

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from direct isomerization of Asp but also, mostly, from hydrolysis of succinimide intermediate. The pH-dependent formation of succinimide intermediate can occur either from Asn deamidation or Asp dehydration.[36] In neutral and alkaline condition, the isoAsp and Asp products formed in a peptide were at a ratio of about 3:1.[79]

Isomerization is also prevalent and difficult to control. Again, many purified proteins contain significant amount of isomerized products, either from deamidation or direct isomerization. A typical example is recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb).[37] In addition, since isomerization occurred at Asp H102 in CDR regions, the activity of the isomerized species is only 9–21% of the major species.[37] Similarly, isomerization of Asp L32 on one light chain in a recombinant monoclonal anti-IgE antibody (E25) reduced the relative binding activity of $F(ab)'_2$ to 42% and the activity of isomerized form on both chains (iso-Asp-iso-Asp) to 15%.[36]

Since formation of the succinimide intermediate does not need participation of water, it can readily occur in solid state. Asp isomerization is one of the major degradation pathways for a lyophilized, monoclonal antibody (type not specified), and increases with increasing storage temperatures both above and below their Tg values.[1]

Like deamidation, the relative rate of isomerization can be influenced strongly by steric effect. For example, a recombinant monoclonal anti-IgE antibody (E25) contains two Asp-Gly sequences within its CDRs, but only one site was found to be labile to isomerization (Asp L32). The unreactivity of one Asp residue is suggested to be due to hydrogen bonding.[36]

Oxidation

The oxidizable residues in proteins include Met, Tyr, Trp, His, and Cys. Although oxidation is not as prevalent as deamidation and isomerization in antibodies, it can easily occur during storage of antibodies. For example, the major route of degradation of a monoclonal antibody, OKT3 (IgG2a), in solution during storage at 5°C is oxidation of a nondisulfide Cys and several Met residues.[10] Oxidation was also observed in rhuMAb anti-CD20 in solution during storage at 40°C for 2 months.[55]

Oxidation of CDP870, a pegylated one-half antibody (one light and one heavy chain) at a Met residue (M3) was also observed after incubation of the protein at 25°C or 40°C for 12 weeks (14% at pH 4.1 and 4.2% at pH 5.5).[80] Light exposure can accelerate baseline oxidation. For example, light exposure (20,000 lux for 2 weeks at 27°C) of recombinant humanized monoclonal antibody HER2, rhuMAb HER2 caused 5–10% increase in oxidation in various liquid formulations at Met H255 (primary site) and Met H431 at temperatures 30 and 40°C.[81]

Formation of Acidic or Basic Species

Antibodies can form acidic or basic species, which are often monitored by IEF or ion exchange chromatography. Among all the possibilities, deamidation is the most likely degradation pathway, leading to formation of acidic species. Therefore, formation of such species is used loosely as an indication of deamidation in the absence of other confirmatory studies. Strictly speaking, formation of such species can only be considered as an indication of chemical instability (see below). A pH-dependency is almost certain for this kind of degradation. In the stabilization of CDP870, a one-half antibody (one light and one heavy chain), which is linked through Cys to a branched (20 kDa each) PEG, Johnson et al.[80] found that the protein generated more acidic species (up to 17% at pH 4.1 and 41% at pH 5.5) by IEF as the solution pH was increased from 4.1, 4.5, 5.0, to 5.5 during storage at 25°C for 12 weeks.[80]

Another possible mechanism for generating acidic species in antibodies is the Maillard reaction, where reducing sugars can react with lysine residues. Such a reation will result in loss of positive charges and formation of apparently more acidic species. This is the case for an spray-dried anti-IgE humanized monoclonal antibody with lactose during storage.[71]

Formation of basic species was also observed in antibodies. Its formation can result from several possibilities, most likely as a result of succinimide formation, removal of sialic acids, or pyroGlu formation. Such a basic species was observed after incubation of a human monoclonal antibody (C23) at 37°C for 14 days in a solution at an acidic pH by IEF.[72]

C-Terminal Clipping

Terminal cleavages can easily occur during normal production of antibodies. For example, the majority of a purified chimeric protein rCD4-IgG lacks the heavy chain C-terminal Lys.[82]

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This is also the case for recombinant humanized monoclonal antibody HER2 (rhuMAb HER2, Herceptin, trastuzuMAb)[37] and a recombinant monoclonal anti-IgE antibody (E25).[36] It was suggested that the cleavage was due to the action of basic carboxypeptidases during production.[37]

Fragmentation

The most likely sequences leading to fragmentation in proteins are Asp-Gly and Asp-Pro,[83] although other sequences can also experience cleavages, such as Asn-Ser.[79] Fragmentation can easily occur in antibodies even during production processes. A small amount of fragment (MW < LC) was detectable under reduced condition in a purified recombinant MAb IgG4 produced in Chinese hamster ovary (CHO) cells.[7] Half molecules should be monitored routinely for IgG4s.[84]

A variety of processing conditions may accelerate fragmentation of antibodies, such as acidic or basic treatment,[72] thermal treatment,[41,67] freeze-thaw,[41] and storage.[17,73,78] Fragments can simply include masses with a loss of a light chain (M-LC), a loss of a Fab arm (M-Fab), and separated heavy-chain (HC) and light-chain (LC), as well as species less than common antibody subunits, resulting from both peptide and/or disulfide bond cleavage.[67] Antibodies are also subject to radiation-induced cleavages.[85]

Maillard Reaction

Proteins may form adducts with sugars. In an investigative study, mouse MAbs were found to form glucose adducts after incubation with 0.5 M glucose at pH 7.4 for 14–21 days at 37°C and the glycated antibodies significantly increased the dissociation of the antibody-antigen binding complex.[86]

ANTIBODY FORMULATION

As mentioned above, antibodies, like other proteins, may generate a variety of degradants during production, processing, and storage both in liquid and solid states. Their tendency to generate such degradants depends very much on their individual sequence, pI, hydrophobicity, and carbohydrate content.[23] The antibody degradation products may have reduced activity and more importantly, increased immunogenicity.[14,87] A strong immune response (antibody formation) may lead to severe neutralization of the protein drug product and even endogenous proteins.

The major purpose of formulating antibodies as therapeutic agents is to control the rate of antibody degradation to provide an acceptable shelf life for worldwide shipping and storage. This can be done by choosing proper formulation excipients and other formulation conditions. It should be stressed that one formulation excipient stabilizing a specific antibody may not be suitable for another because of the differences in their sequence. A proper formulation composition should not only maximally preserve the activity of the antibody but also minimize the potential immune response, as excipients could alter the immune response by changing the presentation of the protein (such as the spacing of epitopes).[14] The following section will discuss critical factors in formulating both liquid and lyophilized antibody products. Advanced formulations will also be briefly described.

Liquid Formulation

Liquid dosage form is usually preferable to lyophilized products as it is easier to administer and less expensive to manufacture. Among all the commercial antibody products, about half are stable enough to be formulated in a liquid form (Tab. 1). Formulating a successful liquid product needs consideration of at least the following aspects.

Protein Concentration

Since the EC50 values of antibodies are often 10–1,000 times higher than for other proteins such as hormones and cytokines,[35] a relatively large amount of antibodies needs to be dosed to achieve any therapeutic effect. A large dose requires that an antibody product needs to be formulated/reconstituted at a high concentration to reduce dose volume, especially for subcutaneous injections; otherwise, a large volume of antibody preparation has to be infused. Since the aggregation process is usually concentration-dependent, antibodies at high concentrations have at least two potential issues: high tendency to aggregate during storage and likely high viscosity, leading to more difficulty during injection (injection time correlated with viscosity).[47] It has been suggested that the concentration-dependent protein aggregation is the greatest challenge to developing high-concentration

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protein formulations.[47] On the other hand, moderate increase in protein concentration may not have a significant effect. In fact, increasing the concentration of antifebrin T2G1s Fab' (IgG1 (κ)), from 0.05 to 5.0 mg/mL in solution resulted in a decrease in dimer formation during storage (73.2% to 22.9% after 13 weeks at 22°C).[61]

An effective way to reduce the viscosity of an antibody solution is to add sufficient amount of NaCl.[5,88] Adjustment of formulation pH could potentially reduce the viscosity of an antibody solution.[88] Although not very effective, histidine has been shown to reduce the solution viscosity of a fully human anti-IL8 monoclonal antibody (ABX-IL8; IgG2) from 20 to about 9 centistokes when its concentration was increased from 0 to 60 mM.[21] However, use of such excipients in reducing viscosity can be limited, as the excipient can adversely affect the stability of the antibody, such as MAb anti-CD20.[55]

Another potential issue in formulating high-concentration antibody products is their solubility limits, as presence of undissolved proteins are generally not acceptable for intravenous injection. Fortunately, the solubility of antibodies seems to be relatively high and solubility-limited formulation difficulty has rarely been reported to our knowledge. To increase the solubility of antibodies, excipients such as surfactants may be used. In a recent report, Golovanov[89] found that a combination of L-Arg and L-Glu at an equimolar concentration (50 mM) significantly increased the solubility of several proteins (either alone does not have a significant effect). In addition, the room-temperature storage stability (fragmentation) of proteins was significantly improved as monitored by SDS–PAGE.

One potential advantage of formulating a protein product at higher concentrations is the greater freeze-thaw stability. Often, proteins at high concentrations are more resistant to freeze-thaw-induced aggregation, as the interface-induced protein denaturation can easily reach a saturation point. However, it does not seem to be the case for antibodies. Increasing the concentration of a chimeric antibody (L6) did not inhibit freeze-thaw-induced aggregation.[41] In addition, surfactants such as Pluronic F68 and Tween 80 did not appreciably prevent antibody aggregation. In a different study, Tween 80 alone (or Pluoronic F68) at 0.1% failed to offer any protection against freeze-thaw-induced aggregation of a single-chain antigen-binding protein CC49/218 sF_v (MW 27,000 d) at 1.45 mg/rnL in sodium PBS at pH 7.3.[56] These results suggest that freeze-thaw-induced antibody aggregation may not be a surface phenomenon.

Effect of Formulation pH

Formulation development often starts with determination of a stable formulation pH. Like other proteins, the pH effect on the stability of antibodies depends on the formulation composition,[55] stress conditions,[41] and even antibody concentration.[84] Formulation pH may affect the physical stability of antibodies as it alters the number and distribution of charges on the protein surface. For example, low pH (below 3) caused a loss of tertiary structure in rhuMAb anti-CD20.[55] Low pH (pH 3 and 4) is also responsible for the precipitation of two mouse monoclonal antibodies IgG2a (κ) and IgG1 (κ) during incubation at 37°C for 32 days.[17] Susceptibility to pH stress varies among different IgG molecules.[68]

Regarding chemical stability, formulation pH may play a critical role in controlling many degradation pathways, such as disulfide bond formation/exchange, deamidation, fragmentation, isomerization, etc. Due to variable effects on different degradation pathways, the optimum pH value varies depending on both the sequence of an antibody and the analytical methods used in monitoring the stability. By IEF, Lam et al. found that rhuMAb anti-CD20 is most stable at pH 5 within the pH range of 3–6 irrespective of protein concentration in formulations containing 10 mM citrate, 8% trehalose, and 0.05% Tween 20.[55] By SEC-HPLC, Usami et al. found that pH 6 was the most stable condition during incubation of a human monoclonal antibody (C23) at 37°C for 14 days in a solution containing isotonic sodium chloride between pH 4 and 10.[72] Sometimes, the optimum pH values reside outside a certain range. In the study of the stability of a chimeric antibody (L6), minimum amount of dimmer formation was observed at pH below 5.5 or above 8.5 (less than 2%) during freeze-thaw.[41]

It needs to be mentioned that oxidation could be inhibited by adjusting formulation pH. In a formulation containing 40 mg/mL MAb anti-CD20, 150 mM trehalose, 0.9% benzyl alcohol, 0.02% Tween 20, and 50 mM histidine, reducing the pH from 7.5 to 5 virtually eliminated the oxidation during storage at 40°C for 2 months.[55] In a different study, oxidation (M3) of PEG-CDP870, a one-half antibody, in a formulation containing 160 mg/mL CDP870, 10 mM sodium acetate, and

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125 mM NaCl was slower at pH 5.5 than at pH 4.1 (4.2% vs. 14% after 12 weeks at 40°C).[80]

Due to the simultaneous presence of multiple antibody degradation pathways, the formulation pH has to be adjusted to balance all the potential degradations. Generally, a weakly acidic condition seems to be the optimum for most antibodies (see Tab. 1).

Effect of Buffering Agents

It has been long recognized that both the type and concentration of a buffering agent may affect the stability of proteins (see review[44]). For example, phosphate buffer accelerated deamidation of an IgG1 relative to citrate buffer at both pH 6.5 and 7.0 during storage at 25°C.[78] Therefore, proper choice of a buffering agent can potentially achieve both pH control and stabilization of antibodies. In rare cases, a buffering agent good for one antibody may be harmful to another. One of these agents is histidine, which has a pKa of pH 6 and potentially good in controlling a weakly acidic condition. It has been shown to provide better protection against precipitation for a fully human anti-IL8 monoclonal antibody (ABX-IL8; IgG2) upon thermal incubation both at 50 and 40°C than citrate at pH 6.[21] Addition of a small amount of histidine (0.4 mM) also increased the freeze-thaw (4×) recovery of a single-chain antigen-binding protein CC49/218 sF_v (MW 27,000 d) at 1.45 mg/rnL in PBS solution at pH 7.3 from 37% to 90%.[56] On the contrary, histidine was found not only to increase the rate of aggregation of rhuMAb anti-CD20 during storage but also to induce coloration of the solution compared to a acetate-buffered antibody solution at pH 5.[55] In addition, oxidation of Fc was also faster in histidine solution.

The concentration effect of a buffering agent was demonstrated in a study where freeze-thaw-induced aggregation of a chimeric antibody (L6) was higher with increasing phosphate buffer concentration (0.01 vs. 0.05).[41] Therefore, both the type and concentration of buffering agents need to be examined.

Effect of Formulation Excipients

Use of formulation excipients remains a major and convenient approach in stabilizing antibodies in solutions. It is so at least in reducing antibody aggregation.[47] A variety of formulation excipients have been shown to stabilize antibodies under different processing conditions and during storage, including sugars,[41] polyols,[41] amino acids,[41,84] surfactants,[84] and polymers.[45,84]

Formulation excipients are effective generally in protecting the physical stability of an antibody. Among these excipients, sugars are the most commonly used. A variety of sugars, such as sucrose, trehalose, glucose, have been shown to reduce the freeze/thaw-induced aggregation of rhuMAb anti-CD20,[55] a chimeric antibody (L6),[41] a human anti-IL8 monoclonal antibody (ABX-IL8; IgG2),[21] and a single-chain antigen-binding protein CC49/218 sF_v (27 kDa).[56] Other excipients can be equally or even more effective in protecting antibodies.. Histidine was shown to be equally effective as sucrose in reducing freeze-thaw induced aggregation of a human anti-IL8 monoclonal antibody (ABX-IL8; IgG2) and combination with Arg resulted in a better protection than sucrose in solution stability at different incubation temperatures.[21] Sugars are not always effective. In the evaluation of freeze-thaw stability of a single-chain antigen-binding protein CC49/218 sF_v (MW 27 kDa) at 1.45 mg/mL in sodium phosphate buffered saline (PBS) at pH 7.3, addition of 10 mM trehalose, lactose, glucose, or mannitol did not offer any protection.[56] In a rare case, sucrose has been shown to promote agitation-induced aggregation of an IgG1 antibody.[90]

Formulation excipients may inhibit chemical degradation of antibodies. Replacing 0.14 M NaCl with 8% trehalose or 4% mannitol in a rhuMAb anti-CD20 increased the chemical stability as measured by IEX during storage at 40°C.[55] Such an effect is likely a result of stabilization of antibody conformation. Some excipients may protect antibodies against oxidation. Replacing NaCl with 4% mannitol and 1% benzyl alcohol protected recombinant humanized monoclonal antibody HER2, rhuMAb HER2, against oxidation (primarily Met-255) at 30 or 40°C.[81] This effect is likely due to a function of mannitol as a free radical scavenger. Some commonly used antioxidants, such as thiosulfate and methionine, are effective in inhibiting antibody oxidation. The minimum effective levels (molar ratios of antibody to antioxidant) required to inhibit temperature-induced oxidation of rhuMAb HER2 were 1:5 and 1:25 for methionine and thiosulfate, respectively.[81] However, use of thiosulfate has led to formation of a thiosulfate adduct of rhuMAb HER2.[81] The safety of such a thio-containing adduct has not been reported.

One of the main excipients often used in antibody formulation is surfactants. They are usually

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effective in reducing shaking/stirring-induced aggregation[91] but may have negative effect during long-term storage.[92] One obvious concern is that such compounds may contain a residual level of peroxides, which have been shown to cause protein oxidation.[93] Therefore, use of surfactants should be kept to a minimum in an antibody formulation if possible. For example, removing Tween 20 in a recombinant humanized monoclonal antibody HER2, rhuMAb HER2 solution reduced the oxidized antibody from 52% to <10% at 40°C.[81]

Effect of Shaking/Shearing

Both shaking and shearing can denature antibodies. It was found that shaking murine antibody-based products caused antibody precipitation and the shape of the precipitates are different depending on the fill volume.[53] In the evaluation of shear effect on the antigen-binding activity of a recombinant scFv antibody fragment in a buffer solution, Harrison et al.[45] found that the binding activity decayed at a mean rate constant of 0.83/h at a shear of approximately 20,000/s.

Effect of Preservatives

A limited number of studies have been conducted on the compatibility of preservatives with antibodies. Compatibility depends both on the antibody and the preservative. In the evaluation of the effect of several preservatives, including benzyl alcohol, chlorobutanol, methylparaben, propylparaben, phenol, and m-cresol, on the stability of a humanized monoclonal antibody, Gupta and Kaisheva[94] found that the antibody was most stable in the presence of methylparaben and propylparaben, compatible with benzyl alcohol and chlorobutanol at low concentrations, and not compatible with phenol and m-cresol, as measured by a variety of assays, including SEC-HPLC, DSC, light scattering, UV, and potency assay.

Effect of Processing Equipment

Another important issue in antibody formulation is the choice of proper processing equipment/containers. A few studies have shown that antibody stability can be significantly affected if an inappropriate choice is made. In the study of the stability of recombinant humanized monoclonal antibody HER2, rhuMAb HER2, in liquid formulations, Lam et al.[81] found that replacing the stainless steel filler with a nonstainless steel filler reduced the oxidized antibody (primarily Met-255) from 52% to 18% after storage for 2 weeks at 40°C. It was suggested that Fe ions, released from erosion of stainless steel by chloride ion at low pH, catalyzed the oxidation. In a similar case, Chen et al.[21] demonstrated that a fully human anti-IL8 monoclonal antibody (ABX-IL8) in aqueous formulations containing 60 mM His had a higher level of aggregates after freeze-thaw in a stainless steel vessel and subsequent storage at 40°C, possibly due to the effect of Fe ions generated from a similar mechanism. In addition, proteins have been shown to facilitate metal corrosion.[95]

Effect of Product Containers

The effect of product containers was clearly demonstrated in a recent study. McCormick et al.[96] reported that Tween 80, intended to replace human albumin in the original formulation, interacted with uncoated rubber stoppers in single-use Eprex syringes. The stoppers leached a small amount of plasticizers in the drug solution, which acted as an adjuvant, and caused a strong IgG response to the recombinant human erythropoietin. The immune response was significantly minimized later by switching to PTFE-coated rubber stoppers. In addition, headspace oxygen can accelerate oxidation of antibodies and replacement with an inert gas could minimize such a reaction.[73]

Accelerated Stability Studies

To accelerate formulation development process, accelerated stability studies are usually conducted. However, estimation of room temperature or 5°C stability based on accelerated stability studies for antibodies, like other proteins, may or may not be possible or accurate. The unpredictability is due to the presence of complex and multiple degradation pathways, which may have different degree of temperature dependencies.[10] Kroon et al.[10] found that relative to other degradation pathways of a monoclonal antibody, OKT3 (IgG2a), Asn deamidation was preferentially accelerated with increasing temperature. Therefore, caution needs to be applied in interpreting such high-temperature-induced deamidation. On the other hand, Poborji et al.[41] found that loss of monomeric chimeric antibody (L6) at pH 7.2 followed Arrhenius behavior in the temperature range of 30–50°C and extrapolation of the high temperature SEC data to 2–8°C at pH 7 and

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5.5 resulted in comparable stability estimates with the available real-time data.

Lyophilized Formulation

Preparation of lyophilized protein formulations has been extensively reviewed.[97–101] Like most proteins, some antibodies are not stable enough in a liquid form and lyophilized dosage forms will have to be considered. Lyophilization was suggested to be one of the two approaches in solving antibody aggregation.[47] This section will discuss some critical issues in formulating a lyophilized antibody product.

Amorphous Versus Crystalline State

It has been commonly believed that proteins are more stable in an amorphous state.[103] This is mainly because proteins need another excipient(s) to replace water molecules to from the required H-bonds as water molecules are removed during drying and a crystalline matrix does not provide intimate H-bonding between the excipient and the protein.[104,105] It appears that if the protein itself can be crystallized during the lyophilization process (may be difficult practically), the protein could be more stable and might not need as much stabilizing agent as in the amorphous state. In a recent report, Shenoy et al.[106] compared the stability of two model proteins, glucose oxidase (GO) and lipase, and demonstrated that dry crystalline formulations are significantly more stable than their amorphous counterparts as monitored by size-exclusion chromatography. It remains to be seen whether this can be applicable to antibodies.

Effect of Formulation Excipients

To make a lyophilized antibody product, at least one formulation excipient, a bulking agent, is needed to confer an acceptable cake. If the antibody is not stable enough in the presence of a bulking agent during lyophilization or storage, a stabilizer(s) is included. The relative amount of formulation excipients (bulking and stabilizing agents) should be carefully chosen as these agents may affect each other's behavior, the tonicity, and stability of the lyophilized products.

Commonly used bulking agents include mannitol and glycine. Crystallization of these agents during lyophilization makes them wonderful bulking agents but poor stabilizing agents.[57] Although mannitol could stabilize an antibody as in the case for a monoclonal antibody-vinca conjugate in a PBS solution at pH 7.4 upon lyophilization,[60] many studies showed that mannitol could not stabilize effectively or even destabilizes antibodies. Such examples include the aggregation of a lyophilized model recombinant humanized monoclonal antibody (rhuMAb HER2) in the presence of mannitol during storage.[3,57] In the lyophilization of a human monoclonal antibody at 1 mg/mL, it was demonstrated that addition of 5% mannitol has no effect on the lyophilization-induced aggregation in PBS or physiological saline as measured by OD600 and addition of 10% mannitol actually accelerated aggregation during the lyophilization process.[58] On the other hand, when used in combination with sucrose or trehalose, similar degree of stabilization to that for sugar alone may be achieved such as the case for model recombinant humanized monoclonal antibody (rhuMAb HER2).[57] The disaccharide/mannitol formulations also inhibited deamidation of this antibody during storage to a greater extent than the lyoprotectant formulations alone.[57]

Sugars are the most common stabilizing agents used in lyophilized formulations. Among these, two nonreducing sugars, sucrose and trehalose, are usually the first choice. Both sugars protected the stability of a few lyophilized antibodies equally well. These antibodies include lyophilized recombinant humanized monoclonal antibody, rhuMAb HER2,[57] IgG1 (containing 12 intra and 4 interchain disulfides),[62] anti-IgG,[107] and chimeric monoclonal antibody.[64] However, sucrose seemed to be more effective in protecting a lyophilized IgG1 against aggregation during storage at 40°C at a sugar:protein weight ratio of 1:1 (Chang et al. 2005b).[102] In another study, sucrose at 5% failed to offer any protection to a lyophilized mouse monoclonal antibody (MN12) (IgG2a (κ)) during storage at 56°C for 18 days.[59] Again, as mentioned in the liquid formulation section, even the most commonly used stabilizers may not stabilize all antibodies in the solid state and antibodies need to be treated as individually different molecules.

When sugars are used as stabilizing agents (lyoprotectants), a sufficient quantity needs to be used to achieve a significant effect depending on the protein concentration. It has been suggested that a molar lyoprotectant:protein ratio of 300:1 or greater should be used.[47] Indeed, the available literature data indicate a ratio higher than 300 is needed for better stabilization. It was shown that sugars protect the stability (aggregation and Asp isomerization) of a lyophilized, monoclonal

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antibody (type not specified) to a significant level when the sugar to protein molar ratio was increased to 500:1, which happens to the theoretical number of water binding sites in the molecule.[1] Similarly, Andya et al.[62] demonstrated that use of sucrose or trehalose inhibited the aggregation of a lyophilized antibody (IgG1—containing 12 intra and 4 interchain disulfides) during storage at 30°C to a maximum degree when the sucrose/trehalose:protein ratio was 500 or higher, which is roughly equivalent to the number of water-binding sites on the surface of the protein (550 estimated). Increasing the trehalose/anti-HER2 ratio from 60 mM (360 molar ratio) to 200 mM (1,200 molar ratio) significantly increased the stability (monomer by SEC-HPLC) of lyophilized formulation at 25 mg/mL at 40°C.[107] In a recent report, it was found that at least a weight ratio of 2:1 (molar ratio of about 800) was needed to achieve a maximum protection of a lyophilized sucrose:IgG1 formulation against both aggregation and chemical degradation during storage at 40°C (Chang et al. 2005a).[101]

Other formulation excipients were also used and some of these are effective in stabilizing certain antibodies. A recent study demonstrated that addition of sorbitol to a sucrose or trehalose formulation resulted in further enhancement of storage stability of a lyophilized IgG1 antibody (Chang et al. 2005b).[102] Either dextran or HB-β-CD (better) protected the activity of a lyophilized mouse monoclonal antibody (MN12) (IgG2a (κ)) during storage.[59] Glucose was shown to inhibit gamma irradiation-induced fragmentation of humanized monoclonal antibodies (hr3).[85]

Effect of Formulation "pH" and Buffering Agents

The pH of the liquid formulation can have a potential effect on the stability of the lyophilized formulation, even though the solid-state "pH" could not be well defined. In the evaluation of the stability of a lyophilized monoclonal antibody-vinca conjugate, aggregation seems to be lower at a neutral pH 7.1 than at either pH 8.5 or 6.1 when the lyophilized formulation was stored at 25°C.[60] In adjusting the formulation pH, use of a buffering agent may have effect on the antibody stability both during lyophilization and storage of the lyophilized products. For example, in the stability study of a fully human anti-IL8 monoclonal antibody (ABX-IL8; IgG2), Chen et al.[21] demonstrated that addition of histidine inhibited the formation of HMW species upon lyophilization and during storage at 37°C in a concentration-dependent manner. Among several excipients including His, Gly, mannitol, Glu, and polysorbate 20, His is the most critical in protecting solid-state stability of the antibody (minimizing aggregation). In a different study, the aggregation rate of a lyophilized anti-IgE at 5°C at 5 mg/mL in 10 mM buffer is affected both by pH and buffers in the following order: Na Phosphate, pH 7 > K Phosphate, pH 7 > Na Succinate, pH 6 or 5 > Histidine, pH 7.[107] It should be noted that some buffering agents may induce significant pH change due to selective crystallization during lyophilization, such as sodium phosphate. Such buffering agents should be avoided in preparing pH-sensitive antibody formulations.

Effect of Protein Concentration

In many cases, increasing the protein concentration increases the stability of the protein during lyophilization (see review).[98] However, antibodies do not seem to follow this trend and many antibodies have been shown to be less stable both during lyophilization and storage at high concentrations. For example, lyophilization of a human monoclonal antibody caused significant aggregation of MAb formulated in PBS or physiological saline as measured by OD600 and increasing the protein concentration from 1 to 2.5 or 5 mg/mL increased the OD600 from 0.194 to 0.311 or 0.427, respectively.[58] Similar trend was also observed during storage of lyophilized formulation. Increasing the concentration of a chimeric monoclonal antibody from 2.5 mg/mL to 25 mg/mL in a lyophilized formulation, containing 31 mg/mL sucrose, 15 mM NaCl, 0.02% Tween 80, 10 mM citrate, increased the aggregate level from 0.4% to 0.6% after 2 months at 5°C.[64] In the evaluation of the stability of a model recombinant humanized monoclonal antibody (rhuMAb HER2), Cleland et al.[57] demonstrated that increasing the protein concentration from 25 mg/mL to 50 mg/mL in a lyophilized formulation (containing 60 mM trehalose, 5 mM His at pH 6) increased the aggregate level from 8.5% to over 30% by SEC-after storage at 40°C for 44 months. Such behavior was also observed of anti-HER2 from 5 to 21 mg/mL containing 250 mannitol.[107]

Effect of Moisture Content

The effect of moisture on the stability of lyophilized antibodies has not been consistent and seem

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to depend on the antibody and the degradation pathways being monitored.[57] Generally, increasing moisture content of a lyophilized antibody will gradually increase the rate of degradation during storage. Such negative effect of moisture was clearly demonstrated in a variety of degradation pathways, including dimerization of T2G1s Fab' (IgG1 (κ)) in a moisture content range of 1.5–12.3%,[61] aggregation of TNF-MAb between 0.68% and 8%,[108] formation of acidic/basic species of rhuMAb HER2 between 1% and 8.4%[57] and fragmentation of a mouse monoclonal antibody (MN12) with and without secondary drying.[59]

In other cases, the effect of moisture is either complex or not significant. For example, Breen et al.[1] found that high-moisture formulations (8%) of a lyophilized monoclonal antibody (type not specified) showed a higher rate of aggregation, fragmentation, and Asp isomerization during storage than those containing 2% or 5% moisture but formulations containing intermediate moisture levels (2–3%) were less prone to aggregation than those containing a lower moisture levels (1%) as measured by SEC under accelerated storage conditions. Similarly, the aggregation of a lyophilized IgG1 was found to be minimal at an intermediate moisture level around 3% at different storage temperatures. (Chang et al. 2005b).[102] In a different study, Cleland et al.[57] found that using a model recombinant humanized monoclonal antibody (rhuMAb HER2), a residual moisture between 1 and 8.4% had no impact on the rate of aggregation during storage at 2–8 or 40°C for 12 months.

Accelerated Stability Studies

Like antibodies in a liquid state, those in a solid state may or may not undergo degradation that is characteristic of Arrhenius behavior. It is generally believed that stability studies should be conducted at least below the glass transition temperature of the formulation. Duddu et al.[64] found that accelerated stability data generated in the glassy state (40°C) seems to be a better predictor of the relative stability of formulations than the data generated at a higher temperature (60°C). In the study of the stability of a high-concentration, lyophilized, monoclonal antibody (type not specified), Breen et al.[1] demonstrated that chemical and physical degradation pathways followed Arrhenius kinetics during storage in the glassy state. Only Asp isomerization followed the Arrhenius model above the Tg value.

Advanced Formulations

In addition to the liquid and lyophilized dosage forms on the market, other dosage forms have been tried and limited success has been reported.

Spray-Dried Formulations

Spray drying is an efficient way of preparing solid dosage forms because of the rapid removal of a solvent(s) from a drug solution. It is a very attractive alternative to lyophilization in preparing solid protein formulations. So far, a number of studies have been conducted for proteins and partly because of the high-temperature exposure in the process, albeit very short, limited success has been achieved. Protein aggregation during spray drying seems to be the major challenge.[65,66,109,110]

Spray drying of antibodies has also been tried. As for other proteins, process-induced protein aggregation seems to be the major issue.[71,110] Careful selection of proper excipients could minimize this problem. In the evaluation of a spray-dried formulation for a rhuMAbE25, it was demonstrated that trehalose or lactose minimized the aggregation during spray drying (aggregate dropped from 5–6% to ≤1%). For trehalose, the molar ratio for significant inhibition of aggregation is at or above 300:1 to 500:1 (excipient: protein).[71] Such a ratio seems to be comparable with that used in the lyophilized formation. The addition of mannitol also reduced aggregation, but only up to a molar ratio of 200:1 and further increase in mannitol content resulted in crystallization, which had a detrimental effect on protein stability and aerosol performance.[71] In a different study, either trehalose or sorbitol could inhibit IgG aggregation during spray drying.[110]

Stabilized Antibodies via Mutagenesis

Antibody fragments, such as scFv, are alternative antibody therapeutics. However, since their stability is not as good as full-length antibodies, mutagenesis, or chemical modifications have been tried to improve its stability. For example, R71A mutagenesis in the heavy chain of an unstable scFv dramatically increased its stability when incubated in human serum while having only a minor effect on the binding affinity of the molecule.[111] A more stable heavy chain, made through mutation, can increase the stability of

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the light chain, and thereby confer more stability to the whole scFv.[24]

Stabilized Antibodies via Chemical Modifications

The clinical performance of an antibody can be desirably changed by conjugation of the antibody to another entity. For example, McIntosh et al.[112] demonstrated that conjugation of carboxymethyl dextran to a tumor-antigen-specific monoclonal antibody (A5B7) increased the clearance of the antibody in mice but conjugation of cisplatin (*cis*-dichlorodiammine platinum II) with the antibody complex restricted its tissue distribution and reduced its systemic clearance.

PEGylated Antibodies

A common method of increasing plasma half-life of proteins is to increase the size of the protein by attaching a PEG moiety. Currently, there are at least four PEGylated commercial protein products on the market. However, the long plasma half-lives (as high as 7–23 days) of antibodies made much less appealing the development of such an antibody product. Since the long half-life was due to the binding of Fc to the Fc-receptor (neonatal Fc receptor, FcRn) in various tissues,[33,35] antibody fragments, such as Fab′ lacking the Fc portion have a much shorter half-life and could be good candidates for PEGylation. Such a modification was made on a humanized IgG Fab′ fragment via site-specific attachment to an additionally engineered Cys residue, as modification via the lysine residues led to substantial losses in binding activity.[29]

Controlled Release Systems

Controlled release systems have been extensively investigated for proteins in the past two decades.[113,114] However, limited work has been conducted in this area for antibodies, partly due to their relatively long plasma half-lives compared with other proteins. To achieve long-term effect, a controlled released system consisting of biodegradable poly (lactic-glycolic) acid (PLGA) was prepared for an anti-cocaine catalytic monoclonal antibody and an *in vivo* release of the antibody for up to 10 days was demonstrated in mice following subcutaneous injection.[115] It is anticipated that such systems could be useful if a minimum of 1-week duration of release is achieved.

SUMMARY

Antibodies have similar tertiary structures. The presence of a significant number of disulfide bonds and intimate domain–domain interactions in antibodies make them relatively stable and more resistant to moderate thermal stress compared to other proteins. Nevertheless, antibodies do experience a variety of instabilities similar to most proteins. These physical and chemical instabilities include denaturation, aggregation, surface adsorption, deamidation, oxidation, isomerization, fragmentation, etc. Due to the significant difference in the primary sequence among different antibodies, the relative severity of these degradation pathways can be significantly different. On the average, aggregation, deamidation, and isomerization seem to be more prevalent in antibodies.

Partly due to the stability difference, some antibody products are made into a liquid form while others are lyophilized (Tab. 1). The solution pH of these commercial products is either neutral or weakly acidic, suggesting that such a pH range is probably optimal for most antibodies. Surfactants have been used in most of these antibody products, presumably to inhibit antibody aggregation, and will likely be used in other antibody drug candidates. Two most commonly used formulation excipients in these antibody formulations are sucrose and NaCl. For liquid formulations, either one can be used if they offer the same level of stability protection. For lyophilized formulations, sucrose is preferable as NaCl does not form intimate H-bonds with the antibody and also reduce the glass transition temperature of formulation, making lyophilization less efficient. All the formulation excipients and buffering agents used in commercial antibody products or discussed in the article should be evaluated individually for each antibody drug candidate through stability studies before they are chosen as part of the product, as antibodies are structurally different.

The available stability data in the literature and the information on the commercial antibody products suggest that antibody formulation seems challenging but relatively manageable, compared to other protein drugs. Three major issues in antibody formulation are apparently challenging and need significant attention in the coming years: (1) development of stable high-concentration formulations, (2) management of the high-concentration-associated viscosity of these formulations,

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and (3) minimization of antibody-formulation-induced immune response.

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HOFFMANN EITLE

HOFFMANN EITLE
Patent- und Rechtsanwälte
Partnerschaftsgesellschaft mbB
Arabellastraße 30
81925 München
Deutschland | Germany
T +49. (0)89. 92 409. 0
F +49. (0)89. 91 83 56
pm@hoffmanneitle.com
www.hoffmanneitle.com

EPO - Munich
101
09. Aug. 2017

HOFFMANN EITLE | Postfach 81 04 20 | 81904 München

European Patent Office

80298 München

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Our Ref.:	**198 441 u6/ne** **Eculizumab Composition / ALEXION**
Opposition to:	**EP 2 359 834 B1 (11001632.6)**
Proprietor:	**Alexion Pharmaceuticals, Inc.** **Cheshire, CT 06410 (US)**
Opponent:	**Hoffmann Eitle** **Patent- und Rechtsanwälte PartmbB** **Arabellastr. 30** **81925 Munich (DE)**

NOTICE OF OPPOSITION

Partnerschaftsregister Amtsgericht München | PR 1372
Eine Liste der Partner i.S.d. PartGG ist einsehbar unter www.hoffmanneitle.com/partner, über die obige Adresse und unser Büro in London:
A list of members of the partnership is open to inspection at www.hoffmanneitle.com/partner, at the above address and our London office:
Hoffmann Eitle | Harmsworth House | 13–15 Bouverie Street | London EC4Y 8DP

In the name and on behalf of

Hoffmann Eitle
Patent- und Rechtsanwälte PartmbB
Arabellastr. 30
81925 Munich (DE)

(hereinafter also referred to as the "***Opponent***")

we hereby lodge an

OPPOSITION

pursuant to **Art. 99 EPC** to

EP 2 359 834 B1

assigned to

Alexion Pharmaceuticals, Inc.
Cheshire, CT 06410 (US)

(hereinafter also referred to as the "***Proprietor***")

entitled:

"Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement".

A debit order to our account in the amount of **€ 785** is enclosed in accordance with **Art. 99(1) EPC** for the payment of the opposition fee.

Our requests and the statement of the grounds of the opposition are set out below.

REQUESTS

On the grounds of **Art. 100(a) EPC** it is petitioned that:

(1) the opposed patent **EP 2 359 834 B1** be revoked, and

(2) the parties be summoned to attend oral proceedings in accordance with **Art. 116(1) EPC** in the event that the Opposition Division is not in a position to immediately grant the request under (1).

REASONS

(1) The claimed teaching according to **EP 2 359 834 B1**, hereinafter also referred to as the "***opposed patent***", does not comply with **Art. 56 EPC**, i.e. it does not involve an inventive step.

(2) References to the specification of the opposed patent or to other patent documents will be made – where appropriate – by citing the relevant paragraphs using their corresponding [4-digit] section numbers.

1. CITED PRIOR ART

(3) The present opposition is based on the following documents:

A	**WO 2007/106585 A1** (application as filed)
B	**EP 2 359 834 B1** (opposed patent)
C	**US 60/783,070** (priority application)
D1	**US 2005/0191298 A1**
D2	**Hillmen et al.**, British Journal Haematol., vol.121, Suppl. 1, p.87, **2003**
D3	**Hillmen et al.**, N Engl. J Med **2004**; 350: 552-559
D4	**Harding,** Drugs of the Future, Prous Science, ES, vol.29, no.7, 673-676, **2004**
D5	**US 2005/221382 A1**
D6	**Hill**, Clinical Advances in Hematology & Oncology, Millennium Medical Pub., New York, US, vol.3, no.11, 849-850, **2005**
D7	**US 6,355,245 B1**
D8	**Thomas et al.,** Molecular Immunology, Vol. 33, No. 17/18, 1389-1401, **1996**
D9	**US 2003/0202972 A1**
D10	**Wang et al., J. pharm. Sci., vol. 96, no. 1, p. 1-26, Jan. 2007**
D11	**US 6,171,586 B1**
D12	**Maloney et al.**, Blood, vol. 90, no.6, **1997**: pp 2188-2195

ANNEX I Commercial monoclonal antibodies 2006 (all modes of administration)
ANNEX II Commercial monoclonal antibodies 2006 (i.v. administration)

(4) Documents **D1** to **D6** correspond to documents D1 to D6 as referenced in the **European Search Report** & **Opinion** dated July 12, 2011. Only **D1** and **D3** are refiled with this notice of opposition, as they will be dealt with in more detail below.

(5) Documents **D7** to **D12**, are new documents introduced herewith for the first time into the proceedings.

2. THE OPPOSED PATENT

(6) The original application (**A**) was filed on March 15, 2007 and published as **WO 2007/106585 A1** on September 20, 2007. The opposed patent (**B**) was filed as divisional application **11001632.6** from parent application **07753249.7** and was granted on Nov. 9, 2016

(7) The opposed patent claims the priority of **US 60/783,070** (**C**) filed on March 15, 2006.

2.1 TECHNICAL OBJECTIVE OF THE OPPOSED PATENT

(8) The opposed patent relates the treatment of patients afflicted with ***paroxysmal nocturnal hemoglobinuria***, also referred to as "***PNH***" (cf. [0001]).

(9) "***Eculizumab***" is a humanized monoclonal antibody directed against the terminal complement protein C5. It was shown that eculizumab is able to reduce intravascular hemolysis when the antibody was administered intravenously to PNH patients (cf. [0003]). The results of a follow-up phase III study ("*TRIUMPH*") indicated that any treatment that decreases hemolysis in a patient would result in an improvement in the "*quality of life*" of said patient (cf. [0006]).

(10) The opposed patent seeks to provide a pharmaceutical composition for use in treating a patient afflicted with PNH.

2.2 TECHNICAL SOLUTION AS CLAIMED

(11) As the technical solution to the above problem, the opposed patent was granted on the basis **claim 1**, which the sole claim of the patent. It reads:

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

2.2.1 Feature Analysis of Claim 1

(12) Accordingly, the pharmaceutical composition of Claim 1 is characterized by following technical features **1** to **7**:

1	*Medical use of the composition is for treating a patient afflicted with **PNH***
2	*the active ingredient of the composition is **eculizumab***
3	*the composition is a solution of a **300 mg eculizumab single-use dosage form***
4	*the **eculizumab concentration** in the composition is **10 mg / ml***
5	*the total **volume** of the composition is **30 ml***
6	*the solution is **sterile***
7	*the solution is **preservation-free***

2.2.2 Volume implicitly follows from of antibody concentration and antibody amount

(13) Notably, claim 1 stipulates that the total volume of the single-use dosage form is **30 ml** (feature 5). This feature, however, directly follows from features 3 and 4: Accordingly, a composition comprising 300 mg eculizumab at a concentration of 10 mg / ml would have a volume of 30 ml, as can be readily figured out by simple mathematical calculation.

2.2.3 Mode of administration is not limited

(14) The pharmaceutical composition of claim 1 is not restricted to any particular mode of administration. According to paragraph [0058] of the description, administration of the antibodies will generally be performed by an intravascular route, e.g. via intravenous infusion by injection. However, *"other routes of administration may be used if desired"*. These routes would include, for example, subcutaneous or intraperitoneal administration.

2.2.4 Method of manufacture is not limited

(15) It is further noted that opposed patent does not provide any specific method how to manufacture the pharmaceutical composition according to claim 1. The only information in this regard can be found in paragraph [0063] merely referring to prior art references, for example ***US 20030202972, US 20040091490, US 20050158316 WO 03/106644, WO 04/066957***, and ***WO 04/091658***.

(16) In this regard, reference is made to **US 2003/0202972**, provided herewith as **D9.** According to [0008] of **D9**, a lyophilized formulation can be reconstituted to generate a stable reconstituted formulation. For specific routes of administration, such as intravenous administration, concentrations of from about ***"10 – 40 mg/ml protein in the reconstituted formulation"*** are suggested (cf. [0107]).

(17) Hence, the antibody composition of opposed patent can be prepared and stored not only in liquid form, but also in lyophilized form, which is just reconstituted to a liquid solution with the features of claim 1 shortly before administration to the subject, for example, by intravenous infusion.

2.3 No Priority

(18) During the examination procedure, the proprietor relied, in particular, on page 5, lines 8-9, page 6, lines 21-23, and page 22, lines 12-14, of the application as filed (**A**) as basis for claim 1 of the granted patent (cf., for example, submission of January 13, 2016; p.2). These passages, however, are completely missing from the priority

document **US 60/783,070 (C)**. In fact, there is no disclosure whatsoever on a specific eculizumab formulation in the priority application.

(19) It follows that the opposed patent does not validly claim the priority of **US 60/783,070**. The relevant date for defining the prior art in accordance with **Art. 54(2) EPC** is the filing date of the original application, i.e. **March 15, 2007**.

3. LACK OF INVENTIVE STEP (ARTICLES 100(A) AND 56 EPC)

(20) Claim 1 of the opposed patent does not involve an inventive step.

3.1 SKILLED PERSON IN THE ART AND COMMON GENERAL KNOWLEDGE

(21) The opposed patent relates to the use of an anti-C5 antibody, specifically the already known antibody eculizumab, for the treatment of PNH. Thus the skilled person was, in general, faced with the task of identifying appropriate dosage forms for proceeding forward with this treatment.

(22) The exercise of developing a suitable dosage form is the rudimentary basis to any clinical program. Such a program involves at least a formulation specialist, who is familiar with the manufacture of protein-containing, in particular antibody-containing compositions for administration to a human subject.

(23) This skilled practitioner may seek support, as necessary, from a clinician who is ultimately responsible for the clinical care of the patients (e.g. diagnosis, examination and determination treatment), or from a clinical pharmacologist, who provides dose and frequency recommendations on the basis of pharmacokinetics and pharmacodynamics.

(24) Said person skilled in the art, or team of experts, is possessed of average knowledge and ability. He or she is aware of what was common general knowledge in the art at the relevant date (cf., for example, **T 4/98**, **T 143/94** and T **426/88**). Articles in technical journals can be representative of common general knowledge (cf. **T**

595/90). This applies in particular to articles providing a **review** or **survey** of a topic (cf. **T 309/88**).

(25) The skilled person in the field of pharmaceutical drug development would have been aware of the common general knowledge, as reflected, for example, by **Wang et al. (2007)** (**D10**). This document was published in January 2007 and belongs to the state of art in accordance with **Art. 54(2) EPC**, since the opposed patent can only claim its actual filing date of March 15, 2007 (cf. point 2.3 above).

(26) **D10** reflects on pharmaceutical antibody formulations that have been approved by the health authorities before the filing date of the opposed patent. It is a **review article** and therefore belongs to the common general knowledge in the sense of **T 309/88**. As stated in the Abstract, by 2006 more than **23 monoclonal antibodies** have entered the US market. An overview on the properties of these commercial antibody products, such as administration route or antibody concentration, is given in **Table 1** of **D10**.

(27) It is readily presumed that a **formulation specialist would have consulted D10 for guidance when tasked with the manufacture of a therapeutical antibody formulation**.

(28) Document **D10** will be discussed in more detail below with respect to inventive step.

3.2 Closest Prior Art

(29) **US 2005/0101298** (**D1**) and **Hillmen et al. 2004** (**D3**) relate to the treatment of patients with infusions of eculizumab. As demonstrated in detail below, these documents relate to the same technical field (therapeutic use) as the opposed patent and would require the minimum of structural modifications to arrive at the teaching of claim 1 (cf. **T606/89**). Both documents therefore serve as alternative starting points, i.e. as closest prior art, for the assessment of inventive step according to the EPO's established "*problem-and-solution*" approach.

3.2.1 Disclosure of US 2005/0101298 (D1)

(30) The disclosure of **D1** relates to a method of treating ***PNH*** in mammals (cf., for example, [0012], [0036]), in particular in human ***patients*** afflicted with this disease (cf. [0067]; Examples).

(31) The Examples report on the implementation of a clinical trial to evaluate the effects of an anti-C5 antibody on PNH and symptoms associated therewith (cf. [0081]). The anti-C5 antibody used was ***eculizumab*** (cf. [0082]; Figures).

(32) "***Eculizumab***" is the tradename for the anti-C5 antibody "***h5G1.1-mAb***" (cf. [0012], penultimate line; [0052]). According to section [0052] of **D1**, the **h5G1.1-mAb**, i.e. eculizumab, and methods for manufacturing it were already known from the prior art:

> *Particularly useful anti-C5-antibodies are* ***h5G1.1-mAb****, h5G1.1-scFv and other functional fragments of h5G1.1.* ***Methods for the preparation of h5G1.1-mAb****, h5G1.1-scFv and other functional fragments of h5G1.1* ***are described in U.S. Pat. No. 6,355,245*** *and "Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single Chains Fv",* ***Thomas et al.,*** *Molecular Immunology, Vol. 33, No. 17/18, pages 1389-1401,* ***1996, the disclosure of which are incorporated herein in their entirety by this reference****. The* ***antibody h5G1.1-mAb is currently undergoing clinical trials under the trade-name eculizumab****.*
> (cf. lower part of [0052]; emphasis added)

(33) **US 6,355,245** and **Thomas et al. 1996** are enclosed with this opposition brief as **D7** and **D8**, respectively. It will be appreciated, however, that according to the above quotation from [0052], both documents shall be regarded as incorporated in **D1** "*in their entirety*". That means that for applying the problem-and-solution approach the entire disclosure of **D1**, **D7** and **D8** **in combination** represent the "closest prior art"

(34) The mode of administration of eculizumab to a patient suggested by **D1** is, *inter alia*, "*via intravenous infusion*" (cf. [0060]) in a variety of "*unit dosage forms*" (cf. [0058]). The actual dosage regimen used in said clinical trial is described in [0082]:

*Over the course of four weeks, each of 11 patients received a weekly **600 mg** intravenous infusion of anti-C5 antibody for **approximately thirty minutes**. The specific anti-C5 antibody used in the study was eculizumab. Patients received **900 mg** of eculizumab 1 week later then 900 mg on a bi-weekly basis.*

(35) In summary, **D1** discloses the treatment of PNH patients with a pharmaceutical composition comprising eculizumab, said pharmaceutical composition being suitable for intravenous infusion.

3.2.2 Disclosure of Hillmen et al. 2004 (D3)

(36) **D3** is a scientific publication corresponding to the clinical study mentioned in the Examples of **D1**. It describes the details of the procedure and the results of the study in more detail. In particular, the clinical efficacy of eculizumab was tested in patients with PNH (cf. "*Background*"). Eleven transfusion-dependent patients with PNH received infusions of eculizumab (600mg) every week for four weeks, followed one week later by a 900-mg dose and then by 900 mg every other week through week 12 (cf. "*Methods*").

Accordingly, **D3** basically comprises the same disclosure as **D1** and could likewise serve as the closest prior art. For the sake of convenience, the following assessment will be based on **D1** as the closest prior art.

3.3 Objective Technical Problem

(37) As outlined above, **D1** (or **D3**) disclose a *pharmaceutical composition for use in treating a patient afflicted with PNH* in the clinical study of the Examples. The active ingredient is eculizumab.

(38) Hence, features 1 and 2 of present claim 1 are disclosed in **D1**. Since the eculizumab comprising composition of **D1** is to be administered via intravenous infusion, it must be constituted as an aqueous solution.

3.3.1 Feature comparison of Claim 1 with D1

(39) **D1** does not particularly specify how the composition is formulated, especially in terms of the absolute amount and concentration of eculizumab in the dosage form.

(40) As compared to **D1**, features 3 to 7 of granted claim **1** provide concrete characteristics of the pharmaceutical composition of the opposed patent. These are:

- the **total amount** of eculizumab in the single-use dosage form is **300 mg** (feature 3),
- the eculizumab **concentration** is **10 mg / ml** (feature 4),
- the **volume** is **30 ml** (feature 5), and
- the solution is **sterile** (feature 6), and
- the solution is **preservative-free** (feature 7).

3.3.2 No technical effect

(41) Features 1 to 7 in combination, in particular with regard to features 3 to 7, are described in sections [0017] and [0057] of the patent specification.

(42) No technical effects or advantages whatsoever contributed by said features 3 to 7, in terms of, for example, stability of the liquid formulation or shelf-life, are disclosed or merely suggested in the patent specification. No comparative experiments with other administration forms had been performed.

(43) Notably, the section "EXEMPLIFICATION" in the opposed patent, which describes the "TRUMPH" clinical study, only specifies the total amount of eculizumab (600 mg or 900 mg) administered to the patients via intravenous infusion (cf. [0074]), but is silent on the other features 3 to 7 of the pharmaceutical composition, such as eculizumab concentration in the solution etc.. Thus, it remains unclear whether the eculizumab formulation as claimed was actually used in the Examples of the opposed patent.

(44) In summary, when reading the specification as a whole, and in particular paragraphs [0063] to [0069] it becomes obvious that the **inventors considered the specific features of the eculizumab formulation rather conventional**. There is no suggestion

whatsoever that there might be a surprising technical effect related to the claimed eculizumab composition, which is neither self-evident nor predictable.

3.3.3 Technical Problem as basis for the problem-and-solution approach

(45) The objective technical problem underlying the opposed patent is therefore to provide a pharmaceutical composition comprising eculizumab for use in the clinical studies described in any of **D1** or **D3**.

(46) Said composition shall be characterized in terms of the absolute amount and concentration of eculizumab, and be suitable for safe administration to human patients.

3.4 CLAIM 1 IS OBVIOUS OVER A COMBINATION OF D1 / D3 IN COMBINATION WITH US 6,171,586 (D11)

(47) In order to solve the objective technical problem of the opposed patent, the skilled person would have readily turned to **D11**.

3.4.1 Teaching of US 6,171,586 (D11)

(48) **D11** generally discloses a *stable aqueous* ***pharmaceutical formulation*** *comprising a therapeutically effective amount of an* ***antibody*** (cf. abstract; claim 1; col.2, l.25-33). In this regard, **D11** points to typical problems in connection with biological proteins like antibodies, such as degradation, chemical and physical instability; the most common protein degradation pathways being protein aggregation, deamination and oxidation (cf. col.1, l.15-38).

(49) The specification of **D11** provides abundant technical teaching how to overcome these problems, for example, by carefully controlling buffer composition, pH, and additives, such as surfactant and polyol. Accordingly, an antibody composition of **D11** is stable at a temperature of about 2 – 8°C for at least one year, and/or is stable at a temperature of about 30°C for at least one month, and/or is stable following freezing and thawing of the formulation (cf. col.2, l.25-34).

(50) The general principles of this document are not limited to a specific antibody, but are rather applicable to antibodies in general. This becomes clear already from the formulation of the technical object underlying **D11**:

> *There is a need in the art for a **stable aqueous pharmaceutical formulation comprising an antibody,** such as an anti-CD18 or anti-CD20 antibody, which is **suitable for therapeutic use.***
> (cf. col.2, l.19-22; emphasis added)

(51) The antibodies for incorporation into the stable pharmaceutical composition of **D11** can be directed to a vast number of highly different protein antigens. A non-limiting list of such antigens is provided in column 10, lines 1 to 67 of the specification. The wording "*such as*" in the above quotation makes it clear that the specific anti-CD18 or anti-CD20 antibodies just represent exemplary embodiments of suitable antibodies. The skilled person would understand that the examples of **D11** dealing with anti CD18 and CD20 antibodies just serve to demonstrate the applicability of the invention of **D11**, but would not be construed as limiting the scope of the invention in terms of the antibody specificity (cf. col.24, l.22-26).

(52) Further, the antibodies of **D11** are not limited to specific classes or types of monoclonal antibodies, including antibody fragments, chimeric or "*humanized*" forms (cf. col.8, in particular l.54). Even if not specifically mentioned in the specification, the person skilled in the art would readily understand that also eculizumab could equally well be processed into a stable and safe pharmaceutical composition applying the methods of **D11**.

(53) **D11** also relates to containers holding said pharmaceutical formulation (cf. col.2, l.34-39). Suitable containers include, for example, bottles and vials formed from glass or plastic. Exemplary containers may 3 to 100 ml glass vials (cf. col.24, l.7-21).

(54) It therefore follows that the skilled person was clearly **motivated** to turn to **D11** for guidance when faced with the task of providing a pharmaceutical antibody formulation for use in the clinical study of **D1**. In doing so, the skilled person would have arrived at the pharmaceutical antibody composition according to claim 1 without any inventive effort, as outlined below:

3.4.2 Total amount of 300 mg eculizumab in a single use-dosage form (feature 3)

(55) In the clinical study of **D1**, patients received two distinct doses of the active ingredient: First, **600 mg** doses of eculizumab were intravenously administered every week for four weeks. Then doses of **900 mg** were administered every other week.

(56) It is immediately obvious to the skilled person that the composition should be formulated as a **single-use dosage form comprising 300 mg eculizumab** (feature 3). This would allow conveniently using one and the same dosage form for both regimens, i.e. **two** single-use dosage forms for the 600 mg administration, and **three** single-use dosage forms for the 900 mg administration.

3.4.3 Eculizumab concentration of 10 mg / ml (feature 4)

(57) For the clinical study of **D1**...

> *.... each of 11 patients received a weekly **600 mg intravenous infusion** of anti-C5 antibody for approximately **thirty minutes**.*
> (cf. **D1**, [0082]; emphasis added)

(58) The skilled person was therefore set to the task to select a concentration of the antibody and a volume such that two single-use dosage forms of the pharmaceutical formulation each comprising 300 mg antibody can be intravenously administered within a period of thirty minutes.

(59) In order to implement the specific concentration of antibody / volume, the skilled person would have found further guidance in documents relating to antibody formulations for pharmaceutical applications, for example, **D11**.

(60) Accordingly, the antibody concentration in the formulations of **D11** is typically from about 0.1 to about 50 mg / ml (cf. claim 13). Preferred antibody concentrations are mentioned in column 22, lines 13 to 17 of the specification:

> *From about 0.1 mg / ml to about 50 mg / ml, preferably, from about 0.5 mg / ml to about 25 mg / ml, and **most preferably** from 2 mg / ml to*

> *about **10 mg / ml** is an exemplary antibody concentration in the formulation (cf. col. 22, l.13-17).*
> (emphasis added)

(61) The above passage is quoted from the general description of **D11** and does not relate to any antibody in particular. It would therefore, *prima facie*, be applicable to any antibody. It should be particularly emphasized that the antibody concentration of "***10 mg / ml***" is **expressly** mentioned in **D11** as belonging to the **most preferred** concentration range.

(62) It was obvious to the skilled person with a reasonable expectation of success that the antibody concentrations mentioned in **D11** would be also applicable for a pharmaceutical eculizumab formulation. Feature 4 relating to the antibody concentration of 10 mg / ml is therefore an entirely obvious choice.

(63) Regarding the general applicability of **D11** with respect to different antibodies, and regarding the skilled person's expectation that the most preferred antibody concentrations suggested in **D11**, in particular 10 mg / ml, would have successfully worked also for eculizumab, see also point 3.5 below.

3.4.4 Total volume 30 ml (feature 5)

(64) As explained above, the volume of the composition implicitly, but nevertheless directly and unambiguously, follows from the absolute amount (300 mg; feature 3) and the concentration of the active ingredient in the solution (10 mg / ml; feature 4). Since both features 3 and 4 are obvious as demonstrated above, also feature 5 relating to the volume of 30 ml is obvious (300 mg / (10 mg / ml) = 30 ml).

3.4.5 Solution is sterile (feature 6)

(65) It goes without saying that formulations to be used for *in vivo* administration to a human subject must be sterile. This is common general knowledge and is, of course, appreciated by **D11**, too:

> *The formulations to be used for in vivo administration* ***must*** *be* ***sterile****. This is readily accomplished by filtration through* ***sterile*** *filtration membranes, prior to, of following preparation of the formulation.*
> (cf. col. 23, l.27-30; emphasis added)

(66) Feature 6 does therefore not make any inventive contribution.

3.4.6 Solution is preservative-free (feature 7)

(67) According to the original application of the opposed patent, the pharmaceutical antibody compositions **may** or **may not** include preservatives (cf. **A**, for example, p.6, l.20, and p.24, l.23). Notably, even in the specification of the patent as granted it is still mentioned that preservatives can be included in the composition, leaving some doubts on the scope of granted claim 1:

> *Wetting agents, emulsifiers and lubricants, [.....] and perfuming agents,* ***preservatives*** *and anti-oxidants* ***can also be present*** *in the pharmaceutical compositions of the application.*
> (cf. [0064]; emphasis added)

(68) A similar disclosure can be found in paragraph [0058] of the opposed patent, stating that the "*formulations may contain pharmaceutically acceptable auxiliary substances as required, such as [....],* ***preservatives****, [....], and the like*".

(69) It is important to emphasize that no specific technical effect has been demonstrated in regard of the absence of preservatives. The limitation to "*preservative-free*" was therefore an obvious choice without any inventive contribution.

(70) In any event, **D11** expressly discloses the feature "*preservative-free*" as an alternative to the presence of preservatives, thereby clearly suggesting that preservatives are not necessary to obtain stable pharmaceutical antibody formulations:

> *In one embodiment, the formulation contains the above-identified agents (i.e. antibody, buffer, polyol and surfactant) and is* ***essentially free of one or more preservatives****, such as benzyl alcohol, phenol, m-cresol,*

chlorobutanol and benzethonium C1.
(cf. col. 22, l.62-64; emphasis added).

(71) In conclusion, the teaching of claim 1 does not involve an inventive step.

3.5 CLAIMED ANTIBODY CONCENTRATION IS COMMON GENERAL KNOWLEDGE

(72) The common general knowledge, as reflected, for example, by **D10**, confirms the universal applicability of **D11** for the manufacture of various stable antibody formulations, in particular with respect to the concentration of the antibody of **10 mg / ml**.

3.5.1 Antibody concentrations of D11 are typical for commercial antibody formulations

(73) As mentioned in point 3.4.3 above, the broadest range for the antibody concentration suggested in **D11** is from **0.1 mg / ml to 50 mg / ml**, a preferred range being from **0.5 mg/ml to 25 mg/ml**, and the most preferred range being from **2 mg/ml to 10 mg/ml** (cf. col.22; l.13-17).

(74) Table 1 of **D10** lists **23 commercial therapeutical products** comprising authorized antibodies. The antibody concentration in the formulation for each product is given in the column headed "***Mab Conc***". One can reasonably presume that a skilled person - commissioned to prepare a therapeutical formulation for a new antibody - would have oriented himself on existing commercial antibody formulations, in particular with respect of such a mandatory parameter as the antibody concentration. All the more so because the number of approved antibody at the priority date was only 23, i.e. fairly manageable.

(75) In the table of **ANNEX I** submitted with this opposition, the antibodies of Table 1 of **D10** were grouped according the three concentration ranges of **D11**. That is: if the concentration of a specific antibody formulation fell within the range the broadest range of 0.1 to 50 mg / ml, the box in the corresponding column was checked (5th column of ANNEX I). If the concentration fell into the preferred range of 0.5 mg / ml – 25 mg / ml, the box in this column (6th col.) was checked, too, and so forth. In case

the antibody concentration was exactly 10 mg / ml, the box in the last column (10 mg / ml) was checked.

(76) Since the antibody formulation of the present invention is not limited to any mode of administration, also routes other than intravenous administration were considered. Moreover, since the formulation according to claim 1 can also be reconstructed from a lyophilized powder formulation, such commercial products were likewise included.

(77) As one can take from column 5 of **ANNEX I**, 20 out of 23 therapeutic antibody formulations **(87%)** have a concentration within the range of 0.1 to 50 mg / ml. Still 18 of 23 antibody concentrations **(78%)** fall within the preferred range of 0.5 to 25 mg / ml, and 9 out of 23 antibody concentrations **(39%)** are within the most preferred range of **D11**, i.e. 2 to 10 mg / ml. Most remarkably, the number of commercial antibody formulations having a concentration of exactly **10 mg / ml** was still as high as **22%** (5 out of 23)!

(78) The individual antibody concentrations of the respective antibodies vary within the above ranges, but it is to be emphasized that **10 mg / ml is the most commonly used concentration** (5 formulations, versus 2 formulations with 0.5 mg / ml or 2 mg / ml, respectively).

(79) The clear and straightforward preference for an antibody concentration of 10 mg / ml becomes even more manifest if only antibody formulations for intravenous administration (18 antibody products) are considered. According to **ANNEX II**, 18 out of 18 therapeutic antibody formulations **(100%)** have a concentration within the range of 0.1 to 50 mg / ml. 17 of 18 antibody concentrations **(94%)** fall within the preferred range of 0.5 to 25 mg / ml, and 8 out of 18 antibody concentrations **(44%)** are within the most preferred range of 2 to 10 mg / ml. The number of antibody formulations having a concentration of exactly **10 mg/ml** is still **22%** (4 out of 18).

3.5.2 Preferred antibodies of D11 are commercially used at a concentration of 10 mg / ml

(80) As an antigen of special interest **D11** mentions the **CD20 surface antigen** which can be targeted for treating B cell lymphomas (cf. col.2, l.59-61). Several antibodies

against CD20 were known at the filing date of **D11**, including the chimeric antibody termed "***C2B8***" (cf. col.2, lines 14-18 & reference to US 5,736,137 by Idec Pharmaceutical Corporation). Idec's C2B8 antibody is also known by the INN (international nonproprietary name) "***rituximab***", see for example **Maloney et al. 1997** (**D12**; ct. title).

(81) The antibody product "**Rituxan**" comprising rituximab is listed among the 23 approved pharmaceutical antibody formulation of **D10**. According to Table 1, no 16, Rituxan comprises "**10 mg / ml**" of antibody in a solution of intravenous administration.

(82) Feature 4 would therefore belong to the common general knowledge.

3.5.3 Concentration of 10 mg / ml was obvious to try

(83) Thus, the skilled person would conclude from these data that the antibody concentrations suggested in **D11**, in particular 10 mg / ml would be generally applicable for many different antibodies. In fact, every 5th approved antibody that was commercialized before the priority date of the opposed patent, was successfully used at exactly the same concentration as claimed in the opposed patent, i.e. 10 mg/ml.

(84) It was therefore obvious for the skilled person to try out this concentration also for eculizumab with a reasonable expectation of success. The selection of 10 mg/ml according to feature 4 does not involve an inventive step.

4. CONCLUSION

(85) It clearly follows from the above that the arbitrary provision of a formulation form is not patentable merely because it potentially "enriches" the already existing repertoire of formulation forms. All of the features in combination as claimed in the opposed patent were obvious over **D1** (or **D3**) in combination with **D11,** or common general knowledge as reflected by **D10**.

(86) Consequently, the opposed patent does not meet the requirements of the EPC. It has therefore to be revoked *in toto*.

Leo Polz

DR. LEO POLZ

European Patent Attorney
Hoffmann Eitle Patent-und Rechtsanwälte PartmbB
Association number 151

Enclosures:

- Debit order in the amount of **€ 785.00** for the payment of the opposition fee
- Documents under **SECTION 1** above (except for D2, and D4 to D6).

Europäisches Patentamt
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101
09. Aug. 2017

Zur Kasse
185

Notice of opposition to a European patent

I. Patent opposed

Patent No.	2 359 834
Application No.	11 001 632.6
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	
Title of the invention	Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement

II. Proprietor of the patent
first named in the patent specification

	Alexion Pharmaceuticals, Inc.
Opponent's or representative's reference (max. 15 keystrokes)	198 441 u6/ne

III. Opponent

Name	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB
Address	Arabellastr. 30 81925 Munich (DE)
State of residence or of principal place of business	DE
Nationality	
Telephone/Fax	
Multiple opponents (see additional sheet)	☐

IV. Authorisation

1. Representative (name only one representative or name of association of representatives to whom notification is to be made)	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB
Address of place of business	Arabellastraße 30 81925 Munich Germany Association No. 151
Telephone/Fax	089 / 92409-0 | 089 / 918356
Additional representative(s) on additional sheet/see authorisation	☐

Opponent's reference
198 441 u6/ne

EPO 2300.1 12.07

2. Name(s) of employee(s) of the opponent authorised to act in these opposition proceedings under Art. 133(3) EPC

Authorisation(s) to 1./2.

not considered necessary [x]

has/have been registered under No. [ ]

is/are enclosed [ ]

V. Opposition is filed against

• the patent as a whole [x]

• claim(s) No(s). [ ]

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC) [ ]

• it does not involve an inventive step (Art. 52(1); Art. 56 EPC) [x]

• patentability is excluded on other grounds, i.e. Article [ ] Art.

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). [ ]

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). [ ]

VII. Facts (Rule 76(2)(c) EPC) presented in support of the opposition are submitted herewith on a separate sheet (annex 1) [X]

VIII. Other requests:

Oral proceedings if the maintenance of the patent amended or unamended is considered.

Opponent's reference
198 441 u6/ne

IX. Evidence presented

Evidence — is enclosed [x]

will be filed at a later date [ ]

A. Publications:

1

Particular relevance (page, column, line, fig.):

B: EP 2 359 834 B1 (opposed patent)

2

Particular relevance (page, column, line, fig.):

A: WO 2007/106585 A1 (application as filed)

3

Particular relevance (page, column, line, fig.):

C: US 60/783,070 (priority application)

4

Particular relevance (page, column, line, fig.):

D1: US 2005/0191298 A1

5

Particular relevance (page, column, line, fig.):

D3: Hillmen et al., N Engl. J Med 2004; 350: 552-559

6

Particular relevance (page, column, line, fig.):

D7: US 6,355,245 B1

Continued on additional sheet [x]

B. Other evidence

Continued on additional sheet [ ]

Opponent's reference
198 441 u6/ne

X. Payment of the opposition fee is made

- as indicated in the enclosed voucher for payment of fees and costs (EPO Form 1010) [x]
- via EPO Online Services [ ]

XI. List of documents

Enclosure No.

0	Form for notice of opposition	[X]
1	Facts (see VII.)	[X]
2	Copies of documents presented as evidence (see IX.)	
	a Publications	[x]
	b Other documents	[ ]
3	Signed authorisation(s) (see IV.)	[ ]
4	Voucher for payment of fees and costs (see X.)	[x]
5	Cheque	[ ]
6	Additional sheet(s)	[x] Number of sheets: 1
7	Other	[x]

Please specify here:

- receipt form

XII. Signature of opponent or representative

Place: Munich

Date: Aug. 09, 2017

Signature: Leo Polz

Name (block capitals): DR. L. POLZ
Hoffmann Eitle PartmbB, Association No. 151

In case of legal persons, signatory's position within company:

Opponent's reference: 198 441 u6/ne

EPO 2300.4 12.07

Samsung Bioepis Exhibit No. 1002
Page 808

Zusatzblatt / Supplementary Sheet

IX. A. Publications (cont.)

7 D8: Thomas et al., Molecular Immunology, Vol. 33, No. 17/18, 1389-1401, 1996

8 D9: US 2003/0202972 A1

9 D10: Wang et al., J. pharm. Sci., vol. 96, no. 1, p. 1-26, Jan. 2007

10 D11: US 6,171,586 B1

11 D12: Maloney et al., Blood, vol. 90, no.6, 1997: pp 2188-2195

12 ANNEX I: Commercial monoclonal antibodies 2006 (all modes of administration)

13 ANNEX II: Commercial monoclonal antibodies 2006 (i.v. administration)

DR. L. POLZ
Hoffmann Eitle PartmbB, Association No. 151

dfmp
Dörries Frank-Molnia & Pohlman
Patentanwälte Rechtsanwälte PartG mbB

Patents – Trademarks – Designs

Theatinerstraße 16
80333 Munich
Germany

Phone +49 89 210296-0
Fax +49 89 210296-33

info@df-mp.com
www.df-mp.com

European Patent Office
Bob-van-Benthem-Platz 1
80469 Munich

August 4, 2017

Opposition against European patent 2 359 834 (Application No. 11 001 632.6)

Title:	Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement
Proprietor:	Alexion Pharmaceuticals, Inc.
Opponent:	Amgen Inc.
Our Ref.:	AMG17203OP

On behalf of

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
USA

we herewith file a **Notice of Opposition** pursuant to Article 99(1) EPC against

European Patent No. 2 359 834 B1
(European Appl. No. 11 001 632.6)

Publication and mention of the grant: 09.11.2016

Title of the patent: Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement

Proprietor:

Alexion Pharmaceuticals Inc.
100 College Street
New Haven, CT 06510 / US

We request that the opposition fee in the amount of EUR 785.00 be debited from our deposit account No. 28001000 (see also the corresponding debit order on the form accompanying the online submission of the present Notice of Opposition).

H. Ulrich Dörries [1234]
Dr. sc. nat., Dipl.-Biol.

David Molnia [12347]
M.S. Elec. Eng., B.S. Physics

Sandra Pohlman [568]
B.S. Biology

Michael Eder [1234]
Dr. sc. nat., Dipl.-Chem.

Oliver Schulz [1234]
Dipl.-Phys.

Rainer Friedrich [1234]
Dr. rer. nat., Dipl.-Biochem.

Elisabeth Greiner [1234]
Dr. rer. nat., Mag. pharm.

Philipp Nordmeyer [1234]
LL.M., Dipl.-Phys.

Dominik Ho [1234]
Dr. rer. nat., MEng (Cornell)

Holger Schimmel [1234]
Dr. rer. nat., Dipl.-Ing.

Annette Hilgendorf [1234]
Dr. rer. nat., Dipl.-Biotech.

Solveig Moré [1234]
Dr. rer. nat., Dipl.-Biochem.

Florian Brandt [1234]
Dr. rer. nat., Dipl.-Biochem.

Andreas Brzank [1234]
Dr. rer. nat., Dipl.-Phys.

René Okoampah [1234]
Dipl.-Ing.

Julia Mössinger [1234]
Dr. rer. nat., Dipl.-Biol.

Judith Hesse [8]
LL.M.

Helena Bertelsmeier [8]
LL.M.

Barbara Englert [234]
Dr. rer. nat., Dipl.-Phys.

1 European Patent Attorney
2 European Trademark Attorney
3 European Design Attorney
4 Patentanwalt
5 Solicitor (England & Wales)
6 U.S. Patent Attorney
7 U.S. Patent Agent
8 Rechtsanwalt

Partnerschaftsregister des AG München
PR-Nr. 1278

I. Extent of the Opposition and Requests

1. The opposition is directed against the (sole) claim of European patent 2 359 834 B1 (hereinafter referred to as "the opposed patent"). It is requested that the opposed patent be revoked in its entirety pursuant to Article 101(2) EPC.

2. Oral Proceedings are requested in accordance with Article 116(1) EPC in the event that the Opposition Division does not consider the above request justified on the basis of our written submissions.

II. Grounds in Support of the Opposition

3. The opposition is based on the following grounds:

   i) The claimed subject matter of the opposed patent extends beyond the content of the earlier application as filed (Art. 100(c) EPC in connection with Art. 76(1) EPC, 123(2) EPC).
   ii) The subject matter of the opposed patent is not based on an inventive step (Art. 100(a) EPC in connection with Art. 56 EPC).
   iii) The subject matter of the opposed patent is insufficiently disclosed (Art. 100(b) EPC).

III. List of Documents

4. The following documents were cited during the prosecution of the patent EP 2 359 834 B1, hereinafter "the opposed patent"; they are enclosed herewith except for **D6** which we were unable to retrieve:

D1 US 2005/191298 A1 (Bell, Leonard *et al.*; September 1, 2005).

D2 Hillmen *et al.*, *Br. J. Hematol.* **2003**, *121 (Suppl. 1)*, 87-95.

D3 Hillmen *et al.*, *N. Engl. J. Med.* **2004**, *350(6)*, 552-559.

D4 Harding, *Drugs Future* **2004**, *29(7)*, 673-676.

D5 US 2005/221382 A1 (Rother, P. Russell; October 6, 2005)

D6 Hill, *Clin. Adv. Hematol. Oncol.* **2005**, *3(11)*, 849-50.

D7 Morris et al., *South. Med. J.* **1992**, *85(19)*, 1030-1031.

D8 Corvini *et al.*, *Ann. Allerg. Asth. Immunol.* **2004**, *93(2)*, 200-205.

D9 Sierra *et al.*, *NIPH Annals* **1991**, *14(2)*, 195-210.

5. The following additional documents are also referred to herein and submitted herewith:

P US 2006/0783070 P (Bell, Leonard *et al.*; March 15, 2006).

WO WO 2007/106585 A1.

A1 EP 2 359 834 A1.

D10 US Pharmacopeia (USP29-NF24), p. 2989;
retrieved from http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1136.html
on May 17, 2017.

D11 Adis Data information, *Drugs R. D.* **2007**, *8(1)*, 61-68.

D12 Hill *et al.*, *Blood* **2005**, *106(7)*, 2559-2565.

D13 Thomas *et al.*, *Mol. Immunol.* **1996**, *33(17/18)*, 1389-1401.

D14 Mueller *et al.*, *Mol. Immunol.* **1997**, *34(6)*, 441-452.

D15 WO 97/11971 A1 (Mueller, John *et al.*, April 3, 1997).

D16 WO 2005/007809 A2 (Rother, Russell *et al.*, January 27, 2005).

D17 US 6,355,245 B1 (Evans, Mark J. *et al.*, March 12, 2002).

D18 Hillmen *et al.*, *N. Engl. J. Med.* **2006**, *355(12)*, 1233-1243.

D19 EMEA, CPMP, 20 February 2003, *Note for guidance on excipients, antioxidants and antimicrobial preservatives in the dossier for application for marketing authorization of a medicinal product*.

D20 Wang *et al.*, *J. Pharm. Sci.* **2007**, *96(1)*, 1-26. (published January 2007).

D21 Daugherty *et al.*, *Adv. Drug Del. Rev.* **2006**, *58*, 686-706.

D22 US 2005/0271660 A1 (Wang, Yi; December 8, 2005).

D23 Expert declaration by Dr. Michael Treuheit.

D24 Soliris® (eculizumab) *Highlights of prescribing information*.

D25 US 2012/0230982 A1 (Zhou, Xiao-Hong *et al.*, September 13, 2012).

D26 WO 2007/002571 A2 (Rother, January 4, 2007).

D27 Hill *et al.*, *Blood* **2004**, *104*;2823-2824.

IV. The Claimed Subject Matter

6. The opposed patent claims a pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml sterile, preservative free solution.

V. Inadmissible Amendment (Art. 100 (c) EPC / Art. 76 (1) EPC, 123(2) EPC)

7. The parent application as filed (**WO**), only teaches a pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml sterile, preservative free solution in the context of a *single unit dosage form*, both on page 5, lines 3-9 and page 22, lines 7-14.

8. The same applies for the corresponding passages of the divisional application **A1**, which also require a single unit dosage form (paragraphs [0018] and [0024)]. This understanding is confirmed by claim 1 of **A1**, which recites: *"[a] pharmaceutical composition comprising* ***a single unit dosage form*** *of an anti-C5 antibody"* (emphasis added).

9. It is noted in this context that the skilled person would understand a single-use dosage form to be for single use only, i.e., it cannot be used more than once. In contrast, a single unit dosage form would be understood to be synonymous to a single-unit container, which, as evidenced by the US Pharmacopeia (submitted as **D10** herewith), "*is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened*".

10. As an essential element present in the parent application as filed as well as the divisional application as filed, namely, the requirement for administration of the 300 mg dose as a single dose is missing from the claim as granted, the claim is not clearly and unambiguously derivable from the application as filed, contrary to Art. 76(1) EPC.

VI. No Entitlement to Priority

11. The opposed application claims priority of US provisional application US 783070 P (**P**). Said application does not contain any disclosure of a pharmaceutical composition comprising 300 mg of eculizumab in a volume of 30 mL, at a concentration of 10 mg/mL in a single-use dosage form of a sterile, preservative-free solution. None of these specific details, let alone their combination, is disclosed in **P**.

12. The claim of the opposed patent thus is not entitled to priority. Consequently, all documents available before the **filing date of March 15, 2007** are considered relevant state of the art.

VII. Lack of Inventive Step (Article 100(a) EPC / Article 56 EPC)

VII.1 The state of the art

13. Eculizumab, also referred to as h5G1.1 (**D11**, abstract; **D4**, abstract; **D1**, [0052]); opposed patent [0054]), is a long-acting, humanized version of the anti-C5 antibody 5G1.1 that has been under development as a therapeutic for a range of different indications since 1995 (**D11**). Indications known before the filing date of the opposed patent include rheumatic disorders, transplant rejection, adult respiratory distress syndrome, lupus nephritis and systemic lupus erythematosus, glomerulonephritis, psoriasis, dermatomyositis, pulmonary diseases, sickle cell disease, and also paroxysmal hemoglobinuria (PNH) (**D11**, Table II; **D4**, abstract and "Clinical Studies" on pages 674-675; **D22**, claims 1, 2, and 7; **D26**, e.g., claims 1 and 14; **D5** abstract, par. [0027] and [0040]).

14. The complement cascade is a part of the human immune system that binds and removes foreign particles, but can also attack and destroy endogenous cells (such as red blood cells) or tissue. The antibody eculizumab has been developed to inhibit the terminal steps of the complement cascade, in particular, eculizumab suppresses the cleavage of complement component 5 (or C5) into C5a and C5b (**D12**, p. 2559, right column, **D4**, page 673, right column, 2nd full paragraph).

15. The opposed patent at [0054] states that eculizumab is disclosed in **D17**. The variable heavy and light chain regions of eculizumab/h5G1.1 were disclosed in **D17** in the context of antibody fragments, such as an scFv (**D17**, SEQ ID NO: 20, "5G1.1 scFv CO12 (humanized)"). This document states that preferred constant regions for forming full length antibodies would be "IgG constant regions, which may be unaltered or constructed of a mixture of constant domains from IgGs of various subtypes, e.g., IgG1 and IgG4." (**D17**, col. 45, li. 24-33).

16. The first humanized 5G1.1 antibody (h5G1.1) was published in 1996 (**D13**, p. 1392, Fig. 1 A and B).

17. An advantageous combination of h5G1.1, and in particular h5G1.1 CO12, with chimeric human IgG2/IgG4 heavy chain constant regions is shown and/or suggested in **D14, D15** and **D16**: **D14** shows optimization of the antibody by the introduction of a chimeric human IgG2/IgG4 heavy chain constant region (**D14**, Fig. 7, Fig. 9, and paragraph bridging pages 450/451 and 2nd paragraph on p. 451; see also **D15**, e.g., p. 42-43; and **D16**, Fig. 2 and claim 3), which was shown to advantageously avoid undesired immune responses, FcR binding and complement activation (**D14**, paragraph bridging pages 450/451; **D15**, Fig. 15 and p. 12, li. 37; **D16,** Fig. 2, paragraph bridging pages 5 and 6).

18. The mechanism of action of eculizumab and preferred antibody structures were thus known prior to the filing date of the opposed patent, and eculizumab had been used as a therapeutic agent for a number of indications aside from PNH.

19. PNH is a hematologic disorder, symptomatically characterized by red blood cell destruction, aenemia, hemoglobinuria and thrombosis. The symptoms result from somatically mutated hematopoietic blood cells, causing a deficiency of glycosylphosphatidylinositol (GPI) anchored cell surface proteins. Among these proteins are complement inhibitors that normally protect red blood cells from complement-mediated lysis (**D12**).

20. The treatment of patients suffering from PNH with anti-C5 antibodies, such as eculizumab or pexelizumab was also widely known before the filing date. In the case of PNH, the blockade of the terminal steps of the complement cascade by eculizumab serves to block the undesired destruction of red blood cells; however, it preserves the ability of the complement system to clear microorganisms and immune complexes (**D12**, p. 2559, right column).

21. A treatment with eculizumab in a dosage of 600 mg over the first four weeks, followed by an administration of 900 mg as the fifth dose one week later, and subsequent administration of 900 mg on a bi-weekly basis is disclosed, e.g., in **D1** (par. [0082]). The route of administration was intravenous infusion (ibid.). This corresponds exactly to the dosage regimen described in the opposed patent ([0057]).

22. Further successful clinical trials of eculizumab are described in detail, in e.g. **D2** (in 2003), **D3** (in 2004), **D4** (in 2004), **D12** (in 2005), **D18** (in 2006) and **D11** (in 2007). **D27** (from 2004, abstract) teaches that treatment of PNH by eculizumab has been shown to be safe and effective for over two years of therapy. Dosage regimens requiring administration of both 600 and 900 mg eculizumab for treatment of PNH are explicitly disclosed in **D2** (li. 7 and 8), **D3** (Abstract), **D4** (page 674, last full paragraph), **D11** (last paragraph on page 66) and **D18** (page 1233, Methods), so they can be considered to be conventional.

23. **D18** in fact discloses the clinical trial that serves as the sole example in the opposed patent (the TRIUMPH trial). This includes the vaccination of all treated patients against *Neisseria meningitides* (**D18**, p. 1234, right column, 1st full paragraph), a feature that was brought forward by the applicant in the course of the prosecution in an attempt to distinguish the alleged invention from the state of the art, and later dropped again. The vaccination serves to

avoid side effects of the inhibition of complement formation in the treated patients leading to a higher susceptibility to *Neisseria* infections. This problem and its solution were well known in the art, as pointed out by the examiner with reference to **D6**, **D7** and **D8**.

24. The skilled person was consequently aware of suitable formulations for the intravenous administration of eculizumab, and these had already been successfully used in several clinical trials for PNH, as well as for treatment of numerous other diseases.

VII.2 *The closest prior art*

25. **D1** – or any of the reports of intravenous treatment of PNH with eculizumab at doses of 600 or 900 mg/ml, i.e., **D2** to **D4**, **D11** and **D18** - can be considered the closest prior art document, as all of them are highly promising springboards for the claimed subject matter.

26. We submit that it is an implicit feature of all compositions for intravenous administration that they are sterile. **D1** not only discloses the treatment of PNH with eculizumab and dosing regimen, in particular doses of 600 and 900 mg in par. [0082], as mentioned above, but also explicitly teaches that suitable formulations

> *"[…]* ***must be sterile*** *and non-pyrogenic, and generally will include a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The formulations* ***may contain*** *pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents,* ***preservatives****, stabilizers, and the like."* (**D1**, par. [0062], emphasis added)

D1 thus also teaches that in contrast to the strict requirement for sterility, the presence of preservatives is optional. We thus suggest **D1** as the closest prior art document.

VII.3 *The subject matter of the claim*

27. The opposed patent claims a pharmaceutical composition for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein the composition is a 300 mg eculizumab single-use dosage form comprising 30 ml of a 10 mg eculizumab/ml sterile, preservative free solution.

28. **D1** does not explicitly teach that eculizumab is in a single-use dosage form of 300 mg comprising 30 ml of a concentration of 10 mg/ml, or that the composition is preservative free. It is noted that the amount of antibody and the concentration thereof define the volume of the composition, which consequently cannot be considered an independent technical feature.

VII.4 The technical effect and the problem solved

29. Notably, the opposed patent is silent about supposed technical effects or advantages of any one of these features.

30. As the treatment of patients suffering from PNH with eculizumab was well known, and a suitable pharmaceutical formulation for the antibody thus clearly already existed prior to the filing of the opposed patent, it is not apparent which technical problem is solved by the alleged invention.

31. Submissions by the applicant in the communications dated February 6, 2016 (p. 6, item 3.2) and January 13, 2016 (p. 5, item 4.3.1) imply that the technical problem to be solved was the provision of a stable and easy-to-use solution of eculizumab. This is nowhere mentioned in the opposed patent itself. The only evidence brought forward by the applicant with regard to the alleged technical effect is the package leaflet of Soliris® (eculizumab). This is supposed to prove that the marketed concentration is in fact the "*ideal and clinically approved*" concentration for the antibody (communication dated January 13, 2016, item 4.3.1). While it obviously is the clinically approved concentration, this does not represent evidence for 10 mg/mL being the "ideal" concentration. It merely shows that formulating eculizumab at 10 mg/mL is feasible. Accordingly, there is no evidence for an allegedly ideal increased stability.

32. **D1** does not teach if the administered composition comprises preservatives.

33. **D19**, a note for guidance to industry from EMEA, which can be considered to represent common general knowledge, states that the properties of antioxidants and antimicrobial preservatives are due to certain chemical groups which are usually aggressive towards living cells and which lead to certain risks when used in man. Thus, if it is not absolutely necessary to add these substances in medicinal products, they must be avoided (**D19**, page 1/9, paragraphs 4-6 of introduction).

34. Accordingly, the fact that the claimed compositions do not contain preservatives has the technical effect that potential issues connected to the use of preservatives, both from the medical and the regulatory viewpoint, are avoided.

35. Consequently, the problem solved by the invention can be considered to be provision of a composition which avoids potential medical and/or the regulatory issues connected to the use of preservatives.

VII.5 *The subject matter of the claim lacks inventive step in light of **D1** in combination with **D22** and common general knowledge, represented by **D19** and **D20-D21**.*

36. It has to be noted that the opposed patent teaches no advantageous effect of not using **preservatives**. In contrast, it states that among other excipients, preservatives can be present in the pharmaceutical compositions of the alleged invention (par. [0058] and [0064]).

37. Nevertheless, the skilled person who intends to produce eculizumab compositions for therapeutic application, as in **D1** (or in the opposed patent), is motivated to exclude preservatives for regulatory reasons. The German Bundesgerichtshof in "Anthocyanverbindung" (X ZR 4/11, 10.12.2013) recently confirmed that legal (including regulatory) considerations are to be taken into account by the skilled person:

> "*The skilled person to which provision of a compound for a certain application is assigned has occasion to check according to the relevant legal provisions which solutions have adequate prospects of success with regard to legal aspects*" (headnote; our translation).

38. **D19**, as cited above, not only provides such a relevant legal provision, i.e., a motivation to avoid preservatives (**D19**, page 1/9, paragraphs 4-6 of introduction), but also teaches that multi-dose preparations are most problematic with regard to the risk of contamination by micro-organisms (pages 8-9/9, section "Antimicrobial Preservatives", In the last sentence on page 9/9, the document clearly teaches:

> "*If products do not contain a preservative and do not have inherent preservative efficacy they must not be packaged in multidose presentations without a sound justification.*"

39. Accordingly, **D19**, which we submit is representative of common general knowledge, can be summarized to teach away from the use of preservatives and, accordingly, multidose presentations. Following this clear teaching, the skilled person would turn to **single-use** packaging to avoid the requirement for preservatives.

40. The skilled person would also not have expected any difficulties with this approach, as it was well known to the person of skill that antibody formulations for intravenous delivery can be prepared without using preservatives, as **D20** (p. 2-4, Table 1) and **D21** (p. 697, Table 1) show. In fact, the majority of antibody formulations reviewed in these documents do not contain preservatives. In addition, **D22** specifically discloses a formulation of eculizumab that does not contain preservatives (**D22**, Fig. 10). As a consequence, the person of skill would have readily assumed, based on the state of the art, that a single-use pharmaceutical formulation comprising eculizumab would not require the use of preservatives.

41. The skilled person was consequently faced with the selection of an appropriate **amount of antibody** to include in the single-use package.

42. As discussed above, e.g., **D1** (par. [0082]) teaches that the administration of either 600 mg, or 900 mg is the established dosing regimen for eculizumab. In full agreement with the examiner (communication dated July 21, 2011), we note that 300 mg is the obvious and most convenient single dose that enables supplying both therapeutic doses of 600 and 900 mg, while avoiding a waste of active agent. We note that the applicant did not argue that there is any unexpected technical effect or advantage associated with this feature. The amount of antibody included is thus rendered obvious by **D1** itself.

43. This leaves the antibody **concentration of 10 mg/mL** as a distinguishing feature. The applicant in his communications dated February 6, 2014 and January 13, 2016 alleged that the concentration was an inventive feature:

> *"At a minimum, in order to arrive at the instantly-claimed dosage forms at all, the inventors had to know that eculizumab was soluble. In order to produce a solution of an antibody (e.g., at 10 mg/mL), the inventors had to know the solubility of eculizumab and that eculizumab was sufficiently soluble for a 10 mg/mL formulation. Moreover, in order for a pharmaceutical solution to be commercially viable, the inventors had to know the shelf-life stability of eculizumab in solution; for if its stability was too low, a pharmaceutical solution would not have been an option. Thus, even assuming arguendo that the instantly claimed compositions are convenient, it is clear that the skilled person reading the cited references could not have arrived at the particular instantly claimed compositions by convenience. They would have required the knowledge supporting the instant invention. And none of that knowledge is disclosed or even suggested by the cited references."* (Communication submitted by applicant on February 6, 2014, p. 6, item 3.2, emphasis added)

and

> *"As indicated in section 3.2 of our petition of February 6, 2014 it was to be established at which concentration eculizumab can be solved and it was found that 10 mg eculizumab can solved in 1 ml of a sterile, preservative free solution. In addition it was to be determined whether eculizumab is storage-stable at a concentration of 10 mg/ml."* (Communication submitted by applicant on January 13, 2016, p. 5, item 4.3.1, emphasis added)

44. In contrast, we submit that the concentration of 10 mg/ml is an arbitrary choice made by the skilled person in the context of routine experimentation. Determining solubility and stability furthermore is part of routine experimentation in protein formulation and does not involve any inventive activity.

45. In a highly similar case, concerned with liquid stable protein formulations (**T 1241/03**), the Board of Appeals ruled that despite the understandable uncertainties, which are associated

with developing liquid stable protein formulations, obviousness is not only at hand when the results are clearly predictable, but also when there is a reasonable expectation of success (**T 149/93**). This does not require certainty (**T 338/97**). Even in the absence of a reasonable expectation of success, the person of skill would adopt a "try and see" attitude (**T 333/97**).

46. **D5**, a document concerned with use of eculizumab for treatment of rheumatoid arthritis, filed by a co-inventor of the opposed patent, already teaches that possible formulations for complement inhibiting antibodies such as 5G1.1-mAb (claim 4), including those for intravenous infusion, that *"may conveniently be presented in unit-dosage form [and] may be prepared according to conventional techniques well known in the pharmaceutical industry"* (**D5**, par. [0043]). Paragraph [0046] similarly refers the skilled person to guidance in the literature and common general knowledge regarding particular dosages and methods of delivery. This confirms that the skilled person did not consider formulation of eculizumab as requiring anything more than common general knowledge and routine experimentation.

47. We agree with **D5** that there certainly was guidance in the prior art for comparable antibody formulations, e.g., **D20**, **D21** and **D22,** so that the skilled person had good reasons to assume that 10 mg/mL would represent a suitable concentration. The review articles **D20** (p. 2-4, Table 1) and **D21** (p. 697, Table 1) show that it was common general knowledge that 10 mg/mL was a common concentration for antibody formulations for intravenous delivery. The formulations listed in these documents comprise antibody concentrations ranging from 0.25 mg/mL to 100 mg/mL for intravenous (IV) delivery. **D21** lists 15 different antibody formulations for IV delivery (Table 1), wherein 10 mg/mL is one of the three most common. **D20** lists 18 formulations for IV delivery, of which 10 mg/mL is the most common (Table 1, entries 3, 14, 16 and 20).

48. At the same time, **D22** indicates that the very same antibody as presently claimed, eculizumab, can be formulated in concentrations ranging from 1-30 mg/mL (**D22**, Fig. 10 and par. [0170] to [0172]). A formulation of eculizumab at 30 mg/mL is shown to be suitable for nebulization. While **D22** is concerned with antibody formulations for a different route of delivery, this does not affect the need for both stability and solubility of the antibody. Based on **D22**, there would thus have been no uncertainties left for the skilled person that 10 mg/mL were stable and soluble, and thus a suitable concentration. At least, the formulation disclosed in said document would have provided the skilled person with a reasonable expectation of success when formulating eculizumab at 10 mg/mL.

49. We furthermore submit that the specific concentration of 10 mg/mL is an arbitrary choice, and, consequently, this feature cannot contribute to inventiveness, as established in **T 206/91** (item 5.5) and **T 37/82** (item 3). We herewith provide the results of a study of the solubility and the long-term stability of eculizumab at various concentrations in the form of a declaration submitted as **D23**.

50. The eculizumab used in the study described in **D23** was recombinantly expressed. The sequence of the heavy and light chains were confirmed to be correct by comparison to peptide

mapping of commercially acquired eculizumab in Soliris® and to the sequences provided within publically available documents the patentee filed with government agencies.

51. For the analysis, the antibody was dissolved in phosphate buffered saline (pH = 7), supplemented with polysorbate 80. These buffer conditions are identical to those used for the pharmaceutical composition of the opposed patent (see prescribing information for Soliris® (eculizumab), **D24**). The stability of solutions containing 2 mg/ml, 5 mg/ml, 10 mg/mL, 30 mg/mL and 50 mg/mL was monitored over a time course of 13 weeks at storage conditions (4 °C) and at elevated temperature (25 °C). Physical and chemical stability were analyzed by size-exclusion ultra high-performance liquid chromatography (SE-UHPLC), anion exchange high-performance liquid chromatography (AEX-HPLC), and reduce sodium dodecyl sulfate capillary electrophoresis (rCE-SDS).

52. Aggregation of the antibody results in the formation of high molecular weight (HMW) species that can be visualized by SE-UHPLC. A large degree of HMW formation is a sign of low long-term stability. All of the eculizumab solutions stored at 4°C and 25°C were sufficiently stable throughout the study, i.e., there was no significant loss in main peak for any of the protein concentrations examined. (**D23**, Appendix A)

53. The storage of antibodies in solution can result in chemical degradation, leading to the formation of acidic species (e.g. by deamidation of asparagine residues), which can be detected by AEX-HPLC. A high degree of acidic species is a sign of low chemical stability. Analysis of the eculizumab solutions (**D23**, Appendix B) shows that all tested samples suffer from some chemical degradation under the tested conditions and the degradation increases over time upon storage at the elevated temperature. There is no significant difference in chemical stability between 10 mg/mL and the other concentrations.

54. rCE-SDS offers high resolution separation of most types of chemically or structurally altered species from the main (intact) species for both heavy chain (HC) and light chain (LC) of the antibody. Analysis of the eculizumab solutions by rCE-SDS (**D23**, Appendix C) shows that a detectable decrease of the main species (HC+LC) occurs at both tested temperatures for all samples. However, in agreement with the AEX-HPLC measurements, there is no significant difference across protein concentrations.

55. Taken together, this shows that solutions of eculizumab possess similar long-term stability at concentrations of 2 mg/ml, 5 mg/ml, 10 mg/mL, 30 mg/mL or 50 mg/mL. The 10 mg/mL concentration offers no apparent advantage over the other tested concentrations.

56. Document **D25** also discloses formulations of anti-C5 antibodies and specifically eculizumab (**D25**, e.g., par. [0019], [0030], [0042], [0074], Fig. 1) at concentrations ranging from 10 mg/mL to more than 200 mg/mL (**D25**, e.g., par. [0061], [0062], [0076]). Formulations of eculizumab at various concentrations were found to be stable over a period of two years (**D25**, par. [0304]). While **D25** was published after the filing date of the opposed patent, it confirms that eculizumab can be stably formulated in various buffers in a wide range of concentrations.

57. In summary, in light of **D1**,

    - the skilled person was motivated to formulate eculizumab for treatment of PNH as a single-use dosage form avoiding the use of preservatives at least due to regulatory aspects and common general knowledge (as evidenced by **D19**);

    - the amount of antibody of 300 mg included in the single-use dosage form is rendered obvious by **D1** itself;

    - it was common general knowledge (**D20**, **D21**) that 10 mg/mL is a conventional concentration for antibody formulations for intravenous delivery; and there was a reasonable expectation of success for this concentration of eculizumab to be stable and soluble in light of **D22**; furthermore, as confirmed by **D25** and **D23**, the concentration of 10 mg/mL was an arbitrary choice.

58. Accordingly, the claimed subject matter lacks an inventive step in light of **D1** in combination with **D22** and common general knowledge (**D19**, **D20**, **D21**), contrary to Article 56 EPC.

VIII. Insufficient Disclosure (Article 100(b) EPC)

59. The opposed patent claims a pharmaceutical composition, wherein the composition is a solution of "eculizumab". While we hold that eculizumab is clearly and unambiguously disclosed by the cited prior art (e.g., **D1** to **D5**, **D11** to **D15**, **D17**, **D18**, **D22**, **D26**, **D27**), we submit that the skilled person may be confused in this regard by the information contained in the opposed patent, to the extent that the skilled person may no longer be able to carry out the teaching of the patent. In particular, the description offers divergent definitions of the antibody eculizumab and fails to provide a correct sequence of the light chain of the antibody.

60. First, SEQ ID NOs 1 to 4 of the opposed patent supposedly define the variable heavy chain (SEQ ID NO: 1) and light chain (SEQ ID NO: 3) segments and the full length heavy chain (SEQ ID NO: 2) and light chain (SEQ ID NO: 4) of eculizumab. We note that the sequence given for the full length light chain of eculizumab is not identical to the sequence of eculizumab in the post-published document **D25** (par. [0094]), which has a length of 214 amino acids. This length of 214 amino acids is in accordance with the prescribing information for Soliris® (**D24**, item 11). To the contrary, SEQ ID NO: 4 of the opposed patent contains 22 additional N-terminal amino acids and has a length of 236 amino acids.

61. It may be concluded that the antibody described in the opposed patent, comprising heavy chains with a sequence of SEQ ID NO: 2 and light chains with a sequence of SEQ ID NO: 4 is in fact not eculizumab.

62. In conclusion, the skilled person seeking to reproduce the alleged invention would be misguided by the opposed patent into using an antibody that may not be eculizumab. Use of the antibody eculizumab for treatment of PNH can thus be considered insufficiently disclosed by the opposed patent.

63. The claim of the opposed patent violates Article 83 EPC.

IX. Conclusion

64. As the subject matter of the claim of the opposed patent

- is not clearly and unambiguously derivable form the parent application as filed, contrary to Art. 76(1) EPC and Art. 123(2) EPC,
- lacks inventive step over **D1** in combination with **D22** and common general knowledge, as evidenced by **D19** and **D20**-**D21**,
- is insufficiently disclosed,

revocation of European patent EP 2 359 834 B1 in its entirety is justified.

Respectfully submitted,

Dr. H. Ulrich Dörries
European Patent Attorney

UD/MO/SI/KS

Enclosures
Documents P, WO, A1, D1-D5 to D7-D27

Europäisches Patentamt
European Patent Office
Office européen des brevets

Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP2359834
Application No.	EP11001632.6
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	09 November 2016
Title of the invention	Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement

II. Proprietor of the patent

first named in the patent specification	ALEXION PHARMACEUTICALS, INC.
Opponent's or representative's reference	AMG17203OP

III. Opponent

Name	Amgen Inc.
Address:	One Amgen Center Drive Thousand Oaks CA California 91320-1799 United States of America
State of residence or of principal place of business	United States of America
Multiple opponents (see additional sheet)	☐

IV. Authorisation

1. Representative

	Dörries, Mr H. Ulrich	
Company:	df-mp	
Address of place of business	Fünf Höfe Theatinerstraße 16 80333 Munich Germany	
Telephone/Fax	+49 89 2102960	+49 89 21029633
E-mail:	info@df-mp.com	

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Multiple representatives (see additional sheet) ☐

Authorisation(s)

is/are enclosed ☐

has/have been registered under No. ☐

V. Opposition is filed against

the patent as a whole ☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

• it is not new (Art. 52(1); Art. 54 EPC) ☐

• it does not involve an inventive step (Art. 52(1); Art. 56 EPC) ☒

• patentability is excluded on other grounds, namely articles ☐

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). ☒

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). ☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith on an attached document ☒

VIII. Other requests:

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IX. Evidence presented

A1	Patent document	EP2359834 (A1) original file name: A1_EP 2 359 834 A1.pdf attached as: Published-Evidence-3.pdf
D1	Patent document	US2005/0191298 (A1) particular relevance: Bell, Leonard et al.; September 1, 2005 original file name: D1.pdf attached as: Published-Evidence-18.pdf
D10	Non-patent literature - internet	U.S. Pharmacopeia, "Customized plastic packaging - applied to every need" , [cited 17.05.2017] Available from: [http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1136.html] original file name: D10.pdf attached as: Published-Evidence-4.pdf
D11	Other evidence	Adis Data information, Drugs R. D. 2007, 8(1), 61-68 original file name: D11.pdf attached as: Other-evidence-1.pdf
D12	Non-patent literature - article	Hill, Anita et al., "Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria" Bloodjournal, Vol. 106, No. 7, 2007 particular relevance: 2559-2565 original file name: D12.pdf attached as: Published-Evidence-5.pdf
D13	Non-patent literature - article	Thomas, Thomas C. et al., "INHIBITION OF COMPLEMENT ACTIVITY VY HUMANIZED ANTI-C5 ANTIBODY AND SINGLE-CHAIN Fv." Moleculary Immunology, Vol. 33, No. 17/18, 1996 particular relevance: 1389-1401 original file name: D13.pdf attached as: Published-Evidence-6.pdf
D14	Non-patent literature - article	Mueller, John P. et al., "HUMANIZED PORCINE VCAM-SPECIFIC MONOCLONAL ANTIBODIES WITH CHIMERIC IgG2/G4 CONSTANT REGIONS BLOCK HUMAN LEUKOCYTE BINDING TO PORCINE ENDOTHELIAL CELLS" Molecular Immunology, Vol. 34, No. 6, 1997 particular relevance: 441-452 original file name: D14.pdf attached as: Published-Evidence-7.pdf
D15	Patent document	WO97/11971 (A1) particular relevance: Mueller, John et. al.; April 3, 1997 original file name: D15.pdf attached as: Published-Evidence-8.pdf
D16	Patent document	WO2005/007809 (A2) particular relevance: Rother, Russell et al., January 27, 2005 original file name: D16.pdf attached as: Published-Evidence-9.pdf
D17	Patent document	US6,355,245 (B1) particular relevance: Evans, Mark J. et al., March 12, 2002 original file name: D17.pdf attached as: Published-Evidence-10.pdf

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D18	Non-patent literature - article	Hillmen, M.B., Ch.N., PhD., Peter et al., "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria" THE NEW ENGLAND JOURNAL OF MEDICINE, 2006 original file name: D18.pdf attached as: Published-Evidence-11.pdf
D19	Other evidence	EMEA, CPMP, 20 February 2003, Note for guidance on excipients original file name: D19.pdf attached as: Other-evidence-2.pdf
D2	Non-patent literature - article	Hillmen, P. et al., "Oral Communication; Presidents Free Communications 257-280" Br. J. Hematol., Vol. 121, 2003 particular relevance: (Suppl. 1), 87-95 original file name: D2.pdf attached as: Published-Evidence-19.pdf
D20	Non-patent literature - article	Wei, Wang et al., "Anitbody Structure, Instability, and Formulation" Journal of Pharmaceutical Sciences, Vol. 96, No. 1, January 2007 original file name: D20.pdf attached as: Published-Evidence-12.pdf
D21	Non-patent literature - article	Daugherty, Ann L. et al., "Formulation and delivery issues for monoclonal antibody therapeutics" ScienceDirect - Advanced Drug Delivery Reviews, Vol. 58, May 2006 particular relevance: 686-706 original file name: D21.pdf attached as: Published-Evidence-13.pdf
D22	Patent document	US2005/0271660 (A1) particular relevance: Wang, Yi; December 8, 2005 original file name: D22.pdf attached as: Published-Evidence-14.pdf
D23	Other evidence	Expert declaration by Dr. Michael Treuheit; CV; Appendix A-C original file name: D23.pdf attached as: Other-evidence-3.pdf
D24	Other evidence	Soliris® (eculizumab) Highlights of prescribing information original file name: D24.pdf attached as: Other-evidence-4.pdf
D25	Patent document	US2012/0230982 (A1) particular relevance: Zhou, Xiao-Hong et al., September 13, 2012 original file name: D25.pdf attached as: Published-Evidence-15.pdf
D26	Patent document	WO2007/002571 (A2) particular relevance: Rother, January 4, 2007 original file name: D26.pdf attached as: Published-Evidence-16.pdf
D27	Non-patent literature - article	Hill, Anita et al., "Sustained Control of Hemolysis and Symptoms and Reduced Transfusion Requirements over a Period of 2 Years in Paroxysmal Nocturnal Hemoglobinuria (PNH) with Eculizumab Therapy" Blood, Vol. 104, 2004 particular relevance: 2823-2824 original file name: D27.pdf

		attached as: Published-Evidence-17.pdf
D3	Non-patent literature - article	Hillmen, M.B., Ph.D., Peter et al., "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria" THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 350, No. 6, 2004 particular relevance: 552-559 original file name: D3.pdf attached as: Published-Evidence-20.pdf
D4	Non-patent literature - article	Harding et al., "Eculizumab - Huminazed Anti-C5 Monoclonal Antibody" Drugs of the Future, Vol. 29, No. 7, 2004 particular relevance: 673-676 original file name: D4.pdf attached as: Published-Evidence-21.pdf
D5	Patent document	US2005/0221382 (A1) particular relevance: Rother, P. Russell; October 6, 2005 original file name: D5.pdf attached as: Published-Evidence-22.pdf
D7	Non-patent literature - article	Morris et al., "Recurrence of neisserial meningococcemia due to deficiency of terminal complement component" Southern medical journal, Vol. 25, No. 19, 1992 ISSN: 1541-8243 particular relevance: 1030-1031 original file name: D7.pdf attached as: Published-Evidence-23.pdf
D8	Non-patent literature - article	Corvini MD, Michael et al., "Complement C7 deficiency presenting as recurrent aseptic meningitis" ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY, Vol. 93, No. 2, 2004 particular relevance: 200-205 original file name: D8.pdf attached as: Published-Evidence-24.pdf
D9	Non-patent literature - article	GVG, Sierra et al., "Vaccine Against Group B Neisseria Meningitidis: Protection Trial And Mass Caccination Results In Cuba" Niph Annals, Vol. 14, No. 2, 1991 ISSN: 0332-5652 original file name: D9.pdf attached as: Published-Evidence-25.pdf
P	Patent document	US2006/0783070 P (P) particular relevance: Bell, Leonard et. al.; March 15, 2006 original file name: P.pdf attached as: Published-Evidence-1.pdf
WO	Patent document	WO2007/106585 (A1) original file name: WO.pdf attached as: Published-Evidence-2.pdf

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X. Payment

Mode of payment	Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency:	EUR
Deposit account number:	28001000
Account holder:	df-mp

Refunds

Any refunds should be made to EPO deposit account:	28001000
Account holder:	df-mp

Fees

	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	785.00	785.00
Total:		EUR	785.00

A Forms

	Details:	System file name:
A-1	Form for notice of opposition	ep-oppo.pdf

B Attached document files

	Original file name:	System file name:
B-1 1. Facts and arguments	AMG17203OP_Notice of Opposition.pdf	OPPO.pdf

C Attached evidence files

	Original file name:	System file name:
C-1 1. Patent document	P.pdf	Published-Evidence-1.pdf
C-2 2. Patent document	WO.pdf	Published-Evidence-2.pdf
C-3 3. Patent document	A1_EP 2 359 834 A1.pdf	Published-Evidence-3.pdf
C-4 4. Patent document	D15.pdf	Published-Evidence-8.pdf
C-5 5. Patent document	D16.pdf	Published-Evidence-9.pdf
C-6 6. Patent document	D17.pdf	Published-Evidence-10.pdf
C-7 7. Patent document	D22.pdf	Published-Evidence-14.pdf

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C-8	8. Patent document	D25.pdf	Published-Evidence-15.pdf
C-9	9. Patent document	D26.pdf	Published-Evidence-16.pdf
C-10	10. Patent document	D1.pdf	Published-Evidence-18.pdf
C-11	11. Patent document	D5.pdf	Published-Evidence-22.pdf
C-12	1. Non-patent literature - article	D12.pdf	Published-Evidence-5.pdf
C-13	2. Non-patent literature - article	D13.pdf	Published-Evidence-6.pdf
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C-16	5. Non-patent literature - article	D20.pdf	Published-Evidence-12.pdf
C-17	6. Non-patent literature - article	D21.pdf	Published-Evidence-13.pdf
C-18	7. Non-patent literature - article	D27.pdf	Published-Evidence-17.pdf
C-19	8. Non-patent literature - article	D2.pdf	Published-Evidence-19.pdf
C-20	9. Non-patent literature - article	D3.pdf	Published-Evidence-20.pdf
C-21	10. Non-patent literature - article	D4.pdf	Published-Evidence-21.pdf
C-22	11. Non-patent literature - article	D7.pdf	Published-Evidence-23.pdf
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C-24	13. Non-patent literature - article	D9.pdf	Published-Evidence-25.pdf
C-25	14. Non-patent literature - internet	D10.pdf	Published-Evidence-4.pdf
C-26	1. Other evidence	D11.pdf	Other-evidence-1.pdf
C-27	2. Other evidence	D19.pdf	Other-evidence-2.pdf
C-28	3. Other evidence	D24.pdf	Other-evidence-4.pdf
C-29	4. Other evidence	D23.pdf	Other-evidence-3.pdf

Signature of opponent or representative

Place	**Munich, Germany**
Date:	**04 August 2017**
Signed by:	**Hans Doerries 13689**
Representative name:	**H. Ulrich Dörries**
Capacity:	**(Representative)**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SOLIRIS safely and effectively. See full prescribing information for SOLIRIS.

Soliris® (eculizumab) injection, for intravenous use

Initial U.S. Approval: 2007

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

See full prescribing information for complete boxed warning

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. [see *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection].**
- **Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program (5.2).

INDICATIONS AND USAGE

Soliris is a complement inhibitor indicated for:

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis (1.1).
- The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (1.2).

Limitation of Use

Soliris is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

DOSAGE AND ADMINISTRATION

Only administer as an intravenous infusion

PNH Dosage Regimen: (2.1)
aHUS Dosage Regimen: (2.2)

D24

DOSAGE FORMS AND STRENGTHS

300 mg single-dose vials each containing 30 mL of 10 mg/mL sterile, preservative-free solution (3).

CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection (5.1).

WARNINGS AND PRECAUTIONS

- Discontinue Soliris in patients who are being treated for serious meningococcal infections.
- Use caution when administering Soliris to patients with any other systemic infection (5.2).

ADVERSE REACTIONS

The most frequently reported adverse reactions in the PNH randomized trial (≥10% overall and greater than placebo) are: headache, nasopharyngitis, back pain, and nausea (6.1).

The most frequently reported adverse reactions in aHUS single arm prospective trials (≥20%) are: headache, diarrhea, hypertension, upper respiratory infection, abdominal pain, vomiting, nasopharyngitis, anemia, cough, peripheral edema, nausea, urinary tract infections, pyrexia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at) 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, Soliris may cause fetal harm (8.1).
Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early [*see Warnings and Precautions* (5.1)].

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines least 2 weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection. [see *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of meningococcal infection].**
- **Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program [*see Warnings and Precautions (5.2)*]. Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at solirisrems.com.

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

Soliris is indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis.

1.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Soliris is indicated for the treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy.

Limitation of Use

Soliris is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Soliris must enroll in the Soliris REMS [*see Warnings and Precautions (5.2)*].

Vaccinate patients according to current ACIP guidelines to reduce the risk of serious infection [*see Warnings and Precautions (5.1) and (5.2)*].

Only administer as an intravenous infusion.

2.1 Recommended Dosage Regimen - PNH

Soliris therapy consists of:

- 600 mg weekly for the first 4 weeks, followed by
- 900 mg for the fifth dose 1 week later, then
- 900 mg every 2 weeks thereafter.

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points *[see Warnings and Precautions (5.6)]*.

2.2 Recommended Dosage Regimen - aHUS

For patients 18 years of age and older, Soliris therapy consists of:

- 900 mg weekly for the first 4 weeks, followed by
- 1200 mg for the fifth dose 1 week later, then
- 1200 mg every 2 weeks thereafter.

For patients less than 18 years of age, administer Soliris based upon body weight, according to the following schedule (Table 1):

Table 1: Dosing recommendations in patients less than 18 years of age

Patient Body Weight	Induction	Maintenance
40 kg and over	900 mg weekly x 4 doses	1200 mg at week 5; then 1200 mg every 2 weeks
30 kg to less than 40 kg	600 mg weekly x 2 doses	900 mg at week 3; then 900 mg every 2 weeks
20 kg to less than 30 kg	600 mg weekly x 2 doses	600 mg at week 3; then 600 mg every 2 weeks
10 kg to less than 20 kg	600 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 2 weeks
5 kg to less than 10 kg	300 mg weekly x 1 dose	300 mg at week 2; then 300 mg every 3 weeks

Administer Soliris at the recommended dosage regimen time points, or within two days of these time points.

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Supplemental dosing of Soliris is required in the setting of concomitant support with PE/PI (plasmapheresis or plasma exchange; or fresh frozen plasma infusion) (Table 2).

Table 2: Supplemental dose of Soliris after PE/PI

Type of Intervention	Most Recent Soliris Dose	Supplemental Soliris Dose With Each PE/PI Intervention	Timing of Supplemental Soliris Dose
Plasmapheresis or plasma exchange	300 mg	300 mg per each plasmapheresis or plasma exchange session	Within 60 minutes after each plasmapheresis or plasma exchange
	600 mg or more	600 mg per each plasmapheresis or plasma exchange session	
Fresh frozen plasma infusion	300 mg or more	300 mg per infusion of fresh frozen plasma	60 minutes prior to each infusion of fresh frozen plasma

2.3 Preparation and Administration

Dilute Soliris to a final admixture concentration of 5 mg/mL using the following steps:

- Withdraw the required amount of Soliris from the vial into a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Soliris to a final concentration of 5 mg/mL by adding the appropriate amount (equal volume of diluent to drug volume) of 0.9% Sodium Chloride Injection, USP; 0.45% Sodium Chloride Injection, USP; 5% Dextrose in Water Injection, USP; or Ringer's Injection, USP to the infusion bag.

The final admixed Soliris 5 mg/mL infusion volume is 60 mL for 300 mg doses, 120 mL for 600 mg doses, 180 mL for 900 mg doses or 240 mL for 1200 mg doses (Table 3).

Table 3: Preparation and Reconstitution of Soliris

Soliris Dose	Diluent Volume	Final Volume
300 mg	30 mL	60 mL
600 mg	60 mL	120 mL
900 mg	90 mL	180 mL
1200 mg	120 mL	240 mL

Gently invert the infusion bag containing the diluted Soliris solution to ensure thorough mixing of the product and diluent. Discard any unused portion left in a vial, as the product contains no preservatives.

Prior to administration, the admixture should be allowed to adjust to room temperature [18°-25° C, 64-77° F]. The admixture must not be heated in a microwave or with any heat source other than ambient air temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.4 Administration

Do Not Administer As An Intravenous Push or Bolus Injection

Administer the Soliris admixture by intravenous infusion over 35 minutes in adults and 1 to 4 hours in pediatric patients via gravity feed, a syringe-type pump, or an infusion pump. Admixed solutions of Soliris are stable for 24 hours at 2-8° C (36-46° F) and at room temperature.

If an adverse reaction occurs during the administration of Soliris, the infusion may be slowed or stopped at the discretion of the physician. If the infusion is slowed, the total infusion time should not exceed two hours in adults. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

3 DOSAGE FORMS AND STRENGTHS

Soliris is supplied as 300 mg single-dose vials each containing 30 mL of 10 mg/mL sterile, preservative-free eculizumab solution.

4 CONTRAINDICATIONS

Soliris is contraindicated in:

- Patients with unresolved serious *Neisseria meningitidis* infection
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Soliris treatment outweigh the risks of developing a meningococcal infection [*see Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Meningococcal Infections

Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. The use of Soliris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis).

Vaccinate for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations, considering the duration of Soliris therapy.

Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris. If urgent Soliris therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible.

In prospective clinical studies, 75/100 patients with aHUS were treated with Soliris less than 2 weeks after meningococcal vaccination and 64 of these 75 patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving Soliris have not been established.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 2 out of 196 PNH patients developed serious meningococcal infections while receiving treatment with Soliris; both had been vaccinated [*see Adverse Reactions (6.1)*]. In clinical studies among non-PNH patients, meningococcal meningitis occurred in one unvaccinated patient. In addition, 3 out of 130 previously vaccinated patients with aHUS developed meningococcal infections while receiving treatment with Soliris [*see Adverse Reactions (6.1)*].

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if an infection is suspected. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Discontinue Soliris in patients who are undergoing treatment for serious meningococcal infections.

5.2 Soliris REMS

Because of the risk of meningococcal infections, Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Soliris REMS, prescribers must enroll in the program.

Prescribers must counsel patients about the risk of meningococcal infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated with a meningococcal vaccine.

Enrollment in the Soliris REMS program and additional information are available by telephone: 1-888-SOLIRIS (1-888-765-4747) or at solirisrems.com.

5.3 Other Infections

Soliris blocks terminal complement activation; therefore patients may have increased susceptibility to infections, especially with encapsulated bacteria. Additionally, Aspergillus infections have occurred in immunocompromised and neutropenic patients. Children treated with Soliris may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) infections according to ACIP guidelines. Use caution when administering Soliris to patients with any systemic infection [*see Warnings and Precautions (5.1)*].

5.4 Monitoring Disease Manifestations After Soliris Discontinuation

Treatment Discontinuation for PNH

Monitor patients after discontinuing Soliris for at least 8 weeks to detect hemolysis.

Treatment Discontinuation for aHUS

After discontinuing Soliris, monitor patients with aHUS for signs and symptoms of thrombotic microangiopathy (TMA) complications for at least 12 weeks. In aHUS clinical trials, 18 patients (5 in the prospective studies) discontinued Soliris treatment. TMA complications occurred following a missed dose in 5 patients, and Soliris was reinitiated in 4 of these 5 patients.

Clinical signs and symptoms of TMA include changes in mental status, seizures, angina, dyspnea, or thrombosis. In addition, the following changes in laboratory parameters may identify a TMA complication: occurrence of two, or repeated measurement of any one of the following: a decrease in platelet count by 25% or more compared to baseline or the peak platelet count during Soliris treatment; an increase in serum creatinine by 25% or more compared to baseline or nadir during Soliris treatment; or, an increase in serum LDH by 25% or more over baseline or nadir during Soliris treatment.

If TMA complications occur after Soliris discontinuation, consider reinstitution of Soliris treatment, plasma therapy [plasmapheresis, plasma exchange, or fresh frozen plasma infusion (PE/PI)], or appropriate organ-specific supportive measures.

5.5 Thrombosis Prevention and Management

The effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established. Therefore, treatment with Soliris should not alter anticoagulant management.

5.6 Infusion Reactions

As with all protein products, administration of Soliris may result in infusion reactions, including anaphylaxis or other hypersensitivity reactions. In clinical trials, no patients experienced an infusion reaction which required discontinuation of Soliris. Interrupt Soliris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Meningococcal Infections [*see Warnings and Precautions (5.1)*]
- Other Infections [*see Warnings and Precautions (5.3)*]
- Monitoring Disease Manifestations After Soliris Discontinuation [*see Warnings and Precautions (5.4)*]
- Thrombosis Prevention and Management [*see Warnings and Precautions (5.5)*]
- Infusion Reactions [*see Warnings and Precautions (5.6)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Meningococcal infections are the most important adverse reactions experienced by patients receiving Soliris. In PNH clinical studies, two patients experienced meningococcal sepsis. Both patients had previously received a meningococcal vaccine. In clinical studies among patients without PNH, meningococcal meningitis occurred in one unvaccinated patient. Meningococcal sepsis occurred in one previously vaccinated patient enrolled in the retrospective aHUS study during the post-study follow-up period [*see Warnings and Precautions (5.1)*].

PNH

The data described below reflect exposure to Soliris in 196 adult patients with PNH, age 18-85, of whom 55% were female. All had signs or symptoms of intravascular hemolysis. Soliris was studied in a placebo-controlled clinical study (in which 43 patients received Soliris and 44, placebo); a single arm clinical study and a long term extension study. 182 patients were exposed for greater than one year. All patients received the recommended Soliris dose regimen.

Table 4 summarizes the adverse reactions that occurred at a numerically higher rate in the Soliris group than the placebo group and at a rate of 5% or more among patients treated with Soliris.

Table 4: Adverse Reactions Reported in 5% or More of Soliris Treated Patients and Greater than Placebo in the Controlled Clinical Study

Reaction	Soliris N = 43 N (%)	Placebo N = 44 N (%)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)

In the placebo-controlled clinical study, serious adverse reactions occurred among 4 (9%) patients receiving Soliris and 9 (21%) patients receiving placebo. The serious reactions included infections and progression of PNH. No deaths occurred in the study and no patients receiving Soliris experienced a thrombotic event; one thrombotic event occurred in a patient receiving placebo.

Among 193 patients with PNH treated with Soliris in the single arm, clinical study or the follow-up study, the adverse reactions were similar to those reported in the placebo-controlled clinical study. Serious adverse reactions occurred among 16% of the patients in these studies. The most common serious adverse reactions were: viral infection (2%), headache (2%), anemia (2%), and pyrexia (2%).

aHUS

The safety of Soliris therapy in patients with aHUS was evaluated in four prospective, single-arm studies, three in adult and adolescent patients (aHUS Studies 1, 2, and 4), one in pediatric and adolescent patients (aHUS Study 5) and one retrospective study (aHUS Study 3).

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The data described below were derived from 78 adult and adolescent patients with aHUS enrolled in aHUS Study 1, aHUS Study 2, and aHUS Study 4. All patients received the recommended dosage of Soliris. Median exposure was 67 weeks (range: 2-145 weeks). Table 5 summarizes all adverse events reported in at least 10% of patients in aHUS Studies 1, 2, and 4 combined.

Table 5: Per Patient Incidence of Adverse Events in 10% or More Adult and Adolescent Patients Enrolled in aHUS Study 1, aHUS Study 2 and aHUS Study 4 Separately and in Total

MedDRA ver. 15.1	Number (%) of Patients			
	Study 1 (n=17)	Study 2 (n=20)	Study 4 (n=41)	Total (n=78)
Vascular Disorders				
Hypertension[a]	10 (59)	9 (45)	7 (17)	26 (33)
Hypotension	2 (12)	4 (20)	7 (17)	13 (17)
Infections and Infestations				
Bronchitis	3 (18)	2 (10)	4 (10)	9 (12)
Nasopharyngitis	3 (18)	11 (55)	7 (17)	21 (27)
Gastroenteritis	3 (18)	4 (20)	2 (5)	9 (12)
Upper respiratory tract infection	5 (29)	8 (40)	2 (5)	15 (19)
Urinary tract infection	6 (35.3)	3 (15)	8 (20)	17 (22)
Gastrointestinal Disorders				
Diarrhea	8 (47)	8 (40)	12 (32)	29 (37)
Vomiting	8 (47)	9 (45)	6 (15)	23 (30)
Nausea	5 (29)	8 (40)	5 (12)	18 (23)
Abdominal pain	3 (18)	6 (30)	6 (15)	15 (19)
Nervous System Disorders				
Headache	7 (41)	10 (50)	15 (37)	32 (41)
Blood and Lymphatic System Disorders				
Anemia	6 (35)	7 (35)	7 (17)	20 (26)
Leukopenia	4 (24)	3 (15)	5 (12)	12 (15)
Psychiatric Disorders				
Insomnia	4 (24)	2 (10)	5 (12)	11 (14)
Renal and Urinary Disorders				
Renal impairment	5 (29)	3 (15)	6 (15)	14 (18)
Proteinuria	2 (12)	1 (5)	5 (12)	8 (10)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	4 (24)	6 (30)	8 (20)	18 (23)
General Disorders and Administration Site Conditions				
Fatigue	3 (18)	4 (20)	3 (7)	10 (13)
Peripheral edema	5 (29)	4 (20)	9 (22)	18 (23)
Pyrexia	4 (24)	5 (25)	7 (17)	16 (21)
Asthenia	3 (18)	4 (20)	6 (15)	13 (17)
Eye Disorder	5 (29)	2 (10)	8 (20)	15 (19)
Metabolism and Nutrition Disorders				
Hypokalaemia	3 (18)	2 (10)	4 (10)	9 (12)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (6)	6 (30)	1 (20)	8 (10)
Skin and Subcutaneous Tissue Disorders				
Rash	2 (12)	3 (15)	6 (15)	11 (14)
Pruritis	1 (6)	3 (15)	4 (10)	8 (10)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	1 (6)	2 (10)	7 (17)	10 (13)
Back pain	3 (18)	3 (15)	2 (5)	8 (10)

[a] includes the preferred terms hypertension, accelerated hypertension, and malignant hypertension.

In aHUS Studies 1, 2, and 4 combined, 60% (47/78) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were infections (24%), hypertension (5%), chronic renal failure (5%), and renal impairment (5%). Five patients discontinued Soliris due to adverse events; three due to worsening renal function, one due to new diagnosis of Systemic Lupus Erythematosus, and one due to meningoccal meningitis.

aHUS Study 5 included 22 pediatric and adolescent patients, of which 18 patients were less than 12 years of age. All patients received the recommended dosage of Soliris. Median exposure was 44 weeks (range: 1 dose-87 weeks). Table 6 summarizes all adverse events reported in at least 10% of patients enrolled in aHUS Study 5.

Table 6: Per Patient Incidence of Adverse Reactions in 10% or More Patients Enrolled in aHUS Study 5

MedDRA ver. 15.1	1 month to <12 yrs (n=18)	Total (n=22)
Eye Disorders	3 (17)	3 (14)
Gastrointestinal Disorders		
Abdominal pain	6 (33)	7 (32)
Diarrhoea	5 (28)	7 (32)
Vomiting	4 (22)	6 (27)
Dyspepsia	0	3 (14)
General Disorders and Administration Site Conditions		
Pyrexia	9 (50)	11 (50)
Infections and Infestations		
Upper respiratory tract infection	5 (28)	7 (32)
Nasopharyngitis	3 (17)	6 (27)
Rhinitis	4 (22)	4 (18)
Urinary Tract infection	3 (17)	4 (18)
Catheter site infection	3 (17)	3 (14)
Musculoskeletal and Connective Tissue Disorders		
Muscle spasms	2 (11)	3 (14)
Nervous System Disorders		
Headache	3 (17)	4 (18)
Renal and Urinary Disorders	3 (17)	4 (18)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	7 (39)	8 (36)
Oropharyngeal pain	1 (6)	3 (14)
Skin and Subcutaneous Tissue Disorders		
Rash	4 (22)	4 (18)
Vascular Disorders		
Hypertension	4 (22)	4 (18)

In aHUS Study 5, 59% (13/22) of patients experienced a serious adverse event (SAE). The most commonly reported SAEs were hypertension (9%), viral gastroenteritis (9%), pyrexia (9%), and upper respiratory infection (9%). One patient discontinued Soliris due to an adverse event (severe agitation).

Analysis of retrospectively collected adverse event data from pediatric and adult patients enrolled in aHUS Study 3 (N=30) revealed a safety profile that was similar to that which was observed in the two prospective studies. aHUS Study 3 included 19 pediatric patients less than 18 years of age. Overall, the safety of Soliris in pediatric patients with aHUS enrolled in Study 3 appeared similar to that observed in adult patients. The most common (≥15%) adverse events occurring in pediatric patients are presented in Table 7.

Table 7: Adverse Reactions Occurring in at Least 15% of Patients Less than 18 Years of Age Enrolled in aHUS Study 3

MedDRA ver. 11.0	Number (%) of Patients			
	< 2 yrs (n=5)	2 to < 12 yrs (n=10)	12 to <18 yrs (n=4)	Total (n=19)
General Disorders and Administration Site Conditions				
Pyrexia	4 (80)	4 (40)	1 (25)	9 (47)
Gastrointestinal Disorders				
Diarrhea	1 (20)	4 (40)	1 (25)	6 (32)
Vomiting	2 (40)	1 (10)	1 (25)	4 (21)
Infections and Infestations				
Upper respiratory tract infection[a]	2 (40)	3 (30)	1 (25)	6 (32)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3 (60)	2 (20)	0 (0)	5 (26)
Nasal congestion	2 (40)	2 (20)	0 (0)	4 (21)
Cardiac Disorders				
Tachycardia	2 (40)	2 (20)	0 (0)	4 (21)

[a] includes the preferred terms upper respiratory tract infection and nasopharyngitis.

6.2 Immunogenicity

As with all proteins, there is a potential for immunogenicity with eculizumab. The immunogenicity of Soliris has been evaluated using two different immunoassays for the detection of anti-eculizumab antibodies: a direct enzyme-linked immunosorbent assay (ELISA) using the Fab fragment of eculizumab as target was used for the PNH indication; and an electro-chemiluminescence (ECL) bridging assay using the eculizumab whole molecule as target was used for the aHUS indication, as well as for additional patients with PNH. In the PNH population, antibodies to Soliris were detected in 3/196 (2%) patients with PNH treated with Soliris using the ELISA assay and in 5/161 (3%) patients treated with Soliris using the ECL assay. In patients with aHUS treated with Soliris, antibodies to Soliris were detected in 3/100 (3%) using the ECL assay. An ECL based neutralizing HAHA assay with a low sensitivity of 2 mcg/mL was performed to detect neutralizing antibodies for the 3 patients with aHUS and also for the 5 patients with PNH with positive samples using the ECL assay. 2/161 patients in the PNH group (1.2%) and 1/100 patients in the aHUS group (1%) had low positive values for neutralizing antibodies. No apparent correlation of antibody development to clinical response was observed in either indication. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Soliris in an ELISA-based assay and/or an ECL-based assay and are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of antibody positivity in the assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Soliris with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Soliris. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Soliris exposure.

Cases of serious or fatal meningococcal infections have been reported.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of Soliris in pregnant women. Soliris, a recombinant IgG molecule (humanized anti-C5 antibody), is expected to cross the placenta. Animal studies using a mouse analogue of the Soliris molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 2-8 times the human dose. Soliris should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 2-4 times (low dose) and 4-8 times (high dose) the recommended human Soliris dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function.

8.3 Nursing Mothers

It is not known whether Soliris is excreted into human milk. IgG is excreted in human milk, so it is expected that Soliris will be present in human milk. However, published data suggest that antibodies in human milk do not enter

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the neonatal and infant circulation in substantial amounts. Caution should be exercised when Soliris is administered to a nursing woman. The unknown risks to the infant from gastrointestinal or limited systemic exposure to Soliris should be weighed against the known benefits of human milk feeding.

8.4 Pediatric Use

The safety and effectiveness of Soliris for the treatment of PNH in pediatric patients have not been established.

The safety and effectiveness of Soliris for the treatment of aHUS have been established in pediatric patients. Use of Soliris in pediatric patients for this indication is supported by evidence from four adequate and well-controlled clinical studies assessing the safety and effectiveness of Soliris for the treatment of aHUS. The studies included a total of 47 pediatric patients (ages 2 months to 17 years). The safety and effectiveness of Soliris for the treatment of aHUS appear similar in pediatric and adult patients [*Adverse Reactions (6.1), and Clinical Studies (14.2)*].

Administer vaccinations for the prevention of infection due to *Neisseria meningitidis, Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) according to ACIP guidelines [*see Warnings and Precautions (5.1, 5.2)*].

8.5 Geriatric Use

Nineteen patients 65 years of age or older (15 with PNH and 4 with aHUS) were treated with Soliris. Although there were no apparent age-related differences observed in these studies, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

10 OVERDOSAGE

No cases of Soliris overdose have been reported during clinical studies.

11 DESCRIPTION

Soliris, a complement inhibitor, is a formulation of eculizumab which is a recombinant humanized monoclonal IgG2/4$_K$ antibody produced by murine myeloma cell culture and purified by standard bioprocess technology. Eculizumab contains human constant regions from human IgG2 sequences and human IgG4 sequences and murine complementarity-determining regions grafted onto the human framework light- and heavy-chain variable regions. Eculizumab is composed of two 448 amino acid heavy chains and two 214 amino acid light chains and has a molecular weight of approximately 148 kDa.

Soliris is a sterile, clear, colorless, preservative-free 10 mg/mL solution for intravenous infusion and is supplied in 30-mL single-dose vials. The product is formulated at pH 7 and each vial contains 300 mg of eculizumab, 13.8 mg sodium phosphate monobasic, 53.4 mg sodium phosphate dibasic, 263.1 mg sodium chloride, 6.6 mg polysorbate 80 (vegetable origin) and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eculizumab, the active ingredient in Soliris, is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Soliris inhibits terminal complement mediated intravascular hemolysis in PNH patients and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

A genetic mutation in patients with PNH leads to the generation of populations of abnormal RBCs (known as PNH cells) that are deficient in terminal complement inhibitors, rendering PNH RBCs sensitive to persistent terminal complement-mediated destruction. The destruction and loss of these PNH cells (intravascular hemolysis) results in low RBC counts (anemia), and also fatigue, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots.

In aHUS, impairment in the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy.

12.2 Pharmacodynamics

In the PNH placebo-controlled clinical study, Soliris when administered as recommended reduced hemolysis as shown by the reduction of serum LDH levels from 2200 ± 1034 U/L (mean ± SD) at baseline to 700 ± 388 U/L by week one and maintained the effect through the end of the study at week 26 (327 ± 433 U/L). In the single arm clinical study, Soliris maintained this effect through 52 weeks [*see Clinical Studies (14)*].

12.3 Pharmacokinetics

A population PK analysis with a standard 1-compartmental model was conducted on the multiple dose PK data from 40 PNH patients receiving the recommended Soliris regimen [*see Dosage and Administration (2.1)*]. In this model, the clearance of Soliris for a typical PNH patient weighing 70 kg was 22 mL/hr and the volume of distribution was 7.7 L. The half-life was 272 ± 82 hrs (mean ± SD). The mean observed peak and trough serum concentrations of Soliris by week 26 were 194 ± 76 mcg/mL and 97 ± 60 mcg/mL, respectively.

A second population PK analysis with a standard 1 compartmental model was conducted on the multiple dose PK data from 57 aHUS patients receiving the recommended Soliris regimen in studies 1, 2 and 3. In this model, the clearance of Soliris for a typical aHUS patient weighing 70 kg was 14.6 mL/hr and the volume of distribution was 6.14 L. The elimination half-life was 291 h (approximately 12.1 days).

The clearance and half-life of eculizumab were also evaluated during plasma exchange interventions. Plasma exchange increased the clearance of eculizumab to 3660 mL/hr and reduced the half-life to 1.26 hours. Supplemental dosing is recommended when Soliris is administered to aHUS patients receiving plasma infusion or exchange [*see Dosage and Administration (2.2)*].

Dedicated studies have not been conducted to evaluate the PK of Soliris in special patient populations identified by gender, race, age (geriatric), or the presence of renal or hepatic impairment. Pediatric and adolescent patients (less than 18 years of age) and patients with renal impairment were included in the aHUS clinical studies [*see Clinical Studies (14)*]. Population PK analysis showed age, gender, race, and renal function do not influence the PK of eculizumab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of eculizumab have not been conducted.

Genotoxicity studies have not been conducted with eculizumab.

Effects of eculizumab upon fertility have not been studied in animals. Intravenous injections of male and female mice with a murine anti-C5 antibody at up to 4-8 times the equivalent of the clinical dose of Soliris had no adverse effects on mating or fertility.

14 CLINICAL STUDIES

14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26 week study (Study 1); PNH patients were also treated with Soliris in a single arm 52 week study (Study 2); and in a long term extension study. Patients received meningococcal vaccination prior to receipt of Soliris. In all studies, the dose of Soliris was 600 mg study drug every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration. Soliris was administered as an intravenous infusion over 25 - 45 minutes.

Study 1:

PNH patients with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter were randomized to either Soliris (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial observation period to confirm the need for RBC transfusion and to identify the hemoglobin concentration (the "set-point") which would define each patient's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Endpoints related to hemolysis included the numbers of patients achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26 week period. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications.

Major baseline characteristics were balanced (see Table 8).

Table 8: PNH Study 1 Patient Baseline Characteristics

Parameter	Study 1 Placebo N = 44	Study 1 Soliris N = 43
Mean age (SD)	38 (13)	42 (16)
Gender - female (%)	29 (66)	23 (54)
History of aplastic anemia or myelodysplastic syndrome (%)	12 (27)	8 (19)
Patients with history of thrombosis (events)	8 (11)	9 (16)
Concomitant anticoagulants (%)	20 (46)	24 (56)
Concomitant steroids/immunosuppressant treatments (%)	16 (36)	14 (33)
Packed RBC units transfused per patient in previous 12 months (median (Q1,Q3))	17 (14, 25)	18 (12, 24)
Mean Hgb level (g/dL) at setpoint (SD)	8 (1)	8 (1)
Pre-treatment LDH levels (median, U/L)	2,234	2,032
Free hemoglobin at baseline (median, mg/dL)	46	41

Patients treated with Soliris had significantly reduced ($p < 0.001$) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients (see Table 9). These effects were seen among patients within each of the three pre-study RBC transfusion strata (4 - 14 units; 15 - 25 units; > 25 units). After 3 weeks of Soliris treatment, patients reported less fatigue and improved health-related quality of life. Because of the study sample size and duration, the effects of Soliris on thrombotic events could not be determined.

Table 9: PNH Study 1 Results

	Placebo N = 44	Soliris N = 43
Percentage of patients with stabilized hemoglobin levels	0	49
Packed RBC units transfused per patient (median)	10	0
(range)	(2 - 21)	(0 - 16)
Transfusion avoidance (%)	0	51
LDH levels at end of study (median, U/L)	2,167	239
Free hemoglobin at end of study (median, mg/dL)	62	5

Study 2 and Extension Study:

PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter received Soliris over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Overall, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. 187 Soliris-treated PNH patients were enrolled in a long term extension study. All patients sustained a reduction in intravascular hemolysis over a total Soliris exposure time ranging from 10 to 54 months. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment. However, the majority of patients received concomitant anticoagulants; the effects of anticoagulant withdrawal during Soliris therapy was not studied [*see Warnings and Precautions (5.4)*].

14.2 Atypical Hemolytic Uremic Syndrome (aHUS)

Five single-arm studies [four prospective (aHUS Studies 1, 2, 4 and 5) and one retrospective (aHUS Study 3)] evaluated the safety and efficacy of Soliris for the treatment of aHUS. Patients with aHUS received meningococcal vaccination prior to receipt of Soliris or received prophylactic treatment with antibiotics until 2 weeks after vaccination. In all studies, the dose of Soliris in adult and adolescent patients was 900 mg every 7 ± 2 days for 4 weeks, followed by 1200 mg 7 ± 2 days later, then 1200 mg every 14 ± 2 days thereafter. The dosage regimen for pediatric patients weighing less than 40 kg enrolled in aHUS Study 3 and Study 5 was based on body weight [*see Dosage and Administration (2.2)*]. Efficacy evaluations were based on thrombotic microangiopathy (TMA) endpoints.

Endpoints related to TMA included the following:

- platelet count change from baseline
- hematologic normalization *(maintenance of normal platelet counts and LDH levels for at least four weeks)*
- complete TMA response *(hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks)*
- TMA-event free status *(absence for at least 12 weeks of a decrease in platelet count of >25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement)*
- Daily TMA intervention rate *(defined as the number of plasma exchange or plasma infusion interventions and the number of new dialyses required per patient per day)*.

aHUS Resistant to PE/PI (aHUS Study 1)

aHUS Study 1 enrolled patients who displayed signs of thrombotic microangiopathy (TMA) despite receiving at least four PE/PI treatments the week prior to screening. One patient had no PE/PI the week prior to screening because of PE/PI intolerance. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 28 (range: 17 to 68 years). Patients enrolled in aHUS Study 1 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 70%-121%. Seventy-six percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 10 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study 1.

Table 10: Baseline Characteristics of Patients Enrolled in aHUS Study 1

Parameter	aHUS Study 1 N = 17
Time from aHUS diagnosis until screening in months, median (min, max)	10 (0.26, 236)
Time from current clinical TMA manifestation until screening in months, median (min, max)	<1 (<1, 4)
Baseline platelet count (× 10^9/L), median (range)	118 (62, 161)
Baseline LDH (U/L), median (range)	269 (134, 634)

Patients in aHUS Study 1 received Soliris for a minimum of 26 weeks. In aHUS Study 1, the median duration of Soliris therapy was approximately 100 weeks (range: 2 weeks to 145 weeks).

Renal function, as measured by eGFR, was improved and maintained during Soliris therapy. The mean eGFR (± SD) increased from 23 ± 15 mL/min/1.73m^2 at baseline to 56 ± 40 mL/min/1.73m^2 by 26 weeks; this effect was maintained through 2 years (56 ± 30 mL/min/1.73m^2). Four of the five patients who required dialysis at baseline were able to discontinue dialysis.

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Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In aHUS Study 1, mean platelet count (± SD) increased from 109 ± 32 x10^9/L at baseline to 169 ± 72 x10^9/L by one week; this effect was maintained through 26 weeks (210 ± 68 x10^9/L), and 2 years (205 ± 46 x10^9/L). When treatment was continued for more than 26 weeks, two additional patients achieved Hematologic Normalization as well as Complete TMA response. Hematologic Normalization and Complete TMA response were maintained by all responders. In aHUS Study 1, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 11 summarizes the efficacy results for aHUS Study 1.

Table 11: Efficacy Results for aHUS Study 1

Efficacy Parameter	aHUS Study 1 at 26 wks[1] N = 17	aHUS Study 1 at 2 yrs[2] N = 17
Complete TMA response, n (%)	11 (65)	13 (77)
Median Duration of complete TMA response, weeks (range)	38 (25, 56)	99 (25, 139)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	9 (53)	10 (59)
Median duration of eGFR improvement, days (range)	251 (70, 392)	ND
Hematologic normalization, n (%)	13 (76)	15 (88)
Median Duration of hematologic normalization, weeks (range)	37 (25, 62)	99 (25, 145)
TMA event-free status, n (%)	15 (88)	15 (88)
Daily TMA intervention rate, median (range)		
Before eculizumab	0.82 (0.04, 1.52)	0.82 (0.04, 1.52)
On eculizumab treatment	0 (0, 0.31)	0 (0, 0.36)

[1] At data cut-off (September 8, 2010).

[2] At data cut-off (April 20, 2012).

aHUS Sensitive to PE/PI (aHUS Study 2)

aHUS Study 2 enrolled patients undergoing chronic PE/PI who generally did not display hematologic signs of ongoing thrombotic microangiopathy (TMA). All patients had received PT at least once every two weeks, but no more than three times per week, for a minimum of eight weeks prior to the first Soliris dose. Patients on chronic dialysis were permitted to enroll in aHUS Study 2. The median patient age was 28 years (range: 13 to 63 years). Patients enrolled in aHUS Study 2 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 37%-118%. Seventy percent of patients had an identified complement regulatory factor mutation or auto-antibody. Table 12 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study 2.

Table 12: Baseline Characteristics of Patients Enrolled in aHUS Study 2

Parameter	aHUS Study 2 N = 20
Time from aHUS diagnosis until screening in months, median (min, max)	48 (0.66, 286)
Time from current clinical TMA manifestation until screening in months, median (min, max)	9 (1, 45)
Baseline platelet count (× 10^9/L), median (range)	218 (105, 421)
Baseline LDH (U/L), median (range)	200 (151, 391)

Patients in aHUS Study 2 received Soliris for a minimum of 26 weeks. In aHUS Study 2, the median duration of Soliris therapy was approximately 114 weeks (range: 26 to 129 weeks).

Renal function, as measured by eGFR, was maintained during Soliris therapy. The mean eGFR (± SD) was 31 ± 19 mL/min/1.73m^2 at baseline, and was maintained through 26 weeks (37 ± 21 mL/min/1.73m^2) and 2 years (40 ± 18 mL/min/1.73m^2). No patient required new dialysis with Soliris.

Reduction in terminal complement activity was observed in all patients after the commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. Platelet counts were maintained at normal levels despite the elimination of PE/PI. The mean platelet count (± SD) was 228 ± 78 x 10^9/L at baseline, 233 ± 69 x 10^9/L at week 26, and 224 ± 52 x 10^9/L at 2 years. When treatment was continued for more than 26 weeks, six additional patients achieved Complete TMA response. Complete TMA Response and Hematologic Normalization were maintained by all responders. In aHUS Study 2, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins.

Table 13 summarizes the efficacy results for aHUS Study 2.

Table 13: Efficacy Results for aHUS Study 2

Efficacy Parameter	aHUS Study 2 at 26 wks[1] N = 20	aHUS Study 2 at 2 yrs[2] N = 20
Complete TMA response, n (%)	5 (25)	11 (55)
Median duration of complete TMA response, weeks (range)	32 (12, 38)	68 (38, 109)
eGFR improvement ≥15 mL/min/1.73 m^2, n (%)	1 (5)	8 (40)
TMA Event-free status n (%)	16 (80)	19 (95)
Daily TMA intervention rate, median (range)		
Before eculizumab	0.23 (0.05, 1.07)	0.23 (0.05, 1.07)
On eculizumab treatment	0	0 (0, 0.01)
Hematologic normalization[4], n (%)	18 (90)	18 (90)
Median duration of hematologic normalization, weeks (range)[3]	38 (22, 52)	114 (33, 125)

[1] At data cut-off (September 8, 2010).

[2] At data cut-off (April 20, 2012).

[3] Calculated at each post-dose day of measurement (excluding Days 1 to 4) using a repeated measurement ANOVA model.

[4] In aHUS Study 2, 85% of patients had normal platelet counts and 80% of patients had normal serum LDH levels at baseline, so hematologic normalization in this population reflects maintenance of normal parameters in the absence of PE/PI.

Retrospective Study in Patients with aHUS (aHUS Study 3)

The efficacy results for the aHUS retrospective study (aHUS Study 3) were generally consistent with results of the two prospective studies. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline. Mean platelet count (± SD) increased from 171 ± 83 x10^9/L at baseline to 233 ±109 x10^9/L after one week of therapy; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 254 ± 79 x10^9/L).

A total of 19 pediatric patients (ages 2 months to 17 years) received Soliris in aHUS Study 3. The median duration of Soliris therapy was 16 weeks (range 4 to 70 weeks) for children <2 years of age (n=5), 31 weeks (range 19 to 63 weeks) for children 2 to <12 years of age (n=10), and 38 weeks (range 1 to 69 weeks) for patients 12 to <18 years of age (n=4). Fifty three percent of pediatric patients had an identified complement regulatory factor mutation or auto-antibody.

Overall, the efficacy results for these pediatric patients appeared consistent with what was observed in patients enrolled in aHUS Studies 1 and 2 (Table 14). No pediatric patient required new dialysis during treatment with Soliris.

Table 14: Efficacy Results in Pediatric Patients Enrolled in aHUS Study 3

Efficacy Parameter	<2 yrs (n=5)	2 to <12 yrs (n=10)	12 to <18 yrs (n=4)	Total (n=19)
Complete TMA response, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m^2, n (%)[2]	2 (40)	6 (60)	1 (25)	9 (47)
Platelet count normalization, n (%)[1]	4 (80)	10 (100)	3 (75)	17 (89)
Hematologic Normalization, n (%)	2 (40)	5 (50)	1 (25)	8 (42)
Daily TMA intervention rate, median (range)				
Before eculizumab	1 (0, 2)	<1 (0.07, 1.46)	<1 (0, 1)	0.31 (0.00, 2.38)
On eculizumab treatment	<1 (0, <1)	0 (0, <1)	0 (0, <1)	0.00 (0.00 , 0.08)

[1] Platelet count normalization was defined as a platelet count of at least 150,000 X 10^9/L on at least two consecutive measurements spanning a period of at least 4 weeks.

[2] Of the 9 patients who experienced an eGFR improvement of at least 15 mL/min/1.73 m^2, one received dialysis throughout the study period and another received Soliris as prophylaxis following renal allograft transplantation.

Adult Patients with aHUS (aHUS Study 4)

aHUS Study 4 enrolled patients who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrollment, patients were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal, without the need for chronic dialysis. The median patient age was 35 (range: 18 to 80 years). All patients enrolled in aHUS Study 4 were required to have ADAMTS13 activity level above 5%; observed range of values in the trial were 28%-116%. Fifty-one percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 35 patients received PE/PI prior to eculizumab. Table 15 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study 4.

Table 15: Baseline Characteristics of Patients Enrolled in aHUS Study 4

Parameter	aHUS Study 4 N = 41
Time from aHUS diagnosis until start of study drug in months, median (range)	0.79 (0.03 – 311)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.52 (0.03-19)
Baseline platelet count (× 10^9/L), median (range)	125 (16 – 332)
Baseline LDH (U/L), median (range)	375 (131 – 3318)

Patients in aHUS Study 4 received Soliris for a minimum of 26 weeks. In aHUS Study 4, the median duration of Soliris therapy was approximately 50 weeks (range: 13 weeks to 86 weeks).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 17 ± 12 mL/min/1.73m^2 at baseline to 47 ± 24 mL/min/1.73m^2 by 26 weeks. Twenty of the 24 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment.

Reduction in terminal complement activity and an increase in platelet count relative to baseline were observed after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. In aHUS Study 4, mean platelet count (± SD) increased from 119 ± 66 x10^9/L at baseline to 200 ± 84 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (± SD) at week 26: 252 ± 70 x10^9/L). In aHUS Study 4, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 16 summarizes the efficacy results for aHUS Study 4.

Table 16: Efficacy Results for aHUS Study 4

Efficacy Parameter	aHUS Study 4 (N = 41)
Complete TMA response, n (%),	23 (56),
95% CI	40,72
Median duration of complete TMA response, weeks (range)	42 (6, 75)
Patients with eGFR improvement ≥ 15 mL/min/1.73 m2, n (%)	22 (54)
Hematologic Normalization, n (%)	36 (88)
Median duration of hematologic normalization, weeks (range)	46 (10, 75)
TMA Event-free Status, n (%)	37 (90)
Daily TMA Intervention Rate, median (range)	
Before eculizumab	0.63 (0, 1.38)
On eculizumab treatment	0 (0, 0.58)

Pediatric and Adolescent Patients with aHUS (aHUS Study 5)

aHUS Study 5 enrolled patients who were required to have a platelet count < lower limit of normal range (LLN), evidence of hemolysis such as an elevation in serum LDH above the upper limits of normal, serum creatinine level ≥97 percentile for age without the need for chronic dialysis. The median patient age was 6.5 (range: 5 months to 17 years). Patients enrolled in aHUS Study 5 were required to have ADAMTS13 activity level above 5%;observed range of values in the trial were 38%-121%. Fifty percent of patients had an identified complement regulatory factor mutation or auto-antibody. A total of 10 patients received PE/PI prior to eculizumab. Table 17 summarizes the key baseline clinical and disease-related characteristics of patients enrolled in aHUS Study 5.

Table 17: Baseline Characteristics of Patients Enrolled in aHUS Study 5

Parameter	Patients 1 month to <12 years (N = 18)	All Patients (N = 22)
Time from aHUS diagnosis until start of study drug in months, median (range)	0.51 (0.03 – 58)	0.56 (0.03-191)
Time from current clinical TMA manifestation until first study dose in months, median (range)	0.23 (0.03 – 4)	0.2 (0.03-4)
Baseline platelet count (x 10^9/L), median (range)	110 (19-146)	91 (19-146)
Baseline LDH (U/L) median (range)	1510 (282-7164)	1244 (282-7164)

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Patients in aHUS Study 5 received Soliris for a minimum of 26 weeks. In aHUS Study 5, the median duration of Soliris therapy was approximately 44 weeks (range: 1 dose to 88 weeks).

Renal function, as measured by eGFR, was improved during Soliris therapy. The mean eGFR (± SD) increased from 33 ± 30 mL/min/1.73m^2 at baseline to 98 ± 44 mL/min/1.73m^2 by 26 weeks. Among the 20 patients with a CKD stage ≥2 at baseline, 17 (85%) achieved a CKD improvement of ≥1 stage. Among the 16 patients ages 1 month to <12 years with a CKD stage ≥2 at baseline, 14 (88%) achieved a CKD improvement by ≥1 stage. Nine of the 11 patients who required dialysis at study baseline were able to discontinue dialysis during Soliris treatment. Responses were observed across all ages from 5 months to 17 years of age.

Reduction in terminal complement activity was observed in all patients after commencement of Soliris. Soliris reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from baseline to 26 weeks. The mean platelet count (± SD) increased from 88 ± 42 x10^9/L at baseline to 281 ± 123 x10^9/L by one week; this effect was maintained through 26 weeks (mean platelet count (±SD) at week 26: 293 ± 106 x10^9/L). In aHUS Study 5, responses to Soliris were similar in patients with and without identified mutations in genes encoding complement regulatory factor proteins or auto-antibodies to factor H.

Table 18 summarizes the efficacy results for aHUS Study 5.

Table 18: Efficacy Results for aHUS Study 5

Efficacy Parameter	Patients 1 month to <12 years (N = 18)	All Patients (N = 22)
Complete TMA response, n (%)	11 (61)	14 (64)
95% CI	36, 83	41, 83
Median Duration of complete TMA response, weeks (range)[1]	40 (14, 77)	37 (14, 77)
eGFR improvement ≥15 mL/min/ 1.73•m^2•n (%)	16 (89)	19 (86)
Complete Hematologic Normalization, n (%)	14 (78)	18 (82)
Median Duration of complete hematologic normalization, weeks (range)	38 (14, 77)	38 (14, 77)
TMA Event-Free Status, n (%)	17 (94)	21 (95)
Daily TMA Intervention rate, median (range)		
Before eculizumab treatment	0.2 (0, 1.7)	0.4 (0, 1.7)
On eculizumab treatment	0 (0, 0.01)	0 (0, 0.01)

[1] through data cutoff (October 12, 2012).

16 HOW SUPPLIED/STORAGE AND HANDLING

Soliris (eculizumab) is supplied as 300 mg single-dose vials containing 30 mL of 10 mg/mL sterile, preservative-free Soliris solution per vial.

Store Soliris vials in the original carton until time of use under refrigerated conditions at 2-8° C (36-46° F) and protected from light. Soliris vials may be held in the original carton at controlled room temperature (not more than 25° C/77° F) for only a single period up to 3 days.Do not use beyond the expiration date stamped on the carton. Refer to [Dosage and Administration (2)] for information on the stability and storage of diluted solutions of Soliris.

DO NOT FREEZE. DO NOT SHAKE.

NDC 25682-001-01 Single unit 300 mg carton: Contains one (1) 30 mL vial of Soliris (10 mg/mL).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Meningococcal Infection

Prior to treatment, patients should fully understand the risks and benefits of Soliris, in particular the risk of meningococcal infection. Ensure that patients receive the Medication Guide.

Inform patients that they are required to receive meningococcal vaccination at least 2 weeks prior to receiving the first dose of Soliris, if they have not previously been vaccinated. They are required to be revaccinated according to current medical guidelines for meningococcal vaccine use while on Soliris therapy. Inform patients that vaccination may not prevent meningococcal infection *[see Warnings and Precautions (5.1)]*.

Signs and Symptoms of Meningococcal Infection

Inform patients about the signs and symptoms of meningococcal infection, and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms are as follows:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Inform patients that they will be given a Soliris Patient Safety Information Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Other Infections

Inform patients that there may be an increased risk of other types of infections, particularly those due to encapsulated bacteria. Additionally, Aspergillus infections have occured in immunocompromised and neutropenic patients. Inform parents or caregivers of children receiving Soliris for the treatment of aHUS that their child should be vaccinated against *Streptococcus pneumoniae* and *Haemophilus influenza* type b (Hib) according to current medical guidelines.

Discontinuation

Inform patients with PNH that they may develop hemolysis due to PNH when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 8 weeks following Soliris discontinuation. Inform patients with aHUS that there is a potential for TMA complications due to aHUS when Soliris is discontinued and that they will be monitored by their healthcare professional for at least 12 weeks following Soliris discontinuation. Inform patients who discontinue Soliris to keep the Soliris Patient Safety Information Card with them for three months after the last Soliris dose, because the increased risk of meningococcal infection persists for several weeks following discontinuation of Soliris.

Manufactured by:

Alexion Pharmaceuticals, Inc.
100 College Street
New Haven, CT 06510 USA

US License Number 1743

This product, or its use, may be covered by one or more US patents, including US Patent No. 6,355,245 in addition to others including patents pending.

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MEDICATION GUIDE

Soliris® (so-leer-is)
(eculizumab)

Read the Medication Guide before you start Soliris and before each infusion. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment. Talk to your doctor if you have any questions about your treatment with Soliris.

What is the most important information I should know about Soliris?

Soliris is a medicine that affects your immune system. Soliris can lower the ability of your immune system to fight infections.

- Soliris increases your chance of getting serious and life-threatening meningococcal infections.

Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.

1. **You must receive meningococcal vaccination at least 2 weeks before your first dose of Soliris unless you have already had this vaccine. If your doctor decided that urgent treatment with Soliris is needed, you should receive meningococcal vaccination as soon as possible.**
2. **If you had a meningococcal vaccine in the past, you might need additional vaccination before starting Soliris. Your doctor will decide if you need additional meningococcal vaccination.**
3. **Meningococcal vaccines do not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:**
   - **headache with nausea or vomiting**
   - **headache and a fever**
   - **headache with a stiff neck or stiff back**
   - **fever**
   - **fever and a rash**
   - **confusion**
   - **muscle aches with flu-like symptoms**
   - **eyes sensitive to light**

Your doctor will give you a **Patient Safety Card** about the risk of meningococcal infection. Carry it with you at all times during treatment and for 3 months after your last Soliris dose. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.

Soliris is only available through a program called the Soliris REMS. Before you can receive Soliris, your doctor must:

- enroll in the Soliris REMS program
- counsel you about the risk of meningococcal infection
- give you information about the symptoms of meningococcal infection
- give you a **Patient Safety Card** about your risk of meningococcal infection, as discussed above
- make sure that you are vaccinated with a meningococcal vaccine

Soliris may also increase the risk of other types of serious infections. If your child is treated with Soliris, make sure that your child receives vaccinations against *Streptococcus pneumoniae* and *Haemophilis influenza* type b (Hib).

What Is Soliris?

Soliris is a prescription medicine called a monoclonal antibody. Soliris is used to treat people with:

- a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH). PNH affects red blood cells.
- A disease called atypical Hemolytic Uremic Syndrome (aHUS). aHUS affects the blood system, kidney, and sometimes other body organs.

Soliris works by blocking part of your immune system. This can help your symptoms but it can also increase your chance for infection.

It is important that you:

- have all recommended vaccinations before you start Soliris
- stay up-to-date with all recommended vaccinations during treatment with Soliris

Who Should Not Receive Soliris?

Do not receive Soliris if you:

- have a meningococcal infection
- have not been vaccinated against meningitis infection unless your doctor decides that urgent treatment with Soliris is needed. See "What is the most important information I should know about Soliris?"

What should I tell my doctor before receiving Soliris?

Before receiving Soliris, tell your doctor if you:

- have an infection or fever
- are pregnant or plan to become pregnant. It is not known if Soliris will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Soliris passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medications you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How will I receive Soliris?

- Soliris is given through a vein (I.V. or intravenous infusion) usually over 35 minutes in adults and 1-4 hours in pediatric patients. If you have an allergic reaction during your Soliris infusion, your doctor may decide to give Soliris more slowly or stop your infusion.
- If you are an adult, you will usually receive a Soliris infusion by your doctor:
  - weekly for five weeks, then
  - every 2 weeks
- If you are less than 18 years of age, your doctor will decide how often you will receive Soliris depending on your age and body weight
- After each infusion, you should be monitored for one hour for allergic reactions. See "What are the possible side effects of Soliris?"
- If you forget or miss a Soliris infusion, call your doctor right away.
- **If you have PNH, your doctor will need to monitor you closely for at least 8 weeks after stopping Soliris. Stopping treatment with Soliris may cause breakdown of your red blood cells due to PNH.**

  Symptoms or problems that can happen due to red blood cell breakdown include:
  - drop in the number of your red blood cell count
  - drop in your platelet count
  - confusion
  - chest pain
  - kidney problems
  - blood clots
  - difficulty breathing
- **If you have aHUS, your doctor will need to monitor you closely during and for at least 12 weeks after stopping treatment for signs of worsening aHUS symptoms or problems related to abnormal clotting (thrombotic microangiopathy).**

  Symptoms or problems that can happen with abnormal clotting may include:
  - stroke
  - confusion
  - seizures
  - chest pain (angina)
  - difficulty breathing
  - kidney problems
  - swelling in arms or legs
  - a drop in your platelet count

What are the possible side effects of Soliris?

Soliris can cause serious side effects including:

- See "What is the most important information I should know about Soliris?"

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- Serious allergic reactions. Serious allergic reactions can happen during your Soliris infusion. Tell your doctor or nurse right away if you get any of these symptoms during your Soliris infusion:
  - chest pain
  - trouble breathing or shortness of breath
  - swelling of your face, tongue, or throat
  - feel faint or pass out

If you have an allergic reaction to Soliris, your doctor may need to infuse Soliris more slowly, or stop Soliris. See "How will I receive Soliris?"

Common side effects in people with PNH treated with Soliris include:

- headaches
- runny nose and colds
- sore throat
- back pain
- nausea

Common side effects in people with aHUS treated with Soliris include:

- headache
- diarrhea
- hypertension
- common cold (upper respiratory infection)
- abdominal pain
- vomiting
- nasopharyngitis
- anemia
- cough
- peripheral edema
- nausea
- urinary tract infections
- pyrexia

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of Soliris. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about Soliris

Medicines are sometimes prescribed for conditions other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Soliris. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Soliris that is written for healthcare professionals.

What are the ingredients in Soliris?

Active ingredient: eculizumab

Inactive ingredients: sodium phosphate monobasic, sodium phosphate dibasic, sodium chloride, polysorbate 80 (vegetable origin) and Water for Injection

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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HUMANIZED PORCINE VCAM-SPECIFIC MONOCLONAL ANTIBODIES WITH CHIMERIC IgG2/G4 CONSTANT REGIONS BLOCK HUMAN LEUKOCYTE BINDING TO PORCINE ENDOTHELIAL CELLS

JOHN P. MUELLER,*MICHELLE A. GIANNONI, SANDRA L. HARTMAN, EILEEN A. ELLIOTT, STEPHEN P. SQUINTO, LOUIS A. MATIS and MARK J. EVANS

Alexion Pharmaceuticals Inc., Departments of Immunobiology and Molecular Development, 25 Science Park Box 15, New Haven, CT 06511, U.S.A.

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Abstract—Discordant xenografts surviving the initial hyperacute rejection phase may be subject to cellular rejection processes mediated by infiltrating leukocytes including T cells, NK cells and monocytes. The stable adhesion of these cell types to endothelial cells is due to the molecular interaction of the integrins VLA-4 and LFA-1 with their ligands vascular cell adhesion molecule (VCAM) and ICAM-1 present on the endothelial cells. Human VLA-4 binds to porcine VCAM, and blocking mAbs specific for porcine VCAM have been developed. We have localized the epitope of the anti-porcine VCAM blocking mAbs 2A2 and 3F4 to domains 1 and 2, respectively. Humanized antibodies (IgG4 isotype) were constructed from these anti-porcine VCAM antibodies and demonstrated to inhibit adhesion of Ramos, Jurkat and YT cells, as well as purified resting and activated human T cells, to porcine aortic endothelial cells (PAEC). These cell types express both LFA-1 as well as VLA-4, suggesting blockade of human VLA-4 interaction with porcine VCAM may alone be sufficient to significantly impair adhesion of human leukocytes to porcine endothelial cells. The chimeric anti-porcine VCAM (pVCAM) HuG4 antibodies promoted increased adhesion of Fc receptor (FcR) positive cells such as U937 monocytic cells to PAEC. In contrast, chimeric anti-porcine VCAM antibodies created using the CH1 and hinge region from human IgG2 and the CH2 and CH3 regions from human IgG4 (HuG2/G4 antibodies) inhibited binding of FcR positive cells to PAEC. These chimeric anti-pVCAM antibodies should allow delineation of the *in vivo* role of VLA-4/VCAM interaction in porcine-to-primate xenotransplants. Further, the design of the HuG2/G4 antibodies should render them efficacious in multiple settings requiring elimination of FcR binding. © 1997 Elsevier Science Ltd.

Key words: adhesion molecules, antibodies, Fc receptors, inflammation, xenotransplantation.

INTRODUCTION

Although much progress has been made in elucidating the molecular mechanisms of hyperacute rejection of xenotransplants (reviewed in Somerville and D'Apice, 1993), the mechanisms of cell mediated rejection of xenografts remain unclear. The cellular infiltrate observed 3 days following transplantation of guinea pig hearts into complement (C)-depleted rats is comprised predominantly of macrophages and natural killer cells, with low numbers of T lymphocytes present (Blakely *et al.*, 1994). Similarly, the cellular infiltrate present 6 days after transplantation of porcine fetal islet clusters into rats is comprised predominantly of macrophages with low numbers of T lymphocytes present primarily at the periphery of the graft (Wallgren *et al.*, 1995). *In vitro* porcine aortic endothelial cells (PAEC) as well as antigen presenting peripheral blood cells can directly activate human CD4+ and CD8+ T lymphocytes (Rollins *et al.*, 1994*a*; Murray *et al.*, 1994; Yamada *et al.*, 1995). Thus the initial phases of cellular rejection of xenotransplants are likely to involve binding and activation of multiple types of leukocytes including not only T lymphocytes but also natural killer cells and monocytes.

The stable adhesion of lymphocytes, natural killer cells, and monocytes to endothelial cells is mediated predominantly by the interaction of the integrins LFA-1 (CD11a/CD18) and VLA-4 (CD49d/CD29) with their cognate ligands ICAM-1 and VCAM-1 on endothelial cells (Allavena *et al.*, 1991; Jonjic *et al.*, 1992). For both monocytes (Luscinskas *et al.*, 1994) and T lymphocytes (Alon *et al.*, 1995; Luscinskas *et al.*, 1995) the binding of VLA-4 to VCAM is an essential component of the *in vitro* adhesive interactions required for stable arrest under

*Author to whom correspondence should be addressed. Tel: 203-776-1790; Fax: 203-772-3655; E-mail: muellerj@alxn.com.

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conditions of flow. *In vitro*, the transmigration of NK cells and monocytes across human umbilical vein endothelial cell (HUVEC) monolayers also utilizes both LFA-1/ICAM-1- and VLA-4/VCAM-dependent pathways (Bianchi *et al.*, 1993; Meershaert and Furie, 1994; Chuluyan *et al.*, 1995). *In vivo*, the interaction of LFA-1 with ICAM-1 may not be completely essential for extravasation of lymphocytes or monocytes since both of these cell types are present in inflammatory infiltrates of leukocyte adhesion deficiency patients who have a genetic deficiency in CD18 and thus lack integrins such as LFA-1 (Hawkins *et al.*, 1992). Finally, numerous studies have demonstrated the potential of blocking antibodies directed against LFA-1 (Issekutz, 1992; Scheynius *et al.*, 1993), VLA-4 (Issekutz, 1991; Yednock *et al.*, 1992; Chisholm *et al.*, 1993), ICAM-1 (Zeng *et al.*, 1994), or VCAM (Orosz *et al.*, 1993; Silber *et al.*, 1995) to inhibit the accumulation of lymphocytes at inflammatory sites in animals.

For xenogeneic cellular interactions it is not yet fully defined which adhesion molecule interactions will function across species barriers. It is likely that at least some xenogeneic receptor–ligand interactions will be nonfunctional. For example, mouse LFA-1 does not bind to human ICAM-1 (Johnston *et al.*, 1990). To explore the molecular basis of adhesive interactions between distinct classes of adhesion molecules on human and porcine cells we have cloned porcine E-selectin and VCAM-1 and have demonstrated that both are capable of mediating the adhesion of human leukocytes (Rollins *et al.*, 1994*a*; Mueller *et al.*, 1995). Further, we have developed murine monoclonal antibodies (mAbs) specific for porcine VCAM which block binding of human VLA-4 to porcine VCAM (Mueller *et al.*, 1995). The functional blocking activity of these antibodies suggests that they will be useful in suppressing the cellular response to a porcine xenograft. However, murine mAbs are not ideally suited for use in primates due to their short half-life and high immunogenicity (Khazaeli *et al.*, 1994). Here we have utilized antibody engineering strategies to create humanized anti-porcine VCAM antibodies that block adhesion of human natural killer cells, monocytes, and T lymphocytes to activated PAEC. Furthermore, we show the choice of human isotype has critical implications for the potential therapeutic use of humanized antibodies in xenotransplantation.

MATERIALS AND METHODS

Cells

Ramos, Jurkat and U-937 cells were obtained from the American Type Culture Collection, YT cells were the gift of Dr J. M. Wang (National Cancer Institute, Frederick, MD, U.S.A.), porcine aortic endothelial cells (PAEC) were obtained from Cell Systems (Kirkland, WA, U.S.A.) and 293-EBNA cells were obtained from Invitrogen (San Diego, CA, U.S.A.). U-937 cells were maintained in RPMI 1640 supplemented with 15% heat-inactivated FBS and 2 mM L-glutamine. Ramos and Jurkat cells were maintained in RPMI 1640 supplemented with 10% heat-inactivated FBS, 2 mM L-glutamine, 20 mM HEPES, 50 μM β-mercaptoethanol, 100 units/ml penicillin and 100 μg/ml streptomycin. YT were maintained in RPMI 1640 containing 10% heat-inactivated FBS, 2 mM L-glutamine, 100 units/ml penicillin and 100 μg/ml streptomycin. PAEC were maintained in medium A consisting of M199 supplemented with 20% heat-inactivated FBS, 0.05 mg/ml ECGF (Biomedical Technologies, Stoughton, MA, U.S.A.), 20 mM HEPES and 0.1 mg/ml heparin, and were used within three passages. 293-EBNA cells were grown in Dulbecco's modified Eagle's medium supplemented with 5% heat-inactivated FBS, 100 units/ml penicillin, 100 μg/ml streptomycin and 250 μg/ml G418. Human T cells were purified as described previously (Mueller *et al.*, 1995).

Production of VCAM/Ig fusions

A plasmid containing the human IgG1 Fc region was obtained from Dr M. J. Lenardo (NIH, Bethesda, MD, U.S.A.). DNA fragments containing various domains of human or porcine VCAM were obtained by PCR amplification of appropriate templates and joined in frame to the human IgG1 Fc coding region using standard molecular biology techniques. The cassettes encoding the fusion proteins were ligated into the expression plasmid pAPEX-3 (Evans *et al.*, 1995*a*). VCAM/Ig fusion proteins were produced by transfection of 293-EBNA cells as described previously (Evans *et al.*, 1995*a*). Three days following transfection the media were harvested, centrifuged to remove debris, and stored at 4°C. For ELISA, PolySorp 96-well microtiter plates (Nunc, Naperville, IL, U.S.A.) were coated overnight at 4°C with 100 ng/well goat anti-human IgG Fc (Sigma, St. Louis, MO, U.S.A.) in 0.1 M carbonate buffer, pH 9.6. The plates were then washed three times with PBS supplemented with 0.5% Tween 20 and incubated with blocking buffer (PBS supplemented with 0.05% Tween 20) at 37°C for 1 hr. After three further washes, various dilutions of conditioned media in blocking buffer were added and incubated at 37°C for 1 hr. Following three further washes, 2A2 or 3F4 mAb in blocking buffer was added and incubated for 1 hr at 37°C. After additional washing, peroxidase-conjugated goat anti-mouse IgG Fc (Sigma) diluted 1:2000 in blocking buffer was added and incubated at 37°C for 1 hr. After three final washes the plate was developed for 15 min with 0.4 mg/ml *o*-phenylenediamine dihydrochloride (Sigma). Reactions were stopped by addition of 1 M sulfuric acid. Quantitation was performed by measuring absorbance at 490 nm using a Bio-Rad model 3550 plate reader.

Production of chimeric antibodies

Variable regions were cloned from the 2A2 and 3F4 hybridomas by PCR amplification as described previously (Evans *et al.*, 1995*a*, 1995*b*). These sequences have been submitted to the EMBL/GenBank/DDBL under accession numbers U78799–U78802. The variable regions were joined to genomic DNA cassettes containing

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either the intact human IgG4 constant regions or the first constant region and hinge linker region from human IgG2 followed by the second and third constant regions from human IgG4 using standard molecular biology techniques. Chimeric antibodies were produced in 293-EBNA cells and purified by chromatography on protein A Sepharose as described (Evans *et al.*, 1995*a*). Each chimeric antibody preparation was greater than 95% pure as judged by Coomassie staining of SDS polyacrylamide gels. F(ab')2 was prepared by digestion of the antibodies with ficin (Pierce, Rockford, IL, U.S.A.) followed by protein A chromatography.

Flow cytometry

Cells used were obtained by trypsinization (PAEC and 293-EBNA) or centrifugation (Ramos, Jurkat, YT and U-937 cells). Harvested cells were washed once with 4°C PBS containing 1% heat-inactivated FBS (PBS/1) and aliquoted at 50 000–100 000 cells per well in 96-well V-bottom plates (Nunc). Cells were washed two additional times with PBS/1, and then incubated with PBS/1 containing 10 μg/ml primary Ab or PBS/1 alone for 30 min at 4°C. For some experiments the chimeric HuG4 or HuG2/G4 was centrifuged at $1 \times 10^5 g$ for 1 hr prior to addition to the cells. The cells were then washed twice with PBS/1 and resuspended in PBS/1 containing the appropriate FITC-conjugated secondary antibodies (1:200 dilution) for 30 min at 4°C. The cells were again washed twice with PBS/1 and resuspended in PBS. Cell fluorescence was determined using a Becton Dickinson FACSort.

Adhesion assays

On day 0 PAEC were plated in medium A at a density of 10 000 cells per well in a 96-well flat bottom plate. On day 1 the PAEC were refed medium A supplemented with 1 μg/ml LPS (Sigma, *E. coli* 0111:B4). On day 2, human cells were resuspended in the appropriate growth medium supplemented with 10 μM calcein AM (Molecular Probes, Eugene, OR, U.S.A.) and incubated at 37°C for 30 min. The cells were subsequently washed three times with growth medium and resuspended at 6×10^6 cells/ml in RPMI 1640 supplemented with 1% heat-inactivated FBS (RPMI/1). The PAEC were washed twice with RPMI/1 and refed 50 μl/well of RPMI/1 containing the indicated concentrations of antibodies. After adding calcein-labeled cells at a density of 3×10^5 cells/well (50 μl), the plate was centrifuged at 200*g* for 1 min and incubated at 37°C for 15 min. The nonadherent cells were removed by washing three to five times with RPMI/1. Adherent cells were lysed with HBSS containing 1% SDS and calcein fluorescence was measured with a Millipore CytoFluor 2350 using an excitation wavelength of 485 nm and an emission wavelength of 530 nm. Background fluorescence was determined from wells containing PAEC that did not receive calcein-labeled cells. Samples were performed in duplicate in each experiment. Adherence was determined by comparing the residual fluorescence concentration in each well to the input fluorescence concentration. In each experiment the specific fluorescence signal obtained in the absence of competing antibody was defined as 100%.

For adhesion assays using purified soluble pVCAM (Mueller *et al.*, 1995), PolySorp 96-well microtiter plates (Nunc) were coated overnight at 4°C with 200 ng/well purified soluble pVCAM in 0.1 M carbonate buffer, pH 9.6. After blocking the plate with RPMI 1640 supplemented with 10 mg/ml BSA (RPMI/BSA), the plates were incubated with RPMI/BSA containing antibody for 1 hr at 37°C. Subsequently, 3×10^5 calcein-labeled U-937 cells in RPMI/BSA were added to each well. The plate was centrifuged upright for 1 min at 200*g* and incubated at 37°C for 15 min. The plate was then centrifuged inverted at 200*g* for 3 min. Adherent cells were lysed by the addition of HBSS containing 1% SDS and calcein fluorescence was measured with a Millipore CytoFluor 2350 using an excitation wavelength of 485 nm and an emission wavelength of 530 nm.

RESULTS

Identification of porcine VCAM domains recognized by blocking mAbs

Previously, we have identified two murine mAbs (3F4 and 2A2) directed against porcine VCAM (pVCAM) which block VLA-4 dependent adhesion of peripheral blood human T cells to PAEC. These two mAbs are specific for pVCAM and do not recognize human VCAM (hVCAM). Here an initial analysis of the epitope specificity of the 2A2 and 3F4 mAbs was performed using fusion proteins consisting of various domains of pVCAM or hVCAM joined to the Fc region of human IgG1. The VCAM/Ig fusion proteins were produced in 293-EBNA cells and assayed for binding of 2A2 and 3F4 mAbs by ELISA (Fig. 1). Both the 2A2 and 3F4 mAbs bound efficiently to proteins containing the first three domains of pVCAM. The 2A2 mAb bound to fusion proteins containing pVCAM domain 1 such as pD1 + pD2 (porcine domain 1 plus porcine domain 2) and pD1 + hD2 (porcine domain 1 plus human domain 2), but did not bind to fusion proteins lacking pVCAM domain 1 such as pD2 + pD3, hD1 + pD2, or hD1 + hD2. Weak binding of the 2A2 mAb could also be detected to a fusion protein containing only porcine domain 1 (pD1) but not to fusion proteins containing only pD2 or pD3. Conversely, the 3F4 mAb bound to fusion proteins containing pVCAM domain 2, such as pD1 + pD2, pD2 + pD3, and hD1 + pD2, but did not bind to fusion proteins lacking pVCAM domain 2, such as pD1 + hD2 and hD1 + hD2. Binding of the 3F4 mAb could not be detected to fusion proteins containing only a single pVCAM domain. The weak binding of 2A2 and 3F4 to fusion proteins containing only a single VCAM domain is similar to previously characterized blocking antibodies specific for human VCAM and ICAM-1 which require the presence of at least two adhesion molecule domains for binding (Pepinsky *et al.*, 1992; Renz *et al.*, 1994). Together, these results suggested the 2A2 mAb specificity is defined by

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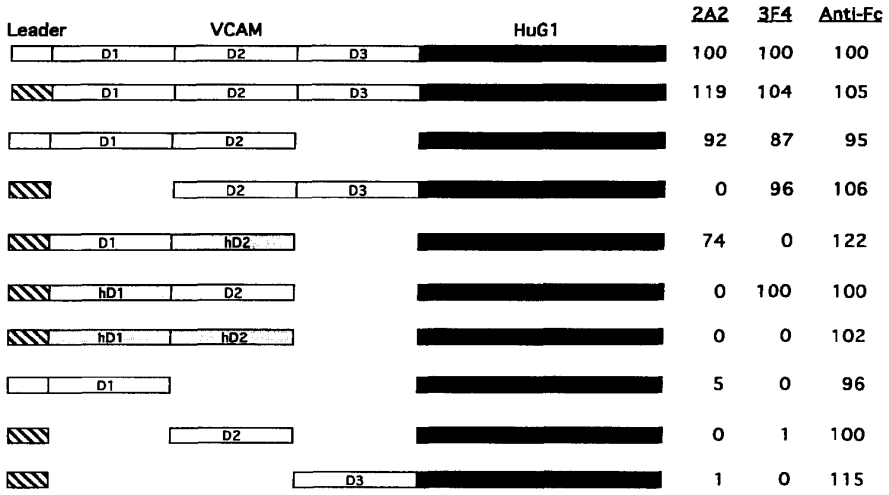

Fig. 1. Binding of 3F4 and 2A2 mAbs to VCAM/Ig fusion proteins. Proteins consisting of domains 1 (D1), 2 (D2), or 3 (D3) from porcine VCAM (open boxes) or human VCAM (gray boxes) joined to the Fc region of human IgG1 (black boxes) were produced in 293-EBNA cells. In some constructs the pVCAM secretory leader sequence was replaced with the secretory leader sequence from human CD59 (striped boxes). The fusion proteins were captured by incubating diluted conditioned media in 96-well plates coated with goat anti-human IgG (Fc specific). After incubation with 2A2 or 3F4 mAb, bound murine mAb was detected using peroxidase-conjugated goat anti-mouse IgG (Fc specific). The total amount of each fusion protein captured per well was quantitated using peroxidase-conjugated goat anti-human IgG (Fc specific). The absorbance signal obtained with the fusion protein containing the intact pVCAM domains 1, 2 and 3 was defined as 100% for each antibody. Binding of the 2A2 and 3F4 mAbs to the remaining fusion proteins is reported as a percentage of this value. Results shown are from a representative experiment of several performed.

pVCAM domain 1 whereas the 3F4 mAb specificity is defined by pVCAM domain 2.

Inhibition of human leukocyte binding to PAEC by chimeric anti-porcine VCAM mAbs

The use of murine antibodies in porcine-to-primate xenotransplantation models or ultimately in porcine-to-human xenotransplants poses several problems including a short half-life of the murine antibody plus development of an immune response directed against the murine antibody. These problems have been significantly reduced by the use of chimeric antibodies consisting of the murine variable regions joined to human constant regions (Khazaeli *et al.*, 1994). To create anti-pVCAM chimeric antibodies we cloned the variable regions from both 2A2 and 3F4. The murine variable heavy regions were joined to the human IgG4 constant region (HuG4) since this isotype does not activate complement (C) (Tao *et al.*, 1993), the predominant mediator of hyperacute rejection of xenografts. The murine variable light regions were joined to the human kappa constant region. Chimeric ch2A2 HuG4 and ch3F4 HuG4 antibodies were produced by coexpression of the chimeric heavy and light chains in 293-EBNA cells and tested for binding to pVCAM by FACS analysis using 293 cells expressing pVCAM (Fig. 2(A)). Both chimeric mAbs produced identical staining profiles as the corresponding murine mAbs, while neither chimeric mAb bound to untransfected 293 cells. Additionally, both the chimeric antibodies and murine mAbs produced identical FACS profiles using LPS-activated porcine aortic endothelial cells (Fig. 2(B)), confirming the chimeric antibodies retained the ability to bind to pVCAM expressed on PAEC.

The ability of the ch2A2 HuG4 and ch3F4 HuG4 antibodies to block the interaction between human VLA-4 and porcine VCAM was assessed by measuring inhibition of Ramos cell binding to activated PAEC (Fig. 3). The murine 3F4 mAb inhibited this binding by 90% when present at concentrations greater than 5 μg/ml. A control humanized antibody directed against human C5 (h5G1.1 HuG4) did not inhibit the binding of Ramos to activated PAEC. The ch2A2 HuG4 and ch3F4 HuG4 produced nearly identical inhibition curves as the murine 3F4 mAb, demonstrating the retention of binding avidity and cell adhesion blocking capabilities in these chimeric antibodies.

The ability of the ch2A2 HuG4 and ch3F4 HuG4 mAbs to inhibit binding of cells expressing both VLA-4 and LFA-1 was next examined using the Jurkat T cell line. Both the ch2A2 HuG4 and ch3F4 HuG4 antibodies inhibited the binding of Jurkat to activated PAEC by up to 90% while the control antibody h5G1.1 HuG4 did not inhibit binding at any concentration (Fig. 4(A)). Similarly, the ch2A2 HuG4 and ch3F4 HuG4 antibodies inhibited the binding of both resting (Fig. 4(B)) and activated (Fig. 4(C)) T cells to activated PAEC, although the

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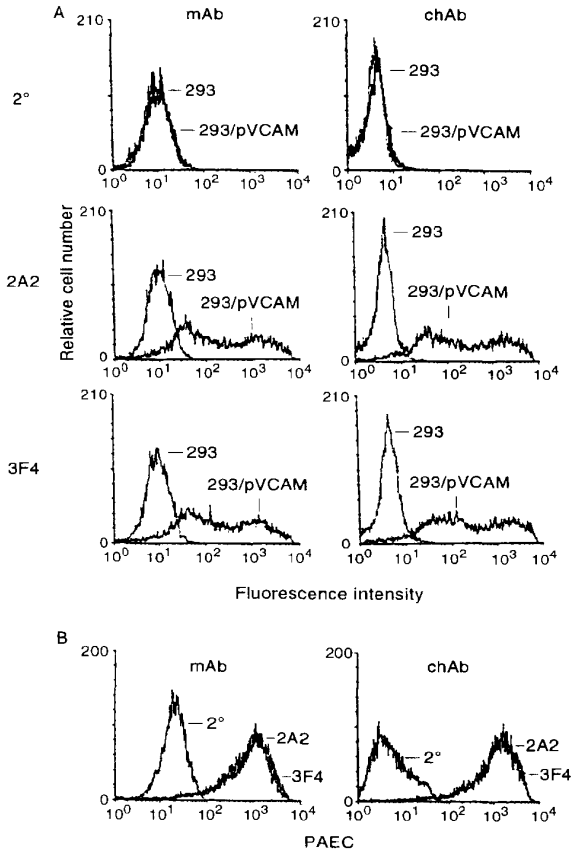

Fig. 2. Binding of 3F4 and 2A2 chimeric antibodies to pVCAM. (A) Chimeric mAbs containing the variable regions of either 2A2 or 3F4 joined to human IgG4 and kappa constant regions were produced in 293-EBNA cells and purified by protein G Sepharose chromatography. Untransfected 293-EBNA cells (293) or 293-EBNA cells expressing pVCAM (293/pVCAM) were incubated with 10 μg/ml purified murine 2A2 mAb, murine 3F4 mAb, ch2A2 HuG4, or ch3F4 HuG4. Bound antibody was detected using either FITC-conjugated goat anti-mouse IgG or FITC-conjugated goat anti-human IgG followed by flow cytometry using a Becton Dickinson FACSort. Data are displayed as histograms with fluorescence intensity plotted on the *x*-axis and relative cell number plotted on the *y*-axis. Background staining by the secondary antibodies is shown in the panels labeled 2°. (B) PAEC were activated by treatment with 1 μg/ml LPS for approximately 16 hr. Cells were then stained with either the murine 2A2 and 3F4 mAbs (left panel) or the ch2A2 HuG4 and ch3F4 HuG4 antibodies (right panel). Background staining by the secondary antibodies (2°) is indicated.

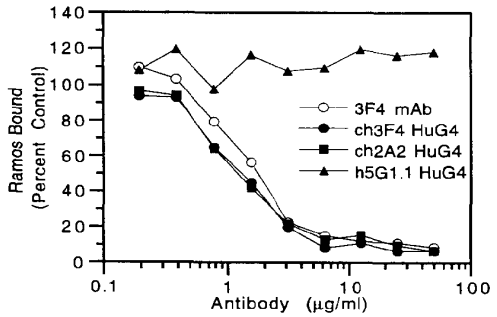

Fig. 3. Binding of Ramos cells to PAEC in the presence of mAbs. On day 0, PAEC were plated at 10 000 cells per well in medium A in 96-well plates. On day 1 the PAEC were activated by adding fresh medium A supplemented with 1 μg/ml LPS. After 16 to 24 hr incubation, the PAEC were washed and refed RPMI 1640 containing 1% FCS plus the indicated concentrations of the murine 3F4 mAb (3F4 mAb), the chimeric 2A2 and 3F4 mAbs (ch2A2 HuG4 and ch3F4 HuG4) or a humanized negative control antibody (h5G1.1 HuG4). Calcein-labeled Ramos cells were added and allowed to adhere to the PAEC under static conditions for 15 min. After nonadherent cells were removed by washing, the remaining bound cells were lysed with SDS. Calcein fluorescence of the SDS supernatant was measured with a Millipore CytoFluor 2350. In each experiment the binding of Ramos cells to PAEC in the absence of antibody was defined as 100%. Results shown are the mean of two to four experiments, with each value determined in duplicate in each experiment.

maximal inhibition achieved was reduced to approximately 60%. Addition of a blocking mAb directed against human VLA-4 also maximally inhibited adhesion by 60% (Fig. 4(C)), confirming the binding inhibition observed was due to blockade of the molecular interaction between human VLA-4 and porcine VCAM.

The potential of the ch2A2 HuG4 and ch3F4 HuG4 antibodies to inhibit binding of natural killer cells and monocytes to activated PAEC was examined using the cell lines YT (Yodio *et al.*, 1985) and U-937 (Sundstron and Nilsson, 1976), respectively. Binding of YT cells to activated PAEC was strongly inhibited by concentrations of 10 μg/ml ch2A2 HuG4 and ch3F4 HuG4 antibodies (Fig. 5(A)). In contrast, the ch2A2 HuG4 and ch3F4 HuG4 antibodies did not inhibit binding of U-937 cells to activated PAEC (Fig. 5(B)). One possible explanation for this failure to inhibit U-937 cell binding could be the presence of elevated levels of VLA-4 on U-937 cells. However, FACS analysis revealed the presence of comparable levels of CD49d and activated CD29 on U-937 cells as on other cell lines such as Jurkat whose adhesion to PAEC was inhibited by the chimeric anti-pVCAM antibodies (Fig. 6). Interestingly, the adhesion of U-937 to PAEC was consistently augmented by approximately 50% in all experiments. This increase was specific for the anti-pVCAM antibodies as no increase in U-937 binding to PAEC was detected in the presence of the control h5G1.1 HuG4 antibody (Fig. 5(B)). This suggested that binding of U-937 to PAEC could be increased through FcR binding to the anti-pVCAM HuG4 antibodies on the PAEC surface. In support of this hypothesis, FACS analysis confirmed the presence of significant levels of FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) on the surface of U-937 cells. In contrast, Jurkat and YT cells had no detectable Fcγ receptors while Ramos cells showed the presence of only low levels of FcγRII (Fig. 6).

Binding of the HuG4 chimeric antibodies to U-937 could be directly demonstrated by flow cytometry (Fig.

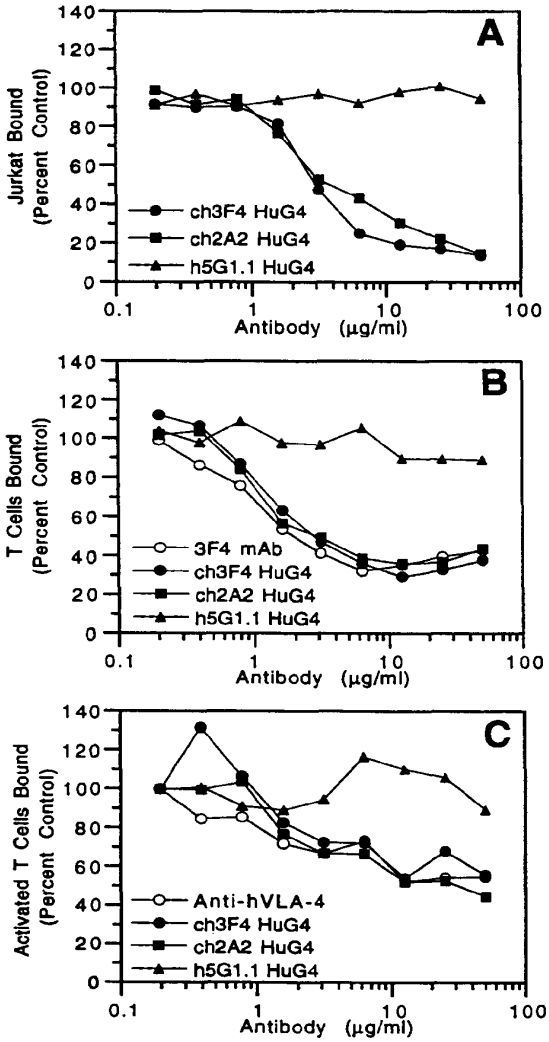

Fig. 4. Binding of Jurkat and human T cells to PAEC in the presence of HuG4 antibodies. Binding experiments were performed as described in Fig. 3 using calcein-labeled Jurkat cells (A) or calcein-labeled purified human T cells (B and C). Human T cells were either assayed immediately after purification (B) or cultured in the presence of 1 μg/ml PHA for 5 days followed by 1 day without PHA stimulation (C) prior to performing the adhesion assay. Results shown are the mean of two to four experiments (A and B) or from an individual experiment (C). Anti-hVLA-4 denotes the blocking murine mAb HP2/1 directed against the α4 subunit of human VLA-4.

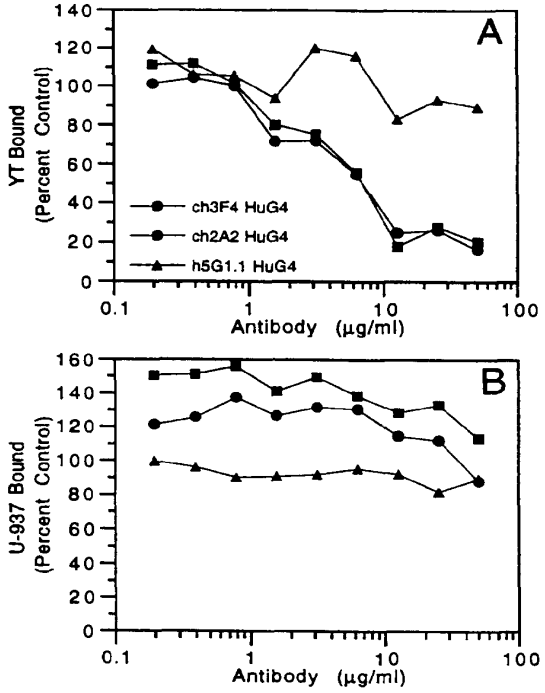

Fig. 5. Binding of YT and U-937 to PAEC in the presence of HuG4 mAbs. Adherence of calcein-labeled YT cells (A) or U-937 cells (B) to PAEC was assayed as described in Fig. 3. Results shown are the mean of two to four experiments.

7). Both the HuG4 antibodies as well as the anti-human C5 HuG4 antibody bound to U-937 cells. In contrast, 293/pVCAM cells bound only the anti-pVCAM antibodies but not the anti-human C5 HuG4 antibody. No binding of the HuG4 chimeric antibodies could be detected with Ramos, Jurkat, or YT cells. These results suggest that the HuG4 chimeric antibodies bound to U-937 cells through interaction of the HuG4 Fc region with the Fc receptors (FcRs) present on U-937 cells. Finally, F(ab')2 fragments prepared from ch3F4 HuG4 strongly inhibited binding of U-937 cells to PAEC (Fig. 8) whereas F(ab')2 fragments prepared from h5G1.1 HuG4 did not inhibit the binding. This result demonstrates that, if antibody crosslinking is prevented, blockade of the interaction between human VLA-4 and porcine VCAM can effectively inhibit the adhesion of human monocytes to PAEC.

Inhibition of FcR binding of humanized mAbs with altered constant regions

Although F(ab')2 fragments proved capable of inhibiting adhesion of U-937 cells, antibody fragments are suboptimal for chronic treatments, as they have much shorter *in vivo* half-lives than intact antibodies (Covell *et al.*, 1986). The use of intact antibodies with human constant regions as anti-rejection agents is complicated by the capacity of such antibodies to fix C and/or to bind FcRs. Human antibodies of the G4 isotype are devoid of C activity (Tao *et al.*, 1993; Smith *et al.*, 1995). Human antibodies of the G2 isotype do not activate C or bind FcRs (Canfield and Morrison, 1991; Burton and Woof, 1992). Rather than altering the specific residues known to mediate C fixation and FcR binding, we explored the possibility of creating an antibody with a composite human constant region. To create chimeric mAbs which would not activate C or bind to FcRs, we utilized the overall similarity in the human G2 and G4 primary

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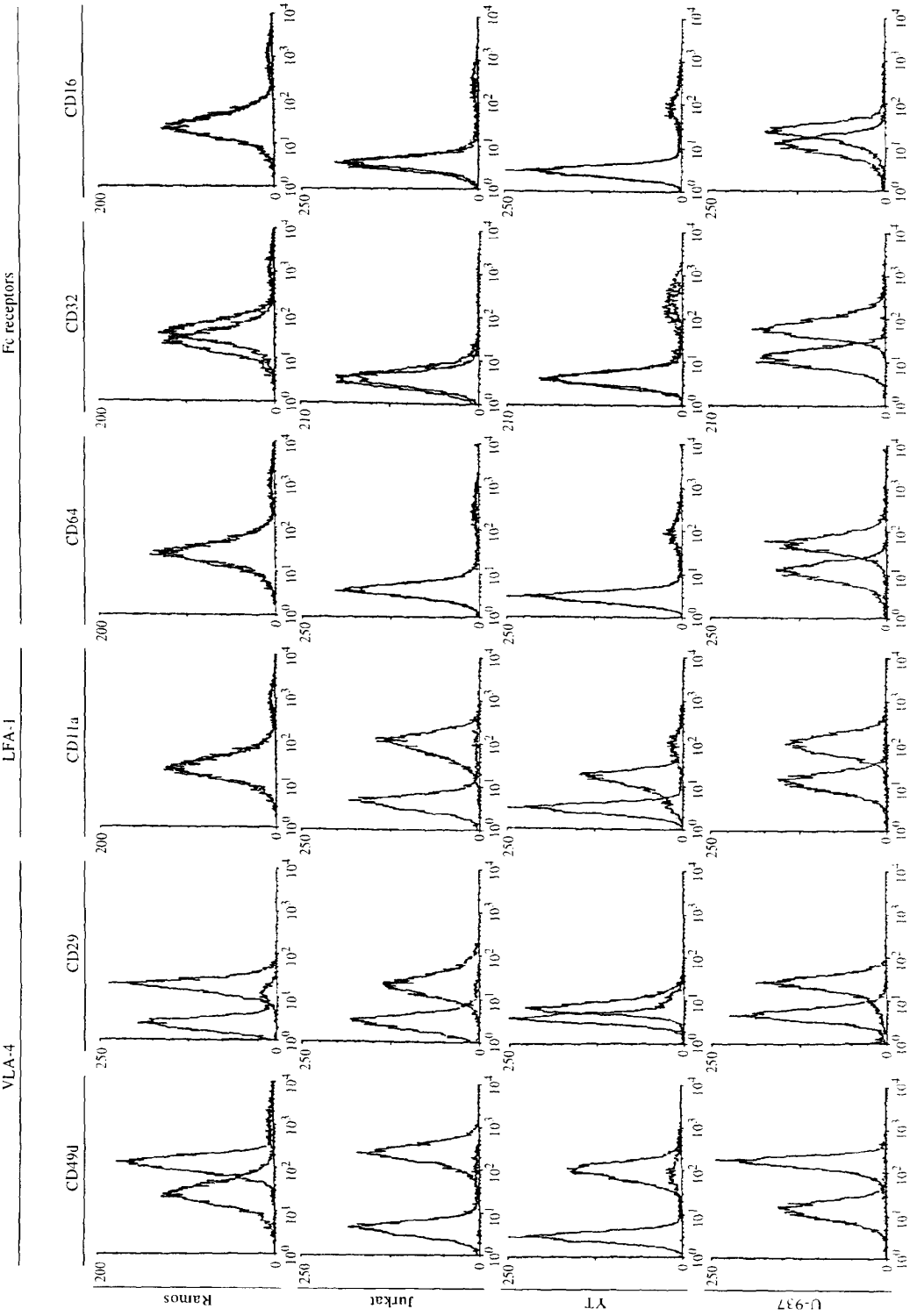

Fig. 6. Expression of VLA-4, LFA-1 and FcRs on the surface of Ramos, Jurkat, YT and U-937 cells. Cells were incubated with 10 μg ml of the following primary antibodies: mouse anti-human CD49d, rat anti-activated human CD29, mouse anti-human CD11a, mouse anti-human CD64 (FcγRI), mouse anti-human CD32 (FcγRII) or mouse anti-human CD16 (FcγRIII). After washing, cells were incubated with either FITC-conjugated goat anti-mouse IgG or FITC-conjugated goat anti-rat IgG as appropriate. Each panel presents the results obtained in the presence of primary plus secondary antibody or in the presence of secondary antibody alone.

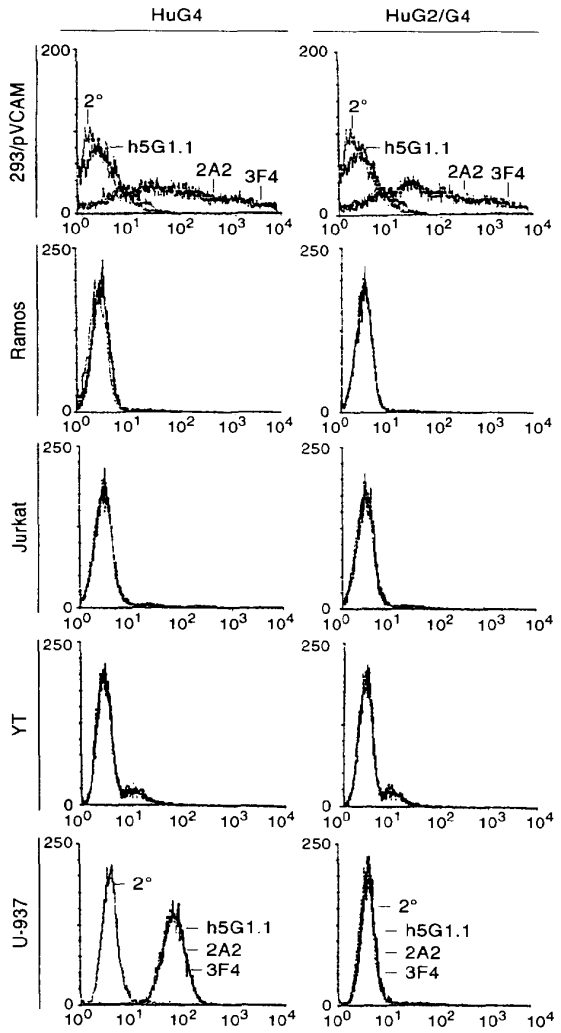

Fig. 7. Binding of chimeric antibodies to 293/pVCAM, Ramos, Jurkat, YT and U-937 cells. Cells were incubated with 10 μg/ml h5G1.1 HuG4, ch2A2 HuG4, or ch3F4 HuG4 (left panels) or 10 μg/ml h5G1.1 HuG2/G4, ch2A2 HuG2/G4, or ch3F4 HuG2/G4 (right panels). After washing, cells were incubated with FITC-conjugated goat anti-human IgG except for Ramos cells which were incubated with FITC-conjugated goat anti-human IgG (γ chain specific). Each panel presents the results obtained with the indicated cell line for h5G1.1 HuG4, ch2A2 HuG4 and ch3F4 HuG4 mAbs as well as the secondary antibody alone (2°) control.

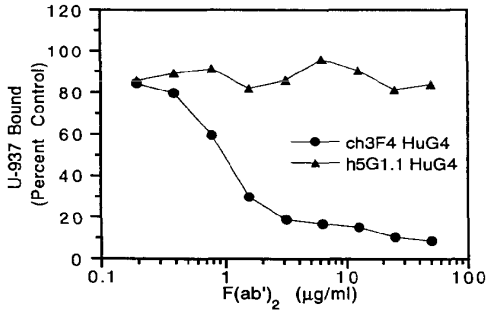

Fig. 8. Binding of U-937 cells to PAEC in the presence of F(ab')2 fragments. F(ab')2 fragments were prepared from h5G1.1 HuG4 and ch3F4 HuG4 by digestion with ficin. Undigested antibody and Fc fragments were removed by protein A chromatography. Adherence of calcein-labeled U-937 cells to PAEC in the presence of F(ab')2 was assayed as described in Fig. 3. Results shown are the mean of five experiments.

sequences to design a HuG2/G4 composite antibody consisting of the first constant region domain and the hinge region from the HuG2 isotype joined to the second and third constant region domains from the HuG4 isotype (Fig. 9). The resulting mAb did not contain the antibody sequences necessary for FcR binding, nor any new epitopes that would likely be immunogenic.

Binding to FcR was examined by using the monocytic cell line U937. FACS analysis demonstrated that the resulting ch3F4 HuG2/G4, ch2A2 HuG2/G4 and h5G1.1 HuG2/G4 antibodies did not bind to U-937 cells (Fig. 7). The ch3F4 HuG2/G4 and ch2A2 HuG2/G4 antibodies maintained the ability to bind pVCAM as demonstrated both by binding to 293/pVCAM cells (Fig. 7) and by inhibition of Jurkat and YT binding to activated PAEC (Fig. 10). For both Jurkat and YT cells inhibition of binding with the chimeric HuG2/G4 was equivalent to the HuG4 or original murine anti-pVCAM antibodies. The binding of U-937 cells to PAEC was now potently inhibited by the presence of either ch2A2 HuG2/G4 or ch3F4 HuG2/G4 antibodies. Finally, the chimeric antibodies were examined for the ability to block the adhesion of U-937 cells to purified soluble pVCAM (Fig. 11). Addition of the ch3F4 HuG4 antibody failed to inhibit binding of U-937 cells to pVCAM unless very high concentrations of antibody were added. In contrast the ch3F4 HuG2/G4 antibody potently inhibited the binding of U-937 cells to pVCAM, while the negative control h5G1.1 HuG2/G4 antibody did not block binding. Together, these results demonstrate the anti-pVCAM HuG2/G4 antibodies specifically inhibited the adhesive interaction of human VLA-4 with porcine VCAM and that disruption of this interaction was sufficient to inhibit binding of numerous human cell types to porcine endothelial cells.

DISCUSSION

Current success in allotransplantation has resulted from the development of effective global immunosuppressive therapies that prevent cellular graft rejection. Recent attempts to develop more specific immunosuppressive strategies have focused on inhibiting interactions between integrins and costimulatory molecules on T cells with their ligands on graft endothelial cells and other antigen presenting cells (reviewed in Faustman, 1995; Guinan *et al.*, 1994). The success of allotransplantation has been limited by the resulting shortage of human donor organs. Recent progress in overcoming the initial

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HuG2      STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HuG2/G4   STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HuG4      STKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV

HuG2      HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
HuG2/G4   HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVE
HuG4      HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVE

                                235
HuG2      RKCCVECPPCPAPPV- AGPSVFLF
HuG2/G4   RKCCVECPPCPAPPV- AGPSVFLF
HuG4      SKYGPPCPSCPAPEFLGGPSVFLF

HuG2      PPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPR
HuG2/G4   PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPR
HuG4      PPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPR

                                                      331
HuG2      EEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKG
HuG2/G4   EEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG
HuG4      EEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG
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Fig. 9. Sequence of the CH1, hinge and CH2 regions of human IgG2 (HuG2), human IgG4 (HuG4), and the chimeric HuG2/G4 construct. Positions where differences occur between the three molecules are double underlined. The amino acid sequence at position 235/236 determines ability to bind to Fcγ receptors (Canfield and Morrison, 1991; Duncan *et al.*, 1988; Alegre *et al.*, 1992; Burton and Woof, 1992) while the presence of a serine at position 331 confers the inability to activate C (Tao *et al.*, 1993).

hyperacute rejection of discordant xenografts suggests the potential for use of porcine xenografts as a clinical option to circumvent this chronic shortage. Although there are limited data regarding the fate of discordant xenografts which survive the initial hyperacute rejection phase, xenograft recipients will likely require continued cellular immunosuppression for the prevention of graft rejection. In this light, xenografts offer a unique opportunity for the development of blocking reagents specific for the graft, thereby avoiding global immunosuppression of the recipient.

To investigate the interactions occurring between human leukocytes and porcine endothelial cells, we have cloned the porcine VCAM molecule and created mAbs specific for porcine VCAM that do not bind to human VCAM (Mueller *et al.*, 1995). Two of these antibodies (3F4 and 2A2) are capable of blocking the interaction between human VLA-4 and porcine VCAM. Here we demonstrate that the binding specificity for 2A2 is located within domain 1 of pVCAM while the binding specificity for 3F4 is located within domain 2. This is identical to the results found with human VCAM, where blocking antibodies have also been shown to be directed against either domains 1 or 2 (Osborn *et al.*, 1992; Vonderheide and Springer, 1992).

The use of murine mAbs in humans and primates presents numerous problems including a short antibody half-life and a high degree of immunogenicity (Khazaeli *et al.*, 1994). To optimize the use of the anti-porcine VCAM antibodies in porcine-to-primate xenograft experiments we developed chimeric antibodies using the variable regions cloned from the 2A2 and 3F4 antibodies joined to the constant regions of the human IgG4,κ isotype. Given the extensive activation of C which occurs within xenografts, the human IgG4 isotype was chosen due to its inability to activate C. The resultant chimeric antibodies (ch2A2 HuG4 and ch3F4 HuG4 antibodies) retained specificity for porcine VCAM and were as potent as the original murine mAbs at blocking adhesion of Ramos cells to activated PAEC by greater than 90% (Fig. 3). In contrast to Ramos, the binding of resting or activated human T cells to activated PAEC was inhibited only approximately 50% by either the chimeric antibodies or the original mAbs (Fig. 4). Activation of human T cells by PAEC can be blocked by antibodies directed against either CD2 or LFA-1 (Rollins *et al.*, 1994*b*), suggesting either of these molecules could mediate the remaining adhesion by interacting with porcine CD58 or porcine ICAM-1, respectively.

The adhesion of human lymphocytes, monocytes or NK cells to activated HUVEC is dependent on the interaction of both LFA-1 with ICAM-1 and VLA-4 with VCAM (Allavena *et al.*, 1991; Jonjic *et al.*, 1992; Vonderheide and Springer, 1992). For each cell type, blocking the VLA-4/VCAM interaction by itself produces only a small reduction in adhesion, while antibodies which disrupt the LFA-1/ICAM-1 interaction provide a greater, although still partial, inhibition of adhesion. Addition of antibodies blocking both VLA-4/VCAM and LFA-1/ICAM-1 is required to completely block adhesion of these cell types to HUVEC. Surprisingly, binding of LFA-1$^+$–VLA$^+$4 Jurkat or YT cells to activated PAEC could be inhibited nearly completely by the ch3F4 HuG4 and ch2A2 HuG4 antibodies. One possible explanation for this could be the lack of interaction between human LFA-1 and porcine ICAM. The conservation of ICAM-1 is relatively low between species, with human and mouse ICAM-1 being only 50% conserved at the amino acid level (reviewed in Carlos and Harlan, 1994), and *in vitro* mouse LFA-1 does not bind to human ICAM-1. Alternatively, human LFA-1 may interact with porcine ICAM-1, but with a reduced affinity. For example, human VLA-4 binds to human VCAM at two independent sites, one within domain 1 and one within

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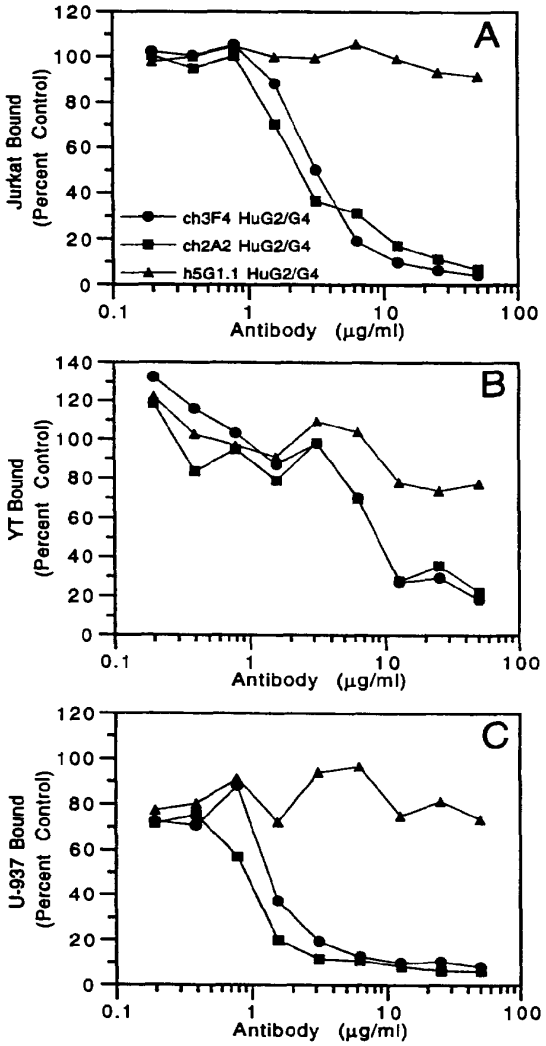

Fig. 10. Binding of Jurkat, YT and U-937 to PAEC in the presence of HuG2/G4 mAbs. Adherence of calcein-labeled Jurkat (A), YT (B) and U-937 (C) cells to PAEC was assayed as described in Fig. 3. Results shown are the mean of two to four experiments.

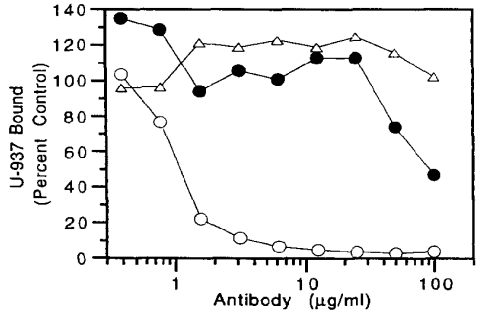

Fig. 11. Binding of U-937 to purified pVCAM. Microtiter plate wells were coated with purified soluble pVCAM. After blocking with FCS, wells received the indicated concentrations of either ch3F4 HuG4 (●), ch3F4 HuG2/G4 (○) or h5G1.1 HuG2/G4 (△) followed by 3×10^5 calcein-labeled U-937 cells. The cells were allowed to adhere at 37°C for 15 min after which non-adherent cells were removed by washing. Adherence of U-937 cells in the absence of competitor antibody was defined as 100%. Results shown are from an individual representative experiment.

domain 4 (Osborn *et al.*, 1992; Vonderheide *et al.*, 1994). In contrast, porcine VCAM lacks domain 4, suggesting the interaction between human VLA-4 and porcine VCAM may be weaker than the interaction between human VLA-4 and human VCAM. Reduced ligand affinities could make the binding of human effector cells to porcine endothelial cells more susceptible to disruption of any one of multiple weak interactions. These observations suggest the potential for significant differences in the therapeutic efficacy achieved by inhibiting particular receptor–ligand interactions with xenografts as compared to allografts.

Although the ch3F4 HuG4 and ch2A2HuG4 blocked binding of Jurkat and YT to activated PAEC, both antibodies failed to block binding of the monocytic U-937 cells to activated PAEC (Fig. 5). The levels of activated $\beta 1$ were comparable on Jurkat and U937 cells indicating an increased level of functional VLA-4 was not the mechanism behind the lack of inhibition of U-937 binding. Additionally, flow cytometry demonstrated the direct binding of the chimeric HuG4 antibodies to U-937 cells (Fig. 7). This binding was not dependent on the antigen specificity of the variable region, suggesting the interaction occurred through the Fc portion of the antibody. Finally, F(ab')2 prepared from 3F4 HuG4 were able to block the adhesion of U-937 cells to activated PAEC by greater than 80% (Fig. 8). Together these results were consistent with a model in which the chimeric anti-pVCAM HuG4 mAbs crosslinked U-937 cells to activated PAEC by simultaneously binding FcRs and cell surface VCAM present on the PAEC. This is comparable to the situation encountered with the anti-CD3 murine monoclonal antibody (mAb) OKT3, which when first administered to patients produces crosslinking of T cells to FcR bearing cells, resulting in the activation of both cell types (Ceuppens *et al.*, 1985; Kan *et al.*, 1986) with resultant toxicity to the patient.

The interaction of antibodies with Fcγ receptors has been found to be dependent on the sequence of the hinge linker region of the CH2 domain (Duncan *et al.*, 1988; Alegre *et al.*, 1992; Burton and Woof, 1992) as well as an additional bend located between two β strands within the CH2 domain (Canfield and Morrison, 1991). In the case of a humanized OKT3 antibody (human IgG4 constant regions), binding to Fcγ receptors has been eliminated by the introduction of amino acid mutations in the hinge linker (Alegre *et al.*, 1992, 1994). In either case the resulting human IgG4 constant region contains amino acid differences which could be immunogenic. Here, we have created chimeric antibodies (designated HuG2/G4) containing the CH1 domain and hinge linker region of

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human IgG2 followed by the CH2 and CH3 domains of the human IgG4 constant region. Due to the similarities between these two isotypes at the amino acid level, the resultant antibody contained no novel peptides less than 30 amino acids in length likely to be presented by MHC class II molecules and invoke an immune response. The chimeric HuG2/G4 antibodies no longer bound to U-937 cells. Moreover, the ch2A2 HuG2/G4 and ch3F4 HuG2/G4 antibodies blocked the binding of Jurkat and YT cells to activated PAEC as potently as the chimeric HuG4 antibodies, demonstrating the alteration of the Fc region did not reduce the antibody avidities. Moreover, the chimeric anti-pVCAM HuG2/G4 recombinant antibodies nearly completely blocked the binding of U-937 cells to activated PAEC and to purified pVCAM. Finally, as predicted from the low affinity of IgG2 and IgG4 for human C1q, our preliminary results indicate that the HuG4 and HuG2/G4 recombinant antibodies show little or no C1q binding (data not shown).

In summary, we have developed humanized mAbs specific for porcine VCAM which potently block the adhesion of multiple human inflammatory cell types to porcine endothelial cells. The lack of binding of these antibodies to human VCAM leaves intact the interaction of human leukocytes with human endothelial cells. The adhesion-blocking properties of these antibodies will allow delineation of the role of VLA-4/VCAM interactions in cellular mediated rejection of porcine-to-primate xenografts. Additionally, the HuG2/G4 antibody design should prove useful in humanization of other antibodies intended for human use where elimination of FcR binding and C activation may be desirable.

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BRIEF REPORT

Recurrence of Neisserial Meningococcemia Due to Deficiency of Terminal Complement Component

MAJ JOSEPH T. MORRIS and MAJ WILLIAM J. KELLY, MC, USA, Fort Sam Houston, Tex

INHERITED AND ACQUIRED DEFECTS of the complement system predispose susceptible individuals to infections with *Neisseria meningitidis*.[1,2] Deficiencies of the terminal complement components (C5, C6, C7, or C8) are mainly associated with mild recurrent meningococcal infections in patients usually more than 10 years old at the time of the first infection.[1,2] The prevalence of complement deficiencies in patients with meningococcal disease ranges from 0 to 30%,[1,3,4] whereas in a white general population the prevalence is estimated to be less than 0.03%.[1,2] *Neisseria meningitidis* infections due to the common serogroups (A, B, C) are seldom associated with complement deficiencies.[1,2,4] Rasmussen et al[5] found no complement deficiencies in any of 132 patients with serogroup B infections. We report the case of a patient with recurrent neisserial meningococcemia due to deficiency of the sixth component of complement.

CASE REPORT

A 21-year-old black man who had had no pertinent past illnesses, came to the emergency room complaining of a severe headache. During the evaluation his mental status deteriorated to the point that he responded only to noxious stimuli. He was subsequently given 4 million units of penicillin G for meningitis and was admitted. His admission temperature was 38.3°C (101°F) rectally, pulse rate 50/min, blood pressure 160/98 mm Hg, and respiratory rate 14/min. Both pupils measured 5 mm and responded sluggishly to light. Nuchal rigidity and Kernig's and Brudzinki's signs were present. Results of lung, cardiac, and abdominal examinations were normal. Petechiae measuring 1 to 2 mm covered the chest, legs, and soles of the feet. Serum chemistry values were sodium 136, potassium 4, chloride 101, and bicarbonate 20 mEq/L; glucose 152, BUN 14, and creatinine 1.4 mg/dL. WBC was 21 600/mm^3 with 67% neutrophils and 22% band forms, and the hematocrit value was 45%. Lumbar puncture showed an opening pressure of 50 cm, and Gram's stain of the purulent CSF showed multiple gram-negative diplococci consistent with *Neisseria meningitidis*. The CSF protein value was 660 and glucose value, 0 mg/dL. Penicillin G therapy was continued at 2 million units every 2 hours intravenously, and 2 doses of methylprednisolone were given (2 g every 6 hours). The patient's mental status returned to normal over the following 72 hours. He received a 14-day course of penicillin G, and rifampin was given to his roommates, household contacts, and girlfriend. The *N meningitidis* was stereotyped as group B. There was no evidence of adrenal insufficiency at discharge from the hospital.

The patient did well until 3 weeks after discharge when he was admitted for evaluation of diffuse myalgias, right-sided neck stiffness, sore throat, and a temperature of 39°C (102.3°F). Physical examination showed no nuchal rigidity or Kernig's sign. WBC was 19 300/mm^3 with a left shift. Lumbar puncture yielded CSF containing 3 WBCs and 13 RBCs/mm^3, with a glucose value of 95 and a protein value of 17 mg/dL. Over the next 24 hours increasing myalgias developed, in addition to palatal petechiae and purpura on the palms and soles. He was given penicillin, gentamicin, and methylprednisolone for possible Waterhouse-Friderichsen syndrome. Blood cultures grew *N meningitidis* group B. Complement determinations showed normal C3, C4, C5, C7, and C8 levels but a CH_{50} of 0 CH U/mL and a greatly reduced C6 level of <1.5 mg/dL (normal 4.8 to 7.2 mg/dL). The patient received a 14-day course of penicillin G for treatment of recurrent neisserial bacteremia. He also received pneumococcal and *Haemophilus influenzae* vaccinations and 2 days of rifampin therapy for elimination of a possible *N meningitidis* carrier state. Methylprednisolone therapy was discontinued after 48 hours when no signs of Waterhouse-Friderichsen syndrome appeared.

DISCUSSION

The alternate and classical pathways of the complement system are important components of the host's immune response to infections caused by encapsulated organisms. Deficiencies of complement components have been associated with recurrent infections due to specific organisms. A number of studies have demonstrated the association of complement deficiencies and *Neisseria meningitidis* infections.[4,6-12] Our patient has C6 deficiency as a cause of his recurrent bacteremia with *Neisseria meningitidis* serogroup B. He had had no previous episodes of neisserial infections.

The median age of first infection in patients with late manifestation of complement deficiency has been reported to be 17 years, despite the presence of the defect since birth and the early peak age-specific incidence of meningococcal disease in the general population (ages 3 to 8 months).[2] Recurrent infections are not unusual with discrete recurrences reported in 45% of complement deficient individuals.[2]

Our patient had recurrent infections with *Neisseria meningitidis* serogroup B. This is an infrequent situation, since recurrent infections with *Neisseria meningitidis* are more commonly caused by serogroup Y than by the common serogroup B.

SUMMARY

Recurrent infections with *Neisseria meningitidis* are attributed to deficiencies of terminal complement components. The sero-

From the Infectious Disease Service, Brooke Army Medical Center, Fort Sam Houston, Tex.

The views of the authors do not necessarily reflect the position of the Department of the Army or the Department of Defense.

Reprint requests to Joseph T. Morris, MD, Infectious Disease Service, Brooke Army Medical Center, Fort Sam Houston, TX 78234-6200.

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type most commonly responsible for recurrent *N meningitidis* infections is serotype Y. We have reported a case of recurrent meningitis due to *N meningitidis* in a patient who was found to be deficient in the sixth component of complement. Complement deficiencies should be considered in any patient with recurrent infections caused by *N meningitidis*.

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〈 1136 〉 PACKAGING—UNIT-OF-USE

INTRODUCTION

This chapter provides guidance in the use and application of unit-of-use packaging and is intended for use by drug manufacturers, repackagers, and pharmacists. Suppliers of packages and packaging components may find the information useful, as well.

The *General Notices* defines a unit-of-use container as one that contains a specific quantity of a drug product that is intended to be dispensed as such without further modification except for the addition of appropriate labeling.

Unit-of-use packaging, when provided by the manufacturer, offers some of the following attractive advantages. (1) A dosage form can be dispensed to a patient in the manufacturer's original container, a practice that recognizes that the suitability of the container has been established on the basis of the manufacturer's stability studies. (2) The counting and repackaging of dosage units in the pharmacy is eliminated, thereby reducing the possibility of human error. (3) The pharmacist is able to affix the label for the patient onto the unit-of-use package and is free to use the manufacturer's expiration date as the beyond-use date. (4) The number of dosage units in a single unit-of-use package may be determined on a case-by-case basis. (5) Patient compliance is improved. (6) The unit-of use package can protect against countertfeiting because traceability of product is ensured through bar coding techniques and NDC numbers.

Unit-of-use packaging, when provided by repackagers, offers the same attractive advantages as those offered by the manufacturer. However, unit-of-use repackagers should conform to all requirements as presented in *Good Repackaging Practices* 〈 1178 〉. There are a number of reasons why repackagers produce unit-of-use packaging: for example, (1) requests from institutions, (2) better inventory control, (3) reduced dispensing times, and (4) variations in some drug therapies.

The packaging of a unit-of-use system may be a multiple container or a single-unit container. A unit-of-use system may contain a drug product in a liquid, semisolid, or solid dosage form (see also *FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics*). [NOTE—The terms "unit-of-use package" and "unit-of-use container" may be used interchangeably.]

The Poison Prevention Packaging Act (PPPA) of 1970 requires in certain cases the use of special packaging—child-resistant and senior-friendly. Child-resistant packaging protects children from serious injury or illness resulting from ingesting or handling hazardous products including drugs.

Because drugs packaged in unit-of-use packaging are intended to be dispensed to the consumer without repackaging by the pharmacist, the manufacturer or repackager is responsible for the special packaging of PPPA-regulated substances in unit-of-use containers (l6 CFR 1701.1).

TYPES OF CONTAINERS FOR UNIT-OF-USE

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Unit-of-use containers are required to be child-resistant if they are intended to be dispensed directly to the patient pursuant to a prescription. Unit-of-use packaging intended for institutional or hospital use may or may not be required to be child-resistant. Unit-of-use containers that are child-resistant single-unit containers include supported blisters, such as separate, peel, push, and tear notch, and enclosed or in-card blisters, such as pull tabs and slide packs. Blister packaging is discussed in the general chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨ 1146 ⟩. Unit-of-use containers that are multiple-unit containers include glass and plastic containers.

Single-Unit Container

A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show any evidence of tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity, and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Unit-Dose Container

A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, directly from the container.

Single-Dose Container

A single-dose container is a single-unit container for articles intended for parenteral administration only. It is labeled as such.

Multiple-Unit Container

A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

PACKAGING FABRICATION MATERIALS

Packaging fabrication materials include substances used to manufacture packaging containers such as glass, plastics (including high-density polyethylene (HDPE), low-density polyethylene (LDPE), polyethylene terephthalate, polyethylene terephthalate G and polypropylene (PP), other resins, and other materials as listed in the general test chapter *Containers* ⟨ 661 ⟩ and in the *FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics*.

Glass

Any glass packaging material used in the immediate container should meet the glass test requirements for *Limits for Glass Types* and *Chemical Resistance—Glass Containers: Powdered Glass Test, Water Attack at 121°*, and *Arsenic* under general test chapter *Containers* ⟨ 661 ⟩.

Plastic

Any plastic packaging material used in the immediate container should meet the plastic test requirements for *Plastics* in the general test chapters *Containers* ⟨ 661 ⟩ and *Containers—Permeation* ⟨ 671 ⟩. Depending on the type of plastic packaging material used, the packaging material meets the requirements for *Biological Tests—Plastics and Other Polymers, Physicochemical Tests—Plastics, Polyethylene Containers, Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles,* and *Polypropylene Containers* under general test chapter *Containers* ⟨ 661 ⟩.

The test for moisture vapor transmission may be carried out as described in the general test chapter *Containers—Permeation* ⟨ 671 ⟩ for multiple-unit and unit-dose containers.

PACKAGING CLOSURE TYPES

Reclosables and nonreclosables may be used for solid, semisolid, and liquid dosage forms. Both must be packaged in compliance with the 16 CFR 1700.15 standards.

Reclosables

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Reclosables are containers with suitable closures that may incorporate tamper evidence and child-resistance capabilities. Reclosables may be used for glass or plastic containers.

Nonreclosables

Nonreclosables are containers with closures that are nonreclosable, such as blisters, sachets, strips, and other single-unit containers. Nonreclosables may include packs such as cold-formed foil blisters, foil strip packs, and PVC/Aclar combining multilayer materials that are thermo-formed or cold-formed foil blisters (see *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨ 1146 ⟩). Nonreclosables may be child resistant depending on the intended use and place of use. Household nonreclosables are subject to the PPPA as defined in 16 CFR 1700.14. However, because of some unit-dose designs, not all unit-dose packages comply with the PPPA.

LABELING

The unit-of-use containers are labeled to include expiration dates, the manufacturer's lot number, the NDC designation, and bar codes as provided in the *Labeling* section of the *General Notices and Requirements* under *Preservation, Packaging, Storage, and Labeling* and in *Good Repackaging Practices* ⟨ 1178 ⟩. Some of the advantages of having bar codes on the label include reduced medication errors, improved inventory control, and improved access to medication identity. The labeling covers information placed in the container by the manufacturer (see *General Notices and Requirements*). Acceptable labeling can range from the full labeling as for multiple-unit containers to an abbreviated labeling when the container is too small to include all the text. Full labeling may also be provided on the carton if it is not present on the immediate container.

REPACKAGING AND REPROCESSING

Unit-of-use containers are reprocessed or repackaged as instructed by the manufacturer or as directed in the general test chapter *Containers* ⟨ 661 ⟩ or in the general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨ 1146 ⟩. A unit-of-use package that is a blister package may not be reprocessed by a pharmacist once it has been deblistered from a unit-dose container (see *General Notices and Requirements* for application of the appropriate beyond-use date for a multiple-unit or unit-dose container). Deblistering is the process of removing medication from a blister-type container. However, under current Good Manufacturing Practices (cGMPs) and tight quality controls, the manufacturer or contract repackager may repackage and reprocess unit-of-use containers.

INFORMATION FROM MANUFACTURERS

The manufacturer should provide appropriate stability information that can be used to determine appropriate labeling, storage, and shipping statements that will properly inform patients and practitioners. The manufacturer may make other assurances based on product information on packaging and distribution arrangements. In the event that a product is not to be repackaged, the manufacturer may so state in the labeling. The manufacturer also includes labeling and information suitable for optimal handling by the practitioner and the patient. The labeling and information should be bar coded to eliminate medication error and promote medication traceability.

RESPONSIBILITY OF THE DISPENSER

Labeling

The labeling on a unit-of-use container also includes a label added at the dispensing stage by the pharmacist. Prior to dispensing the unit-of-use package, the dispenser shall add label(s) that provide the following information:

1. the name of the patient;
2. the name and strength, the directions for use as prescribed by a doctor or health-care provider, and the name of the prescriber; and
3. any storage instruction, beyond-use date, and other information as deemed appropriate by federal and state laws.

In the pharmacy setting, pharmacists are encouraged to use bar codes, in conjunction with computerized prescription orders, to confirm that the right drug is being dispensed to the right patient. Bar coding would minimize errors and create opportunity for medication traceability and accountability.

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Information to Patient

Patients must be given information that applies to the specific prescription being dispensed.

QUALITY CONTROL OF PACKAGING SYSTEM

The packaging system shall meet the general considerations for system suitability, protection, safety, and performance characteristics as described in *FDA Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics*, in the general test chapters *Containers* ⟨ 661 ⟩ and *Containers—Permeation* ⟨ 671 ⟩, and in the general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨ 1146 ⟩.

Auxiliary Information— *Staff Liaison* : Desmond G. Hunt, Ph.D., Senior Scientific Associate
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Declaration by Dr. Michael Treuheit

I, Michael Treuheit, Ph.D., declare that:

1. I am and have been employed by Amgen Inc. since February, 1993. Since 2006, I have held the title of Director Process Development. In this role, I am responsible/oversee formulation development of large molecule therapeutics, such as cytokines, antibodies, and antibody fragments. During my career, I have been directly involved in the formulation of at least 30 clinically tested and/or marketed therapeutic antibodies. A current copy of my CV is provided as **Appendix D**.

2. A study was conducted to demonstrate the stability of eculizumab over a range of concentrations. Eculizumab was formulated at 2 mg/ml (2PBST22), 5 mg/ml (5PBST22), 10 mg/ml (10PBST22), 30 mg/ml (30PBST22), and 50 mg/ml (50PBST22) in 10 mM Na Phosphate, 150 mM NaCl, 0.022 % polysorbate 80 at pH 7.0. Soliris® (eculizumab) is 10 mg/ml eculizumab formulated in 10 mM Na Phosphate, 150 mM NaCl, 0.022 % polysorbate 80 at pH 7.0. The EMA label indicates Soliris should be stored between 2-8°C.

3. Like Soliris®, the eculizumab formulations used in the study were sterile and preservative free.

4. The stability of the 2 mg/ml, 5 mg/ml, 10 mg/ml, 30 mg/ml, and 50 mg/ml eculizumab formulations was monitored over a period of 13 weeks at storage conditions of (4°C) and at elevated temperature (25°C). Storage at the elevated temperature is used to evaluate the product specific routes of degradation in an accelerated manner as compared to recommended storage conditions. Physical and chemical stability were analyzed by size-exclusion ultra high-performance liquid chromatography (SE-UHPLC), anion exchange high-performance liquid chromatography (AEX-HPLC), and reduce sodium dodecyl sulfate capillary electrophoresis (rCE-SDS).

5. Aggregation of the antibody results in the formation of high molecular weight (HMW) species that can be visualized by SE-UHPLC. A large degree of HMW formation is a sign of low long-term stability. All of the eculizumab solutions stored at 4°C and 25°C were sufficiently stable throughout the study, i.e., there was no significant loss in main peak for any of the protein concentrations examined. The results are summarized in **Appendix A**.

6. The storage of antibodies in solution can result in chemical degradation, leading to the formation of acidic species (e.g. by deamidation of asparagine residues), which can be detected by AEX-HPLC. A high degree of acidic species is a sign of low chemical stability. Analysis of the eculizumab solutions stored under label conditions and the elevated temperature showed that all tested antibody concentrations were essentially equivalent. At the elevated temperature, all showed some chemical degradation, which increases over time upon storage, but there is no significant difference in chemical stability between protein concentrations. The results are summarized in **Appendix B**.

7. rCE-SDS offers high resolution separation of most types of chemically or structurally altered species from the main (intact) species for both heavy chain (HC) and light chain (LC) of the antibody. Analysis of the eculizumab solutions by rCE-SDS shows that a detectable decrease of the main species (HC+LC) occurs at both tested temperatures for all samples. However, in agreement with the AEX-HPLC measurements, the antibody solutions were equivalent at the recommended storage conditions and elevated temperature. The results are summarized in **Appendix C**.

8. The results of the SE-UHPLC, AEX-HPLC, and rCE-SDS analyses demonstrate eculizumab is stable at the range of concentration tested, 2-50 mg/ml, and there is no significant difference in stability amongst the concentrations tested. Thus, the 10 mg/ml formulation does not demonstrate superior stability compared to the less- or more-concentrated formulations of eculizumab.

I certify that the above statements are correct to the best of my knowledge and belief.

Amgen Thousand Oaks, CA, Aug 3, 2017

Place and Date

Ph.D.

Dr. Michael Treuheit

Attachments
Appendices A-D

CURRICULUM VITAE

Michael Treuheit, Ph.D.

Education

Doctor of Philosophy in Chemistry, October 1990, University of Cincinnati.
Thesis Title: *Disease-Coupled Specificity In The Glycan Structures of Orosomucoid.*

Bachelor of Science in Biology, June 1980, University of Cincinnati.

Work Experience

Amgen, Inc., 1993-present

Director of Drug Product Formulation Technology in the Department of Product Development leading a group of approximately 30 scientists (15 at the PhD. Level). The group has responsibility for developing FIH and commercial formulations, and for the CMC sections of our large molecule MA's.
Notable past accomplishments include the submission of the Development Pharmaceutics Section in the BLA's for Neulasta , Palifermin and Denosumab along with a variety of IND's and INDa's for our pipeline molecules

University of Cincinnati, College of Medicine, Department of Pharmacology and Cell Biophysics. Postdoctoral Fellowship in the Protein Chemistry Core Laboratory of Dr. Terence L. Kirley, 1990 to 1993.

University of Cincinnati, Department of Chemistry Teaching Assistant, 1985 to 1990.
Taught freshman, Bio-Organic and Biochemistry laboratory and selected lecture courses.

The Christ Hospital, Research Technologist in the Tumor Research Laboratory, experienced in tissue culture techniques (Human Tumor Clonogenic Assay), 1975 to 1989.

Abstracts and Presentations

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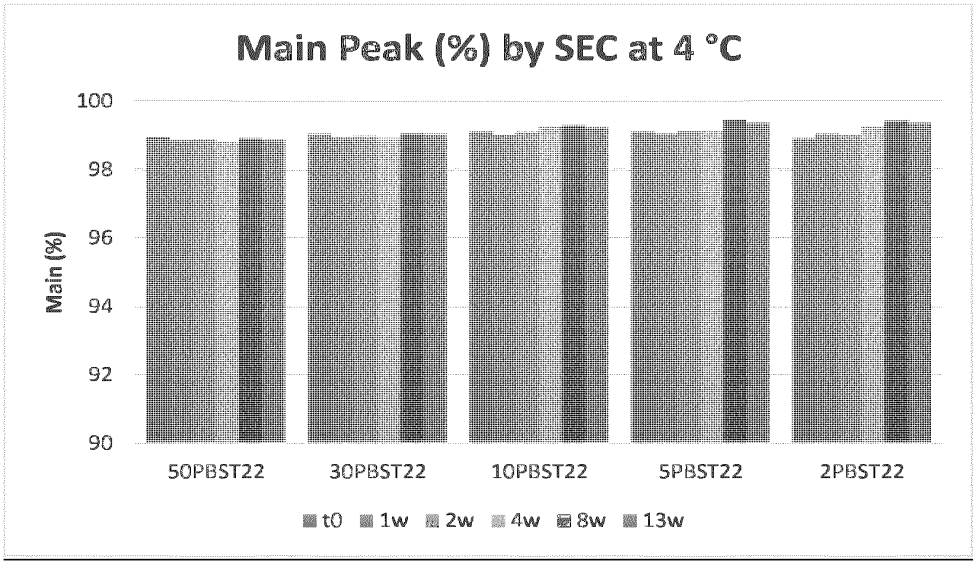
Appendix A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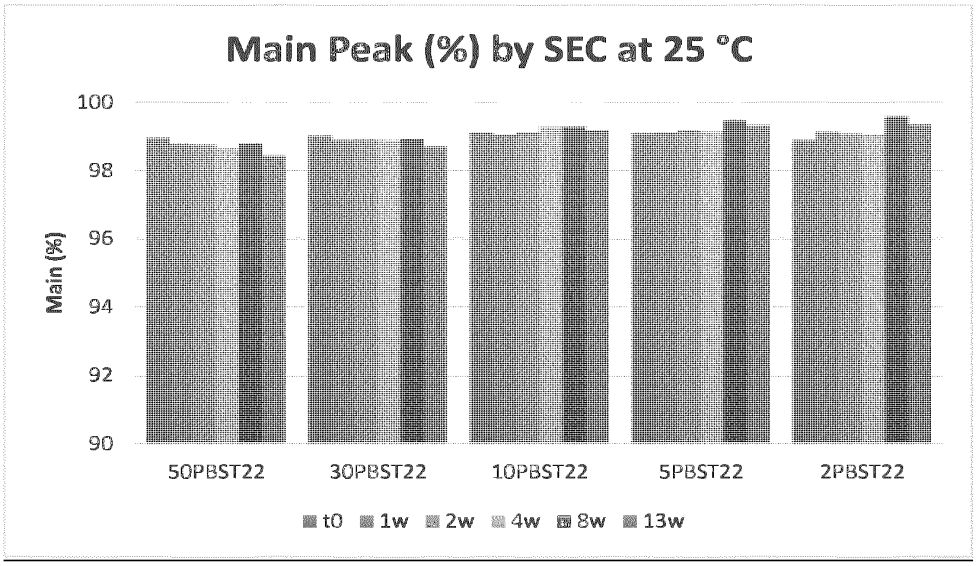
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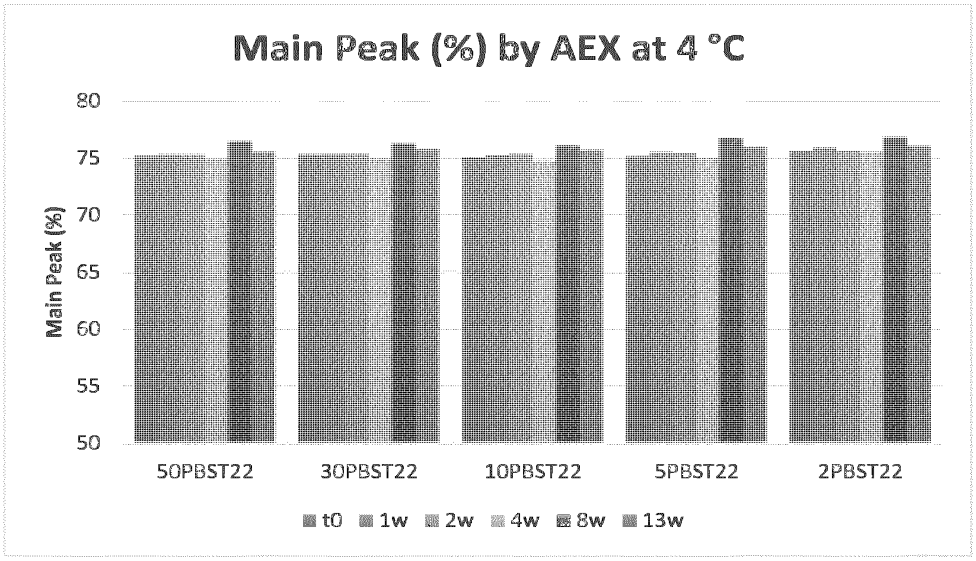
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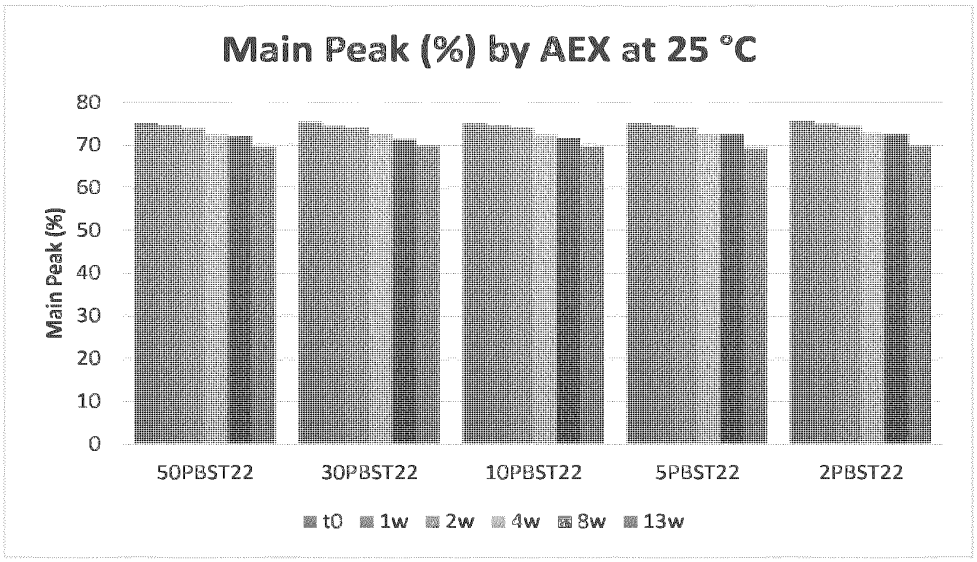
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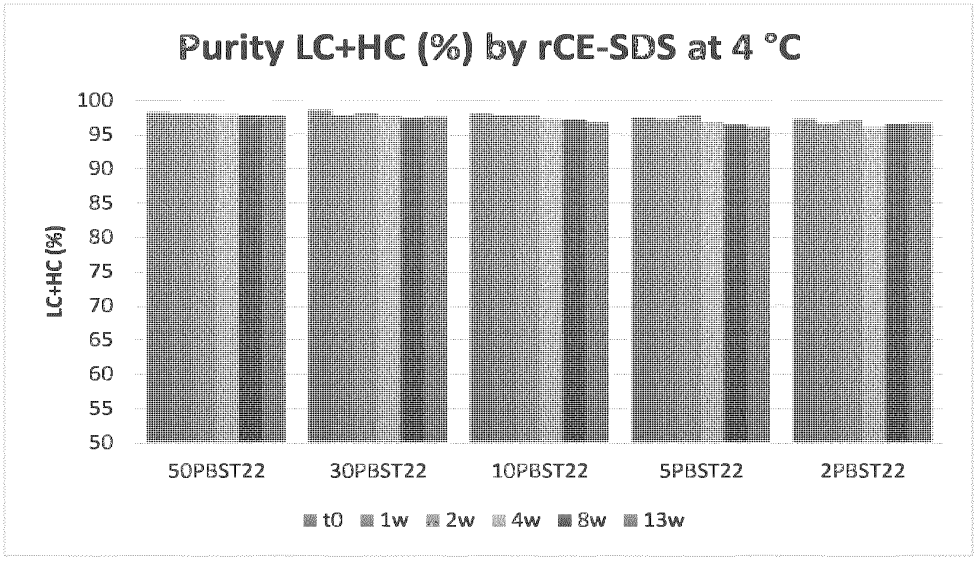
Appendix C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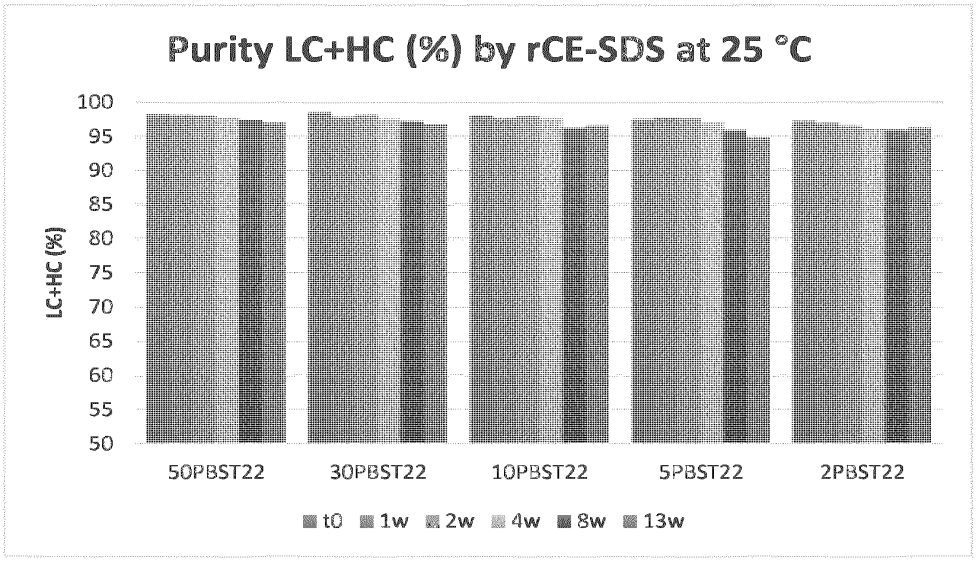
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Case report

Complement C7 deficiency presenting as recurrent aseptic meningitis

Michael Corvini, MD; Christopher Randolph, MD; and Steven I. Aronin, MD

Background: Complement deficiency states are rare inherited disorders that may predispose affected individuals to angioedema, collagen vascular disease, or infection due to encapsulated organisms, especially *Neisseria meningitidis*.

Objectives: To report the case of a 36-year-old man of Irish descent with recurrent culture-negative neutrophilic meningitis, to offer potential reasons for the inability to recover a causative pathogen, and to review the genetics and prevalence of complement deficiency states, the methods of screening for such deficiencies, the features of meningococcal infection as they relate to such deficiencies, and management strategies for clinicians caring for patients with such deficiencies.

Methods: The patient presented in 1988 and again in 2002 with culture-negative neutrophilic meningitis. His second episode was characterized by a rash suggestive of meningococcal infection, prompting immunologic evaluation.

Results: Immunologic evaluation revealed an undetectable CH_{50} level. Levels of C1, C2, and C5 through C9 were normal except for C7, which was undetectable. Further testing revealed that the patient's sister was also C7 deficient.

Conclusions: Complement component deficiencies are relatively rare; individuals with collagen vascular disease and systemic neisserial infection should be screened using either the CH_{50} or the APH-50 assay. Key to the management of a late–complement component–deficient host is counseling, education about meningococcal infection, and discussions about the potential benefits of chemoprophylaxis and immunoprophylaxis. The ability to detect the bacterial cause of meningitis in such patients is organism dependent and may be influenced by factors such as cerebrospinal fluid bacterial concentration and previous antibiotic drug exposure.

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INTRODUCTION

The complement pathways play an integral role in the immune system.[1,2] Deficiencies in any complement components or pathologic activation of a normally functioning complement system can yield clinical disease, typically manifested as angioedema, collagen vascular disease, or infection. The seventh component of complement, C7, is part of the membrane attack complex (MAC) required for complement-dependent bactericidal activity, including defense against neisserial infection.[3,4] In this article, we describe a patient with C7 deficiency presenting with inflammatory arthritis and recurrent culture-negative neutrophilic meningitis.

CASE REPORT

A 36-year-old man was well until April 2002, when he developed transient pharyngitis followed by fever (temperature, 102.2° F), chills, sweats, and malaise. Subsequently, he developed headache, light sensitivity, neck pain and stiffness, nausea, vomiting, and right hip pain with an overlying rash. Five days into his illness, he presented to the emergency department (ED) with ongoing symptoms and a rash now involving his left shoulder, chest, and abdomen.

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The patient was hospitalized 14 years earlier for an illness consistent with bacterial meningitis by clinical presentation and lumbar puncture (LP) but with negative cerebrospinal fluid (CSF) and blood culture findings. He takes no medications, including nonsteroidal anti-inflammatory agents, and has no history of craniofacial trauma or drug allergies. His father died at the age of 45 years of a myocardial infarction. There is no family history of immunodeficiency, meningitis, arthritis, or other inflammatory or inherited disease. He lives with his wife and daughter in Connecticut, smokes cigarettes, and drinks alcohol, but he has never used illicit drugs. He is monogamous with his wife and has no history of sexually transmitted diseases. He is a plumber, has not traveled outside New England, and has no history of tick exposure. He did have contact with rodent droppings 1 day before becoming febrile.

In the ED, the patient appeared ill. His temperature was 101.0° F and his heart rate was 110/min. His blood pressure was normal without orthostatic changes, and his respiratory rate and oxygen saturation were normal. Nuchal rigidity and photophobia were present. Neurologic examination revealed only a positive Brudzinski sign. He had dry mucous membranes, flat neck veins, and no lymphadenopathy. His lungs were clear, his heart was tachycardic, and the results of abdominal examination were normal. There was markedly limited range of motion of the right hip and left shoulder. The

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affected joints were warm but without appreciable erythema or effusion. A scattered, tender, purpuric-petechial rash was distributed over the chest, left shoulder, arms, abdomen, right hip, and groin. The palms and soles were spared.

The leukocyte count was 18,000/mL, with 62% segmented forms and 30% bands; the hematocrit level was 43.4%; andthe platelet count was 228,000/mL. Findings from a comprehensive metabolic profile, coagulation indices, and urinalysis were unremarkable. Findings from chest radiography were normal, and electrocardiography showed sinus tachycardia. Lumbar puncture disclosed hazy CSF, with an opening pressure of 123 mm H_2O, a protein level of 186 mg/dL (normal, 14–45 mg/dL), a glucose level of 49 mg/dL (normal, 45–75 mg/dL), a red blood cell (RBC) count of 128/mL, a white blood cell (WBC) count of 491/mL (90% neutrophils), and moderate polymorphonuclear cells but no organisms on Gram stain.

One hour after ED arrival, a blood sample was cultured, and then 1 g of ceftriaxone was administered. One hour later, LP was performed, and then 1 g of vancomycin and an additional 1 g of ceftriaxone were administered, and a second blood sample was cultured. The patient was placed on "droplet precautions" in the intensive care unit, vigorously hydrated, and empirically treated for bacterial meningitis with ceftriaxone and vancomycin. His meningitic symptoms resolved and his vital signs normalized within 12 hours, whereas his arthritic symptoms recovered more slowly. Left shoulder aspirate yielded 4 mL of frank pus, a WBC count of 234,133/mL (90% neutrophils), and an RBC count of 800/mL. Right hip aspirate was serosanguinous, with a WBC count of 25/mL (45% neutrophils) and an RBC count of 24,747/mL. No crystals or organisms were identified from either specimen. Skin lesion Gram staining was negative for organisms. One of 2 bottles from the first blood culture grew coagulase-negative staphylococcus. Both bottles from the second blood culture were negative. Cerebrospinal fluid, skin lesion, and synovial fluid cultures were negative. Serologic test results for Lyme disease, Rocky Mountain spotted fever, and leptospirosis were negative. Findings from CSF latex agglutination for *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* were negative. The CH_{50} level, determined by enzyme colorimetry, was undetectable at less than 10 U/mL (normal, 26–58 U/mL; Quest Diagnostics Reference Laboratory, Wallingford, CT). Levels of C1, C2, and C5 through C9 (protein quantitation by radial immunodiffusion) were normal except for C7, which was undetectable at less than 2 mg/dL (normal, 4–11 mg/dL; Quest Diagnostics Reference Laboratory). C1 esterase inhibitor, antinuclear antibody, antibody to double-stranded DNA, rheumatoid factor, quantitative immunoglobulin, and human immunodeficiency virus antibody levels were all normal.

The patient completed 14 days of parenteral antibiotic drug therapy and was given the tetravalent meningococcal vaccine and a medical identification bracelet (MedicAlert; MedicAlert Foundation International, Turlock, CA) before hospital discharge. CH_{50} and C7 levels measured during his convalescence remained undetectable. Family members were screened for complement deficiencies (Table 1).

DISCUSSION

Genetically determined complement deficiencies have been described for nearly all of the complement components, including C7, which is inherited in an autosomal-recessive manner.[3] The C6 and C7 genes are polymorphic, closely linked on 5p13, and are close homologues of the C8α, C8β, and C9 genes.[5] The molecular bases of subtotal and total C6 and C7 deficiency have been reported previously.[6,7] Numerous polymorphic DNA markers have been reported for the C6 and C7 genetic region, illustrating the genetic heterogeneity associated with defects in these complement components.[8–15] Such polymorphisms have been described in individuals of Japanese, South African, Russian, Moroccan Sephardic Jewish, and Irish ancestry. The patient's parents emigrated from Ireland, and both must have been carriers for C7 deficiency. His father is deceased, but his mother's serum C7 level was compatible with a carrier state. Further testing revealed that his sister is also C7 deficient (Table 1).

Complement deficiency states are typically identified via the CH_{50} or the APH-50 assay. All of the terminal components of complement (C5-C9) are required to yield normal CH_{50} and APH-50 levels; thus, both assays provide a sensitive means of screening for late–complement component–deficient (LCCD) hosts.[4] Using these assays, the prevalence of complement deficiency states in the general population has been estimated to be 0.03%.[16] Given the rarity of complement

Table 1. Results of Complement Studies Performed on the Proband and His Family Members

Source	Age, y	Health status	Complement, mg/dL								
			CH_{50}*	C2	C3	C4	C5	C6	C7	C8	C9
Proband	36	Normal	<10	3.4	211	25	22	10.6	<2	8.6	73
Daughter	5	Normal	53	2.1	113	17	10	6	6	5.5	24
Brother	39	Diabetes	60	3	117	16	14	6.6	4	5.6	29
Sister	38	Normal	<10						<2	8.7	44
Mother	61	Normal	48	2.5			15	6	2	4.6	29
Paternal aunt	62	Normal	51	2.8			17	3.6	4	5	25
Normal range			26–58	1.6–3.5	88–201	16–47	6–20	3.6–7.5	4–11	2.7–6	6–29

* Measured in units per milliliter.

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deficiency states, the utility of screening assays is greatest in disease populations known to contain the clinical correlates of complement protein abnormalities (patients with collagen vascular disorders and those with systemic neisserial infection).[17] For patients with meningococcal disease, the prevalence of an underlying complement deficiency state varies worldwide (10%–15% in the United States) and is inversely related to the incidence of meningococcal disease by country.[3,17] Such relationships must be considered when making recommendations regarding the value of screening an individual patient with meningococcal infection for an underlying complement deficiency. A CH_{50} level was obtained on our patient because of his history of recurrent meningitis and a rash that was most consistent with meningococcal disease. Once the CH_{50} level indicated a complement deficiency, assays for the individual complement components were performed, and a C7 deficiency was identified. The patient's family was also screened using the CH_{50} assay and then the targeted C7 assay (Table 1).

Neisseria meningitidis causes approximately 80% of the infections in patients with any complement deficiency, and the remainder are due to other encapsulated organisms, such as *S pneumoniae* and *H influenzae*.[17] Infections in LCCD hosts, though, are nearly exclusively due to *N meningitidis*. This can be explained by understanding that the terminal complement components compose the MAC, which is responsible for complement-mediated bacterial cell lysis. Patients who are LCCD, therefore, are unable to assemble the MAC and are unable to effect complement-mediated cell lysis. *Neisseria meningitidis* (in contrast to all gram-positive and some gram-negative organisms) is extremely sensitive to complement-mediated killing,[3] and, thus, LCCD patients are particularly susceptible to meningococcal infection.

The frequency of meningococcal disease is 10,000-fold greater in LCCD hosts vs healthy hosts (57% vs 0.0072%).[17] Furthermore, in LCCD hosts there is a later median age of first meningococcal infection (17 vs 3 years), a higher relapse rate (7.6% vs 0.6%), a higher recurrence rate (41% vs 0.34%), and a 10-fold lower mortality rate (1.5% vs 19%) compared with healthy hosts.[17] Ross and Densen[3] explain these differences using hypothetical relationships among serum bactericidal activity, protective antibody, meningococcal exposure, and age. According to this model, both LCCD and healthy newborns express high levels of maternal protective antibody and serum bactericidal activity. Thereafter, both of these levels fall to their nadir such that, in healthy hosts, there is a narrow window of susceptibility for meningococcal infection between 6 months and 2 years of age. During this window, asymptomatic exposure to *N meningitidis* begins to occur, yielding a rise in serum bactericidal activity and protective antibody. In the LCCD host, serum bactericidal activity remains undetectable, yielding a lifelong, broad window of susceptibility to meningococcal infection. This lifelong window of susceptibility explains why LCCD patients are at increased risk of meningococcal infection, have an older median age of first infection, and have higher recurrence rates compared with healthy hosts.

In terms of the lower mortality rate noted in LCCD patients, some researchers[18] attribute this to ascertainment bias (complement deficiency is usually diagnosed in survivors of meningococcal disease, and complement testing is rarely performed in patients with fatal disease). Those who believe that this difference in prognosis is real offer 2 possible explanations. First, the lack of a MAC, as seen in LCCD hosts, results in preservation of the bacterial cell membrane, and, thus, there is no endotoxin release, septic shock, or death.[18] Second, in contrast to the sporadic cases in healthy hosts, episodes of meningococcal infection in LCCD patients occur in the presence of protective antibody, thus allowing opsonization to occur, which may clear some of the organism by phagocytosis.[3] Assuming that our patient had meningococcal infection at the age of 22 years, and again now, his older age at the first episode, recurrent disease, and survival are all typical features of meningococcal infection in an LCCD host.

Presumed and confirmed meningococcal infection in C7-deficient hosts has been previously reported,[3–8,18–33] mostly in the form of case reports containing incomplete clinical details. Review of 24 C7-deficient patients with a first episode of presumed or documented meningococcal infection reveals no sex preference and a median age of 15 years (range, 3–40 years).[5,7,8,18,22–33] Patients' ethnic origins include Irish, Moroccan, Russian, Japanese, Arab, and Yugoslav. Twenty (83%) of the 24 patients had clinical or laboratory evidence of meningitis either alone or in conjunction with arthritis (n = 4; 17%) or myopericarditis (n = 2; 8%). Three patients had chronic meningococcemia without central nervous system involvement. Rash was reported in 12 patients, and it was characterized as petechial or purpuric in 11 of the 12 patients. The CSF formula was not provided for these 24 patients, but up to 20% of cases of meningococcal meningitis from the literature have a CSF WBC count less than 1,000/mL, and 24% to 55% have a normal CSF glucose concentration.[34–37] Of the 24 C7-deficient patients we reviewed, the clinical diagnosis of meningococcal infection was confirmed by bacterial culture in 15 (63%). Even lower rates of microbiologic confirmation (20%–40%) were reported for 77 episodes of meningococcal infection in 30 patients with either C7 or C8 deficiency[18]; the authors attribute this to exposure to high-dose penicillin 1 to 2 hours before blood and CSF cultures were obtained. Finally, 12 of the 24 C7-deficient patients we reviewed had recurrent meningococcal infection, 3 had multiple recurrences, and all 24 responded to parenteral antibiotic drug therapy without clinical sequelae. Therefore, our patient's age, ethnicity, clinical presentation (now and 14 years ago), CSF formula, and response to therapy are all compatible with recurrent meningococcal infection in a C7-deficient host.

Although it is suggestive that our patient had meningococcal infection, no such organism was identified using routine methods. The possibility remains that he was infected by a bacterium other than *N meningitidis* or by a nonbacterial pathogen or that he experienced a noninfectious meningitis syndrome. Tick-borne bacterial infections, such as Lyme disease, Rocky Mountain spotted fever, and ehrlichiosis, typ-

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ically occur in the late spring and summer months and can manifest as aseptic lymphocytic meningitis with or without joint involvement. Our patient exhibited several features that did not support the diagnosis of a tick-borne infection: his illness occurred in April, he had no history of a tick bite, his rash differed from the characteristic rash of Lyme disease and Rocky Mountain spotted fever, his arthritis developed during the acute phase of illness (as opposed to Lyme arthritis, which is a late manifestation), and he had neutrophilic CSF pleocytosis. Results of short-term serologic testing for the agent of Lyme disease and Rocky Mountain spotted fever were negative. The CSF and Lyme antibody and Lyme polymerase chain reaction on the synovial fluid, however, was not performed. Aseptic meningitis can also be a manifestation of leptospirosis and lymphocytic choriomeningitis. Such infections typically occur during the second phase of disease, 1 to 2 weeks after exposure to rodents or rodent droppings. Our patient's exposure to rodent droppings occurred only 1 day before he became ill, thus making these infections very unlikely. Noninfectious processes that have been associated with aseptic meningitis include collagen vascular disorders, medications,[38] adult-onset Still disease,[39] and complement deficiency itself.[40] In our patient, serologic test results for collagen vascular disorders were negative, he was not taking any medications before becoming ill, and the appearance of his rash was not characteristic of adult-onset Still disease. Furthermore, meningitis as the initial manifestation of adult-onset Still disease is exceedingly rare, and, nearly 2 years later, our patient has not had any further evidence of arthritis.

Perhaps a bacterial etiology could not be identified because the organism was not present at the time of sampling or because the diagnostic tests used could not detect its presence. For pediatric patients with proven bacterial meningitis, blood culture detects the causative organism in 40% to 90%, CSF Gram stain in 60% to 90%, CSF culture in 70% to 85%, and CSF antigen testing in 50% to 100% of cases.[41] Polymerase chain reaction testing for specific meningeal pathogens[42–44] and for a broad range of bacterial pathogens[45] has also been used to determine the bacterial etiology of cases of meningitis. Several investigators[42–44] have shown that compared with CSF culture, polymerase chain reaction is a highly sensitive and specific means of diagnosing meningococcal meningitis. As more experience is gained with this diagnostic test, it will undoubtedly become a powerful tool in the diagnostic approach to patients with meningitis syndromes.

Although the CSF Gram stain is positive in 60% to 90% of cases of bacterial meningitis, results vary by organism and by the concentration of bacteria in the CSF. The CSF Gram stain is positive by organism as follows: *S pneumoniae,* 90%; *H influenzae,* 86%; *N meningitidis,* 75%; gram-negative bacilli, 50%; and *Listeria monocytogenes,* less than 50%.[46] Bacterial concentrations of 10^5 CFU/mL or greater are associated with positive CSF Gram staining in up to 97% of cases, whereas concentrations of 10^3 CFU/mL or less are associated with a positive Gram stain result in approximately 25% of cases.[47] There are limited data defining the CSF bacterial concentration in cases of meningitis due to *N meningitidis*. One study[48] of 9 patients with meningococcal meningitis found a mean concentration of 1.27×10^5 CFU/mL. In this small study, as few as 1,500/mL of meningococcal colonies were found (quantities clearly below the threshold of detection by Gram staining). Low CSF bacterial concentrations could explain why the Gram stain was negative in our patient, but this would not necessarily explain the negative culture findings.

The last potential reason why no bacterial cause was identified relates to the impact of antibiotic drug therapy on the results of diagnostic tests. Although the receipt of antibiotics before CSF sampling does not significantly alter the CSF WBC count, glucose level, or protein concentration,[49] such therapy can certainly affect blood culture and CSF Gram stain and culture results. In the presence of antibiotics, the ability to detect an organism by CSF Gram stain and culture drops to 40% to 60% and less than 50%, respectively,[50] and the rate of recovery from blood culture drops to less than 5%.[51] How fast antibiotics negate the ability to make a microbiologic diagnosis by CSF analysis is not known. A study of experimental pneumococcal meningitis in rabbits illustrates a 2-log drop in CSF bacterial concentration every hour after penicillin administration such that one would expect to see negative smears by 4 hours and sterilization by 8 hours.[52] This study is often quoted as evidence for a 4- to 8-hour window between antibiotic administration and LP before it is too late to make a microbiologic diagnosis. However, it is unclear whether these data can be extrapolated to infection due to organisms other than *S pneumoniae* or to humans.

In humans, the use of repeated LP illustrates that 90% to 100% of CSF cultures are sterile by 24 to 36 hours after the administration of appropriate antibiotics.[50] More precise human data on the rate of CSF sterilization have not been established, but in a recent retrospective study[53] of 128 cases of pediatric meningitis, the authors found that the interval between antibiotic drug administration and a negative CSF culture result ranged from 15 minutes to 60 hours. Three of 15 patients whose CSF was sampled within 1 hour of antibiotic drug administration had a negative CSF culture result, and the infecting organism for each of these 3 cases was *N meningitidis*. Furthermore, CSF sterilization for each of the 37 cases of meningococcal meningitis occurred within 3 hours, suggesting that CSF sterilization, in some cases, occurs faster than previously believed. Therefore, based on the existing literature, our patient's clinical presentation, and the fact that he is an LCCD host, we believe that he likely had meningococcal meningitis. Our inability to detect the organism may relate to 1 or more factors, including low CSF bacterial concentration and previous antibiotic medication exposure. His complement deficiency state itself may have contributed to an abnormal CSF formula (elevated protein level and neutrophilic pleocytosis) and low CSF bacterial concentration, but no data exist on the expected CSF findings in LCCD hosts with bacterial meningitis.

Once an LCCD individual is identified, the clinician should focus on education and counseling.[51] Patients and their

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families should learn how to recognize and respond to the early signs and symptoms of meningococcal sepsis and meningitis. Patients with a good understanding of their condition will likely be able to live a normal life without the overriding fear of recurrent meningococcal infection. A medical identification bracelet should be ordered for the patient, and appropriate family members should be screened to see whether they are unrecognized LCCD hosts.[55] Select patients (and their families) may benefit from meeting with a qualified genetic counselor.

Prophylactic strategies, including long-term chemoprophylaxis and immunoprophylaxis, should also be considered for LCCD hosts. Because complement-deficient hosts develop meningococcal infection relatively infrequently, and because the interval between recurrences may be many years, it is difficult to determine the efficacy of such prophylactic strategies. Antibiotic prophylaxis (ie, penicillin injected monthly) has been used successfully in this situation,[56,57] but there are several downsides to this approach, including difficulties associated with committing a child or young adult to lifelong therapy and the prospect of selecting out for antibiotic-resistant strains. Meningococcal vaccination in LCCD hosts has also been investigated by numerous researchers.[19–21,54,58–60] The tetravalent meningococcal vaccine promotes antibody production to capsular serogroups A, C, Y, and W-135, but LCCD patients must be educated that the vaccine lacks protection against serogroup B infection and fails to fully compensate for the absent complement-mediated serum bactericidal activity. Our patient was fitted for a medical identification bracelet and was administered the tetravalent meningococcal vaccine, and he and his family were educated about meningococcal disease and vaccine efficacy. To date, he has had no evidence of recurrent infection.

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Requests for reprints should be addressed to:
Steven I. Aronin, MD
Waterbury Hospital Health Center
64 Robbins St
Waterbury, CT 06721
E-mail: saronin@wtbyhosp.chime.org

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The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 20 February 2003
CPMP/QWP/419/03

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

<DRAFT>

NOTE FOR GUIDANCE ON EXCIPIENTS, ANTIOXIDANTS AND ANTIMICROBIAL PRESERVATIVES IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT

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Note:
This Note for Guidance replaces 3AQ9a Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Products and CPMP/CVMP/QWP/115/95 Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 8595
E-mail: mail@emea.eu.int http://www.emea.eu.int
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NOTE FOR GUIDANCE ON EXCIPIENTS, ANTIOXIDANTS AND ANTIMICROBIAL PRESERVATIVES IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT

INTRODUCTION

This note for guidance is concerned with the application to excipients, antioxidants and antimicrobial preservatives of Module 3, sections P.1, P.2, P.4, P.5, P.8 of the Common Technical Document with a view to granting a marketing authorisation for a new medicinal product.

The data should be presented according to the standard format described in the CTD Module 3, part P.

Antioxidants and Antimicrobial Preservatives are substances which are used to extend the shelf-life of medicines by respectively retarding the oxidation of active substances and excipients, and by reducing microbial proliferation.

The properties of these substances are due to certain chemical groups which are usually aggressive towards living cells and which lead to certain risks when used in man.

If it is not absolutely necessary to add these substances in medicinal products they must be avoided.

The purpose of this note for guidance is to describe the information that needs to appear in application for marketing authorisations with regards to the addition of any antioxidants or antimicrobial preservatives.

For each antioxidants and antimicrobial preservative the application should contain :

- reason for inclusion
- proof of efficacy
- the method of control in finished product
- details of the labelling of the finished product
- safety information

Several guidelines should be also taken into account :

- ICH Topic Q 6 A : Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products : Chemical Substances (3.3.2.2. Oral liquids : d) Antimicrobial preservative content, e) Antioxidants preservative content ; 3.3.2.3. Parenteral Drug Products : g) h) and Decision Tree 8 : Microbiological Attributes of Non-sterile drug products).
- Note for Guidance on Development Pharmaceutics : 3.3. Liquid and Semi-solid Formulations.
- 3BC7A : Excipients in the Label and Package leaflet of Medicinal Products for Human Use
- Note for guidance on maximum shelf-life for sterile products after first opening or following reconstitution.

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SECTION P.1 Description and Composition of the Drug Product

Excipients must be listed, specifying their common name, their quantity and the use and reference to any relevant standard. When the common name is not sufficient to indicate functional specifications, the brand name with commercial grade should be specified. In the case of excipients presented as a mixture of compounds, details as to the composition should be provided in qualitative and quantitative terms. However, for flavouring agents and aromatic substances, it is permitted to give the qualitative composition only.

Antimicrobial preservatives and antioxidants should be chemically defined (reference to existing European Pharmacopoeia monographs may be used) and designated by the Chemical Abstract Service Registry Number (RN-CAS).

The purpose for the inclusion of any antioxidant or microbial preservative should be stated (antioxidant for the benefit of active substance or excipient or both, or antimicrobial preservative).

SECTION P.2 Pharmaceutical development

SECTION P.2.1 Components of the Drug Product

The section P.2.1.2 should comprise an explanation of the choice of the excipient (and grade where necessary) and the level of excipient according to the note for guidance "Development pharmaceutics and process validation".

For antimicrobial preservatives and antioxidants, during the pharmaceutical development of the product the applicant should demonstrate:

- the necessity to add an antioxidant or preservative to the finished product at the chosen level
- the physical and chemical compatibility of the antioxidant and of the preservative with other constituents of the finished product, the container and the closures.

The used concentration must be justified in terms of efficacy and safety, such that the minimum concentration of preservative is used which gives the required level of efficacy. The appropriate test method for efficacy of antimicrobial preservation is that of the European Pharmacopoeia. This should be used to determine whether the required level of activity is achieved.

In the case of antioxidants, these should only be used once it has been shown that their use cannot be avoided, even if the manufacturing process is optimised to minimise the potential for oxidation, for instance by manufacturing and filling products under an inert headspace gas.

The safety of the antioxidant or preservative should be supported by bibliographic and /or experimental data.

Some antioxidants or antimicrobial preservatives may be undesirable under certain circumstances :

- mercury containing preservatives : see the CPMP Position Paper on Thiomersal, Implementation of the Warning Statement Relating to Sensitisation (CPMP/2612/99) and EMEA Position Statement on recent developments concerning thiomersal in vaccines (EMEA/CPMP/1578/00). This kind of preservative should be strictly avoided except if no other possibility may be considered but in this case the choice should be fully justified.

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- benzyl alcohol : when used in parenteral products for children under the age of two years. Its degradation product and metabolite is the benzaldehyde, toxic for the CNS.
- Benzoic acid esters (Para hydroxy benzoate and their derivates etc) : when used in any dosage-form for parenteral use.
- Sulphites and Metabisulphites.

Parenteral infusions do not contain any added antimicrobial preservatives and no antimicrobial preservatives are added when the medicinal product is intended for administration by routes where for medical reasons an antimicrobial preservative is unacceptable, such as intercisternally or by any other route of administration which gives access to the cerebrospinal fluid or retro-ocularly.

SECTION P.4 Control of Excipients

Examples of different kinds of excipients are given in the annex.

1. Specifications (P.4.1), Analytical Procedures (P.4.2), Validation of Analytical Procedures (P.4.3) and Justification of Specifications (P.4.4) :

1.1 Excipients described in the European Pharmacopoeia or, if not described in the European Pharmacopoeia, pharmacopoeia of a Member State

The routine tests which are to be carried out on each batch of starting materials must be stated in the application for marketing authorisation. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the test methods used are suitable to establish that the starting materials meet the quality requirements of that pharmacopoeia. When the monograph covers a family of related products, the particular specifications chosen for the excipients must be submitted. In addition and when necessary, the test used to determine the quality of the excipient should be shown to be in relation to the function that it fulfils in the medicinal product.

Data on microbiological contamination of the excipients used in the manufacture of sterile products should always be given where membrane filtration is used to achieve sterility.

Antimicrobial preservatives and antioxidants are defined as excipients and as such should be controlled following the rules governing medicinal products in the European Union. These data should be provided in part P.4.

1.2 Excipients not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State

An appropriate specification of the excipient must be established, based on the following types of tests:

* Physical characteristics
* Identification tests
* Purity tests, including limits for total or individual impurities, which should be named. Purity tests may be physical, chemical, biological and, if appropriate, immunological.

  Where sterile filtration is used in the manufacture of a parental medicinal product, data and routine tests on microbiological contamination of excipients should always be given.
* Other relevant tests including, e.g. the tests on parameters which may influence the performance of the dosage form.

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* Assay or limit tests if necessary.

When an excipient is not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State or in an other compendium of established use (e.g. USNF Pharmacopoeia and Japanese Pharmacopoeia), validation data of the test methods used should be presented, where appropriate.

1.3 Justification of Specifications

Justifications of specifications takes into account the choice and use of an excipient which is used for a particular purpose: it will determine the properties which must be checked during the routine tests and which will be the subject of certain specifications in connection with the bioavailability of the product (see Note for Guidance "Specifications and control tests on the finished product").

Nevertheless, justification of specifications are not systematically required for well-known excipients. For example, they are not required for excipients which have been used in similar medicinal products for a long period of time and when their characteristics and properties have not changed significantly.

For solid and semi-solid dosage forms, the justification of specifications should, if necessary, provide information on the relevant characteristics of the excipient. Special tests are often necessary (e.g. to verify the capacity of the excipient to emulsify and disperse, or to measure the viscosity...).

Appropriate data are needed for excipients used in a new route of administration.

Justification of specifications on excipients already included in the European Pharmacopoeia, or if not included in the European Pharmacopoeia, in the pharmacopoeia of a Member State and other well-known excipients already used in a medicinal product.

For these excipients, justification of specifications will normally not be required. However, any particular specification concerning the characteristics, as defined in Section P.2.1.2, should be justified (e.g. sieve analysis, in relation to microcrystallinity).

Excipients of Human or Animal Origin (P.4.5)

Viral Safety and TSE Risk should be documented in accordance with the relevant directives.

Novel Excipients (P.4.6)

For novel excipients : a dossier should be established containing the same data as required for new active substances:

a) A strict definition of the excipient, its function and its conditions of use. If the excipient is complex or is made of a mixture of compounds, the composition must be specified in qualitative and quantitative terms.

b) For new excipients and for excipients presented as a mixture of compounds the following should be taken into consideration:

   i. Any bibliographical data on the chemistry and on the toxicology and the field in which the product is already used.

   ii. The Community provisions concerning additives in foodstuff: any criteria which are based on the toxicological data, with cross-references to these data.

   The quality specifications which have been laid down in the directives are satisfactory as long as the routine control tests used are validated.

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iii. The international specifications (FAO/WHO/JECFA), and other publications such as the Food Chemical Codex.

iv. For medicinal products for topical use, data on the starting material in cosmetic products (Directive 76/768/EEC).

v. Data concerning the toxicology of the new excipient should be presented according to the dosage form and the route of administration of the medicinal product (if applicable).

c) Documentation on chemistry of excipients is required for all new excipients, taking as its basis the Note for Guidance "Chemistry of Active Substances".

* The origin of the excipient, including the name and address of manufacturer.
* A general outline of the synthesis (manufacture and purification).
* Structure.
* Physical, chemical properties, identification and purity tests.
* Validated methods of analysis with a presentation of batch results.
* Miscellaneous information (microbiological tests, etc).
* Contamination, presence of foreign substances, residual solvents, etc.
* In the case of an excipient obtained from a mixture of several components, the quality of each component and the physico-chemical tests for the mixture should be described.

The routine test procedures and limits should be established on the basis of the documentation given in the dossier.

SECTION P.5 Control of Drug Product

Apart from those situations envisaged in the note for guidance "Specifications and control tests on the finished product" it is not usually necessary to carry out identity testing and an assay of the excipients in the finished product at release.

Nevertheless, the finished product release specifications should include an identification test and limits for any antioxidants and antimicrobial preservatives present in the formulation. The finished product specification against which the product is tested throughout its shelf-life should also include limits for the antimicrobial preservatives present.

Where antioxidants are used up during the manufacture of the product, the release limits should be justified by batch data. The adequacy of specified limits should be justified on the basis of controlled conditions and in-use stability testing to ensure that sufficient antioxidant remains to protect the product throughout its entire shelf-life and during the proposed in-use period.

The control of antioxidants and antimicrobial preservatives should comply with the requirements identified in the guideline : ICH Topic Q 6 A : Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products : Chemical Substances .

The antimicrobial preservative and antioxidants must be routinely identified and quantified at release.

P.8 Stability

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The maintenance of the physico-chemical properties of the finished product depend on the properties and the stability of the excipients (see note for guidance "Specifications and control tests on the finished product").

For new excipients, stability data should be provided as required for new active substances.

The application should follow the current QWP/CPMP guidelines on the stability of new dosage forms and should ensure that antimicrobial preservative and antioxidants levels are quantified periodically throughout the shelf-life of the finished product. In addition the efficacy of the preservatives should be established using the European Pharmacopoeia test for efficacy of antimicrobial preservation. This should be performed on the finished product at the end of the shelf-life and at the lower preservative limit in the end of shelf-life specification. The former is necessary, even if no evidence of degradation of the antimicrobial preservative and of the antioxidant is observed on storage, as other chemical and physical changes in the finished product may influence the efficacy of the antimicrobial preservative and the antioxidant.

In the case of products presented in multidose containers, the efficacy of the antimicrobial preservative under simulated in-use conditions must be established. The tests should be performed under the same condition as it is expected to be used by the final user. It may also be appropriate to examine the efficacy of the antimicrobial preservative following storage of opened or used containers for the proposed in use shelf-life.

R LABELLING

- Labelling must in accordance with relevant EC directive 2001/83/EC, Note for Guidance : Excipients in the Label and Package leaflet of Medicinal Products for Human Use and CPMP Position Paper on Thiomersal, Implementation of the Warning Statement Relating to Sensitisation (CPMP/2612/99).

However, if a product is presented in a multidose container without a preservative because :

a) it is intended for single use only (e.g. cytotoxic),

b) the product is self-preserving,

c) the product is oils based,

the labelling and product literature should indicate the absence of a preservative. This would not only emphasise the increased risk associated with the use of such products, but also aid the physician to specifically identify a product without preservative.

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ANNEX

EXAMPLES OF REQUIREMENTS CONCERNING DIFFERENT KINDS OF EXCIPIENTS

1. Excipients, which are a single chemical entity, include, for example, organic and inorganic acids and their salts, sugars and alcohols.

   They may have undergone physical treatments, which gave them special technological characteristics (e.g. micronisation).

2. Chemically transformed excipients include excipients which have undergone a special chemical treatment in order to confer certain technological characteristics (e.g. modified starch). The name and quality of such excipients should be defined in such a way as to avoid confusion with an unmodified excipient.

3. Mixtures of chemically related components include, for example, polyol esters (mixture of mono, di and tri esters), hydrogenated glucose syrup, maltitolsyrup. For these products the dossier should specify the following characteristics of the excipient:

   * the nature and content of each component with a statement of its acceptable limits;
   * technological criteria (appropriate criteria to the performance of dosage form);
   * any additives which may be present.

4. Mixed excipients are ready-for-use preparations, for example for direct compression or film coating.

   * The qualitative and quantitative composition of the mixed excipient should be submitted, the specifications of the product as a whole and of each component must be stated.

5. Excipients of natural origin, so called "natural" products have often undergone some kind of chemical treatment. In general and if relevant for the quality control of the product, data should give an outline of the operations carried out to obtain and to purify the product, and any special characteristics: decomposition products, specific impurities, chemical substances used during the treatment with residual limits, methods of sterilisation or decontamination, with a description of the effect of these processes on the excipient (e.g. modification of the physical structure).

6. For biological excipients of animal or human origin, the risk of transmitting adventitious agents should be considered and appropriate documentation submitted (e.g.; method of preparation and control of tissues and body fluids used as starting material). In addition, the name of the manufacturer and site of manufacture should be specified.

7. Flavouring agents (flavours and aromatic substances) are either natural products and/or products obtained by chemical synthesis. Because of the complexity of their composition, it is only necessary to describe the general qualitative composition mentioning the main constituents with an appropriate process of identification to ensure the consistency of the composition (in particular, identification of the main constituents and if necessary carriers).

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Most constituents of artificial flavours have internationally accepted purity criteria in food use (FAO/WHO). Reference to these standards is acceptable for medicinal products.

8. Colouring matters: - Community legislation on colouring matters in medicinal products is applicable.

ANTIOXIDANTS

Antioxidants are used to reduce the oxidation of active substances and excipients in the finished product. Antioxidants should not be used to disguise poorly formulated products or inadequate packaging. The need to include an antioxidant should be explained and fully justified. Oxidative degradation can be accelerated by light and by the presence of mineral or metallic impurities, due to the formation of free radicals.

There are three types of antioxidants :

Type	Definition	Example
True antioxidants	These are thought to block chain reactions by reacting with free radicals	Butylated hydroxytoluene (BHT)
Reducing agents	These have a lower redox potential than the drug or excipient they are protecting	Ascorbic acid
Antioxidants synergists	These enhance the effects of antioxidants	Sodium edetate

The efficacy obtained for an antioxidants depends on its nature, the stage at which it is incorporated within the finished product, the nature of the container and the formulation.

The efficacy of antioxidants must be assessed in the finished product in conditions, which simulate actual use by measuring the extent of degradation in the finished product, with and without the antioxidant.

Antioxidants should only be included in a formulation if it has been proven hat their use cannot be avoided. This applies to cases where the manufacturing process is optimised to minimise the potential for oxidation.

ANTIMICROBIAL PRESERVATIVES

Antimicrobial Preservatives are used to prevent or inhibit the growth of micro-organisms which could present a risk of infection or degradation of the medicinal product. These micro-organisms may proliferate during normal conditions of use of the product by the patient, particularly in multidose preparations.

On no account should preservatives be used as an alternative to Good Manufacturing Practice (GMP).

Preparations at greatest risk of contamination are those which contain water such as solutions, suspensions and emulsions to be taken orally, solution for external use, creams and sterile preparations used repeatedly (e.g. injectable multidose preparations and eye-drops).

The level of efficacy will vary according to the chemical structure of the preservative, its concentration, the physical and chemical characteristics of the medicinal product (especially pH) and the type and level of initial microbial contamination. The design of the pack and the

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temperature at which the product is stored will also affect of activity of any antimicrobial preservatives present.

The antimicrobial efficacy of the preservative in the finished should be assessed during product development, particularly during stability studies and at the end of the proposed shelf-life, using Pharmacopoeia European test.

If products do not contain a preservative and do not have inherent preservative efficacy they must not be packaged in multidose presentations without a sound justification.

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Formulation and delivery issues for monoclonal antibody therapeutics☆

Ann L. Daugherty [a,*], Randall J. Mrsny [b,1]

[a] *Genentech, Inc., 1 DNA Way South San Francisco, CA 94080, USA*
[b] *Center for Drug Delivery/Biology, Welsh School of Pharmacy, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff CF10 3XF, UK*

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Abstract

Antibodies can have exquisite specificity of target recognition and thus generate highly selective outcomes following their systemic administration. While antibodies can have high specificity, the doses required to treat patients, particularly for a chronic condition, are typically large. Fortunately, advances in production and purification capacities have allowed for the exceptionally large amounts of highly purified monoclonal antibodies to be produced. Additionally, genetic engineering of antibodies has provided a stable of antibody-like proteins that can be easier to prepare. Together, these advances have made antibody-based therapies one of the most commonly pursued pharmaceuticals in biotechnology pipelines. With this success, however, has come a series of technical challenges in the formulation of antibody-based materials to maintain sufficient stability in a variety of configurations and sometimes at particularly high concentrations. This review focuses on issues related to identifying and verifying stable antibody-based formulations.
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Keywords: Antibody; Stability; Delivery; Formulation

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* Corresponding author. Tel.: +1 650 225 2198.
E-mail addresses: masi@gene.com (A.L. Daugherty), mrsnyr@cardiff.ac.uk (R.J. Mrsny).
[1] Tel.: +44 29 2087 4159.

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1. Introduction

Therapeutic and diagnostic antibodies have become the fastest growing area of biopharmaceutical applications. There are now 18 monoclonal antibodies on the market and over 100 in clinical trials, which highlights the significance of these therapeutics and the advances made in antibody engineering. Further, by 2008, engineered antibodies are projected to be the source of over a third of the revenues from biotechnology [1,2].

A few seminal events have led to the current and projected prominence of antibodies as biopharmaceuticals include the identification of methods to generate murine monoclonal versions of antibodies [3], the cloning of human antibody sequences to allow for humanization of murine monoclonal antibodies through complementary-determining region (CDR) grafting [4] and even the establishment of fully humanized systems to generate monoclonal antibodies [5]. With the sequential identification of these technological advances, antibodies for therapeutic and prophylactic indications have moved from fully murine, to partially murine (mostly human) to completely human constructions. Added to these events, dramatic advances in production have led to the ability to prepare monoclonal antibodies at scales that can provide sufficient material at costs that make this area appealing to pharmaceutical companies. One important outcome of these various advances is a greater potential to use antibody drugs in chronic settings, tremendously expanding their biopharmaceutical applications.

The majority of currently approved antibody drugs address previously unmet medical needs in the areas of cancer and inflammation. These indications came from practical considerations related to earlier forms of murine and partially murine antibody therapeutics; the first monoclonal to be approved (OKT-3®, muromonab-CD3) was approved in 1986 for a single treatment regimen to protect from life-threatening tissue rejection following kidney transplant [6]. Adverse reactions due to acute immunogenicity problems due to delivery of a non-self protein limited the use of OKT-3® to only acute application [7,8]. Subsequent partially murine antibodies such as Panorex® (17-1A), Zevalin® (ibritumomab tiuxetan) and Bexxar® (tositumomab) were approved for a limited number of administrations to cancer patients who had failed frontline therapies [2]. With the advent of fully humanized antibodies, chronic therapeutic or prophylactic applications for infectious agents have become a realistic clinical option [2]. Another critical aspect to the success of antibodies as therapeutic agents involves improved methods to express, purify and characterize these proteins [9]. In general, antibody therapeutics are

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large (typically >150 kDa), complex in nature (most are glycosylated) and must be administered in stoichiometric rather than catalytic quantities (nearly a gram per dose is required for many antibodies to be effective). Production and purification scales have thus reached levels of production that were previously assumed impossible in biotech companies [10]. Novel concerns then related to the development of stable formulations and delivery strategies for such large amounts of a complex molecule. Understanding product instability with regard to physicochemical and thermodynamic events becomes more and more critical to ensure market success [11]. The required high concentrations of antibodies in these formulations reduced the need to add a carrier protein, as is the case where serum albumin is commonly added in formulations of highly potent proteins such as erythropoietin alpha (Epogen®) and Factor VIII (Kogenate®) to enhance stability and reduce loss to vial surfaces. Simultaneously, the large amounts of an antibody protein used in these formulations allowed degradation products to be more readily detectable particularly when using the highly sensitive methods designed for evaluating hormone biotherapeutics.

Finally, the ability to prepare large quantities of an antibody that could be administered for chronic therapy resulted in a plethora of new and novel applications [9,10] involving the delivery of chemotherapeutics, radionuclides and imaging agents — to name a few. New issues, related to identifying stable formulations such as high concentration formulations that might reduce the volume of antibody administrations, arose in the move from intravenous infusions to the realm of subcutaneous injection strategies. In some cases the combination of agents with antibodies produced conflicting stability profiles. Additionally, potential new indications for antibody drugs increased the desire to find novel methods for sustained release, intracellular targeting [12] or delivery via methods not involving an injection. Thus, as is the case in most scientific advances, technological advances opened up possibilities for therapeutic opportunities that were not possible previously as well as a totally new set of problems that required solving. In this review we have attempted to identify the major issues associated with formulating and delivering antibody drugs, to recognize challenges already identified accompanied when possible by solutions, as well as to discuss concerns that will need to be addressed in the future as the use of antibody drugs continues to evolve.

2. Antibody characteristics relevant for formulation and delivery

The human body produces several classes of antibodies that appear to perform specific functions under different conditions and at discrete anatomic sites. Most of the currently approved antibody-based drugs are of the IgG1 class [13] and are glycosylated on the Fc (fragment crystallizable) domain. Glycosylation has been shown to participate in specific cell response events mediated by antibodies [14–16]: antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cell-mediated cytotoxicity (CDCC) through receptor recognition events. Individual glycoforms of antibodies can provide improved efficacies for certain clinical outcomes [17]. In general, IgG1 and IgG3 antibodies are effective at initiating ADCC while IgG2 readily fixes complement but is poor at inducing ADCC. IgG4 appears to be inefficient at both ADCC and CDCC [13]. Interestingly, antibodies can be re-engineered to increase their capacity to recruit complement [18] or to adjust their affinities to the various classes of Fc receptors and thus ADCC function through mutation of specific amino acids within the Fc domain [19]. Molecular engineering has also provided a spectrum of new antibodies (Fig. 1). Other chapters in this issue delve deeply into the many characteristics of antibodies that make them remarkable and diversely applicable treatment agents: ligand binding properties, effector functions and potential for modification in their design. Other chapters will also address applications of newly engineered antibody-like molecules that move beyond the realm of intact, full-length IgG antibodies. In the current review, attention will be focused primarily on IgG1 since this is where the majority of published information exists for antibody drug formulation and delivery.

Antibodies, due to their large size (being greater than the filtration cut-off size of the kidney) and their ability to be sequestered for periods of time from the blood, via interactions with FcRn receptors present on

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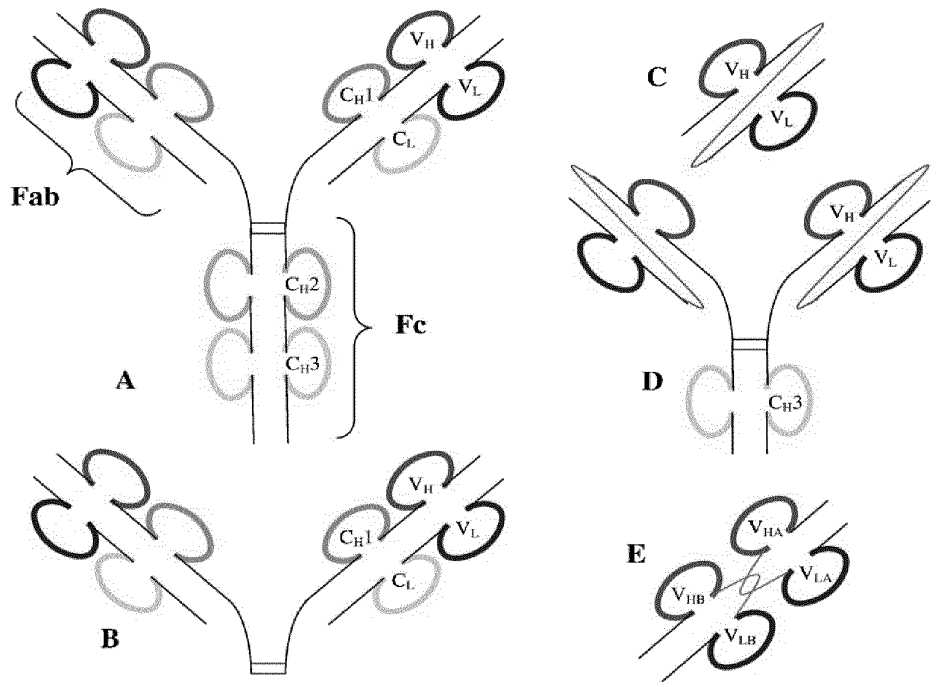

Fig. 1. General antibody structure and some antibody-based protein constructions. A) Human antibodies have a common framework that can be described as Fc (fragment crystallizable) and Fab (fragment antigen binding) domains that are derived from the folded structure of heavy (H) and light (L) chain proteins. Multiple constant (C) regions on both the H and L chain proteins are donated as are the variable (V) segments involved in antigen-specific recognition. B) Removal of the Fc domain produces a F(ab)2 structure. C) Single chain structures of the antigen binding region (scFv) can be prepared by themselves or D) in a construct that includes Fc domain elements. E) Bi-specific antibody elements (diabodies) can be prepared to bring two different antigens into close proximity. C_H, heavy chain constant regions; C_L, light chain constant region; V_H, heavy chain variable region; V_L, light chain variable region.

endothelial cells, can have extended serum profiles in the range of weeks. A number of engineered antibody-like molecules are now being examined for therapeutic applications [20]. Some engineered fragments, such as diabodies and minibodies, are much smaller than intact, full-length IgG1 and have very different properties of systemic distribution and clearance. Additionally, methods to prepare other antibody types such as dimeric secretory IgA [21] and methods to prepare antibodies using non-mammalian cell systems, such as plants [22], from the eggs of chimeric chickens [23] and from transgenic animals [24], are now being explored by academic and industrial groups. As these new approaches gain prominence, more information will be acquired about their unique requirements for successful formulation and delivery. At present, however, there is little information on formulation approaches for antibodies produced using these production processes.

3. General concerns for antibody formulations

Due to their proteinacous nature, antibodies present generic formulation issues that are similar for most protein therapeutics [11]. Proteins, in general, can be degraded under conditions when they are exposed to heat, freezing, light, pH extremes, agitation, sheer-stress, some metals and organic solvents. With ever advancing analytical technologies, the ability to assess the physicochemical and thermodynamic instability of antibody drugs has also led to the identification of several events that are more specific to the unique nature of this particular class of proteins: variations in

Fc glycosylation, partial heavy chain C-terminal Lys processing, Fc methionine oxidation, hinge-region cleavage and glycation of Lys residues [25]. In addition to these issues is the difficulty of preparing dosing materials that might have protein concentrations in the range of 100 mg/ml or greater. Since early preclinical assessment is so critical to successful identification of a new biotherapeutic product, general pre-formulation strategies are usually employed for initial studies with new antibody drugs. An initial formulation effort will likely employ an isotonic, non-hemolytic, slightly acidic solution that can be administered by intravenous infusion or subcutaneous injection in studies employing a relevant animal model. In some cases, some stability information for the antibody drug can be obtained from initial in silico and in vivo testing during this pre-clinical phase that aids in the selection of a formulation that is used in clinical trials [26].

Since most early pre-clinical studies attempt to emulate the delivery strategy that will be used in the clinic, initial studies frequently identify problems with either the initial pre-formulation approach and/or stability issues with the antibody drug itself. In the case of the formulation, protein precipitation can occur with refrigerated storage or with repeated freeze–thaw cycles; events that may be facilitated by an inappropriate pH or buffer selection. Analysis of antibody drugs stored in this initial pre-formulation system may also identify unstable sites within the protein or its linkage to attached molecules (chemotherapeutics, imagining agents, etc.). In the case of the antibody, this information is frequently evaluated to determine if re-engineering of the protein could be performed, for example, to provide greater thermodynamic stability or folding efficiency [27]. Such changes in the Fc region are typically conservative, but might act to modify Fc receptor binding properties to provide a different biological outcome [28,29]. Amino acid substitutions can also be made within the Fv region to improve thermal stability [30], but such changes might also alter antigen binding specificity [31].

4. Stability issues for antibody formulations

If one examines the amino acid sequences for currently approved IgG1-based antibody drugs, it becomes quite clear that only a small segment of these proteins are dramatically different from one another, being the Fv segments that are involved in antigen binding. It should be pointed out, however, that there are some minor differences in conserved regions as well. A priori, one might assume that by finding a stable formulation for one of these antibody drugs, that such a formulation would be good for most if not all, similar antibodies. If this were borne out by experience, there would be no need for a review such as this. Instead, each antibody seems to have a unique personality related to its requirements for stability; a phenomenon derived from the fact that the small differences between these antibodies are focused on surface-exposed amino acid differences that stipulate antigen specificity. Thus, the interfacial surface of each antibody drug is unique and thus requires specific formulation components to provide maximal stability and retention of activity.

Probably the most important aspect of identifying a successful antibody drug formulation is in the identification of truly detrimental alterations rather than all of the modifications that might occur. Although, from a regulatory standpoint, it may be beneficial to understand all of the potential degradation events associated with an antibody formulation, it is the recognition of a stability-indicating parameter (or several parameters) that allows the formulation scientist to focus in on what is critical to development of a successful product. Here, a series of physicochemical and bioanalytical assays can be used to identify these parameters [32]. Although in vivo bioassays may ultimately be required to validate a stability-indicating formulation parameter, the most critical tools at the disposal of the formulation scientist are rapid and reproducible assays to measure protein changes due to oxidation, deamidation, aggregation, fragmentation and other forms of chemical modification that could lead to a loss of function of the antibody drug.

4.1. Oxidation

Methionine and cysteine residues are frequently a site of oxidation in protein drugs and this is also the case for antibody drugs [33]. In the case of antibody-based drugs, specific methionine residues within the Fc domain may be prone to oxidation, resulting in the

production of methionine sulfoxide [25]. While cysteines are present in the Fc framework as disulfide pairs, unpaired cysteines in the variable region may also be sites of oxidation. Besides methionine and cysteine residues, oxidation of histidine, tyrosine, tryptophan and phenylalanine residues can also occur [34]. A number of methods can be used to monitor oxidation of amino acid residues. As a starting point, the number of reactive protein thiols can be monitored using reagents such as 5,5′-dithionitrobenzoic acid or iodoacethyl dansylcadaverine [35], providing a simple readout on the number of protein thiols per protein. Total amino acid analysis can also be used to monitor reductions in methionine, tyrosine and phenylalanine residues. Tryptic digestion and peptide separation by liquid chromatography followed by mass spectroscopy analysis (LC-MS) can be used to identify specific sites of amino acid oxidation.

A careful study of methionine oxidation has been performed for the humanized monoclonal antibody that recognizes the her2/neu gene product. For this protein it was determined that a methionine at position 255 in at heavy chain of the Fc region was the primary site of oxidation and that a methionine at position 431 could also oxidize under more aggressive conditions. In this study, a chromatography assay was used to detect oxidation events following papain digestion to separate Fab and Fc segments of the antibody [36]. Another study on the stability of this same protein provides a valuable template for dealing with antibody oxidation: identification of a critical oxidation event, validation of a robust assay for monitoring that event and comparison of formulation parameters to determine conditions that facilitate oxidation. Addition of antioxidants or stoichiometric levels of free methionine or thiosulfate were found to reduce the extent of oxidation in formulations of this antibody [37].

Issues associated with administration of oxidized forms of an antibody may extend beyond concerns of reduced efficacy. Systemic lupus erythematosus (SLE) is a disease characterized by the induction of anti-double-stranded DNA antibodies. Studies have shown that increased levels of markers of protein oxidation, including those of methionine sulfoxide and 3-nitrotyrosine, correlated with SLE disease activity [38]. Additionally, oxidative modifications of antibodies isolated from synovial fluid samples collected from patients with rheumatoid arthritis suggested alteration of histidine, methionine, tyrosine and cysteine residues [39]. While no direct causal association is shown or implied, these observations bring attention to the issue that we do not fully understand the clinical impact of antibody oxidation events.

4.2. Deamidation

Glutamine and asparagine residues show a propensity for deamidation [40]. Both light and heavy chains of antibodies can undergo deamidation of these amino acids [41] and deamidation events are considered to be one of the major sources of charge heterogeneity of monoclonal antibodies [42]. Deamidation events appear to be highly selective events for individual antibodies. For example, analysis of several monoclonal antibodies that bind the her2/neu gene product demonstrated asparagine 30 deamidation on one or both light chains and asparagine 55 on the heavy chain [43]. Deamidation events lead to more acidic forms of the antibody through the acquisition of additional carboxylic acid groups. Conversely, aspartic acid residues can also undergo modification to a succinimide moiety that results in a basic antibody isoform of the antibody by removal of a carboxylic acid group [43]. In general, deamidation events appear to be relatively slow but are accelerated by unfolding of the antibody [44]. Initial detection of deamidation in antibody preparations is typically identified by differences in charge distribution or content using methods such as isoelectric focusing (IEF) or high-performance cation-exchange chromatography [43].

High performance chromatography can then be used to separate succinimide, isoaspartic and aspartic acid isoforms of tryptic digest fragments of the antibody which can be unambiguously characterized by tandem mass spectroscopy (MS). Correlation between tryptic digest tandem MS results and some other more readily accessible method, such as IEF, can provide a rapid format to follow antibody deamidation events. Using these techniques, asparagine deamidation events residues appears to occur more frequently than glutamine deamidation and specific asparagine residues appear to be selectively targeted for this event [33]. Deamidation of asparagine is frequently associated with rearrangement

events that lead to the formation of isoaspartic acid [42] and this outcome is correlated to amino acids adjacent to the asparagine prone for deamidation [44] that provide a method for prediction of potential deamidation sites (BOX). In particular, asparagine–glycine sequences can demonstrate accelerated deamidation rates since glycine residues lack a side-chain structure that would otherwise act to decreased conformation interference for backbone-associated isoaspartyl formation [45].

Box 1

Amino acid* sequences predicted to deamidate
SNG, LNG, LNN and ENN
(Note these have a following amino acid of G or N)
and those that are less prone to deamidation
GNT, GNS, GNV, TNY, SNY, SNF, SNT, SNK, SNL,
WNS, WNS, FNW, FNS, FNR HNA, HNH, LNW,
CNV, NNF, DNA, and YNP
*standard single amino acid letter nomenclature.

Non-enzymatic parameters of asparagine and glutamine deamidation in proteins have been defined in detail for factors such as pH, temperature and ionic strength [46,47]. The primary sequence dependence of these deamidation events can be explained by a simple steric and catalytic model [46,47]. Prediction of deamidation events based upon three-dimensional structures have also been described but the data set for these studies is not yet sufficient to produce a general model [48]. That asparagine and glutamine deamidation appear to be a constant phenomenon of proteins and correlate with their turnover provides the basis for the hypothesis that the presence and distribution of these amino acids within a protein can act as a molecular clock for its biological turnover [49,50]. For the formulation scientist, empiric assessment of factors such as pH and ionic strength provide the best strategy to identify a formulation that minimizes deamidation events. In general, deamidation does not result in a decrease in potency and deamidation may be hard to detect as the charge difference is small. At times, however, there can be a detrimental effect on potency through the introduction of an unfavorable negative charge that can have further ramification on biological function, particularly when deamidation occurs in the binding regions [51]. As particularly reactive residues are identified, it may be possible to have the antibody engineered to remove the problematic amino acid or to change adjacent residues to reduce its reactivity.

4.3. Aggregation

Liquid formulations of protein therapeutics frequently exhibit a decrease in concentration due to adsorptivity to container walls at low concentration and can show aggregation events at high concentrations. Initial preparations of antibody drugs were administered in acute situations by IV infusion that could allow for medium protein concentration (1–10 mg/ml) formulations not dramatically affected by adherence or aggregation losses. As antibody-based drugs became more widely used in chronic care, high concentration formulations that would allow for clinically acceptable SC injection volumes became desirable and aggregation became an important concern for designing formulations. Along with aggregation events, protein solutions at concentrations >50 mg/ml may become sufficiently viscous as to no longer readily pass through the gauge of a needle that would be comfortable for patients' use. Some antibodies demonstrate high concentration viscosity issues while others do not. For example, the anti-respiratory syncytial viral antibody Synagis® is formulated at 100 mg/ml protein and is administered successfully by IM injection. Thus, addressing viscosity, adsorptive loss and aggregation in any specific antibody formulation will likely be performed on a case-by-case basis.

As protein–protein contact frequency increases at high concentrations, the opportunity for stable aggregate formation increases proportionally. Proteins are folded in such a way as to internalize hydrophobic domains and surface-expose more hydrophilic domains in a thermodynamically stable situation. As folded proteins undergo normal molecular motion transient surface exposure of hydrophobic domains can lead to protein–protein contacts that hide these

surfaces in a more energetically favorable manner. The outcome of these events is the stabilization of these protein–protein contacts with the ultimate outcome of dimerization, trimerization and so on — leading to extended aggregation events [52]. As protein concentration and temperature goes up, so does the probability of energetically favorable contacts leading to aggregation with increased frequency and duration of reversible protein–protein contacts leading to a greater extent of stable (even irreversible) aggregation events. Aggregation (covalent, non-covalent, dissociable, non-dissociable) must be considered a likely degradation event for high concentration antibody formulations.

For some antibodies reduced temperatures can incite reversible self-associations; these molecules are known as cryoimmunoglobulins [53]. IgG3 cryoimmunoglobulins have been shown to self-associate through sugar structures of the Fc domain [54]. Self-association events involving IgG1 antibodies seem to occur primarily through weak ionic and hydrophobic interactions [55]. More recent studies have examined kinetic and thermodynamic aspects of antibody solution dimerization using a recombinant human monoclonal antibody that recognizes vascular endothelial growth factor (rhMab-VEGF) as a model [56]. It was found that for this IgG1 class antibody, aggregation rates were greater in slightly alkaline (pH 7.5–8.5) compared to slightly acidic (pH 6.5–7.5) conditions. A high salt environment (1 M NaCl) also enhanced dimerization. Not surprisingly, self-association events were accelerated as the storage temperature was increased. One of the most striking aspects of these dimerization studies on rhMab-VEGF is that trastuzumab, another genetically engineered antibody with the same IgG1 framework and a 92% sequence homology with rhMab-VEGF, fails to demonstrate aggregation events under the same conditions.

A number of additives have been identified that can reduce the rate of protein aggregation [52,57]. A rather wide spectrum of agents can reduce protein aggregation rates: urea, guanidinium chloride, amino acids (in particular glycine and arginine), various sugars, polyalcohols, polymers (including polyethylene glycol and dextrans), surfactants and even antibodies themselves. Studies have shown that different proteins benefit from different types of anti-aggregating factors, consistent with the notion that the interfacial surfaces that drive interactions leading to aggregation are protein-specific. Conceptually, anti-aggregating agents might fall into one of two categories: small agents that fit into channels or grooves and large agents that might interact with lower-curvature surfaces of the protein. In essence, the small agents would act to stabilize a protein from acquiring a conformation that might be more reactive toward aggregation while a large agent might act to reduce the frequency of surface contacts that lead to an aggregation event. In the case of antibody formulation, either or both may be important. As we will discuss, agents found to effectively protect an antibody from aggregation may differ for various stress conditions; antibodies in solution that are undergoing agitation and thermal stress may differ from those of the same antibody as it undergoes lyophilization and reconstitution.

Protection from aggregation can be limited in antibody formulations by the addition of surface-active agents such as detergents, both charged and uncharged. As an interesting aside, such surface-active agents can help reduce protein loss due to adherence to surfaces that can occur with low concentration protein formulations. Polysorbate 20 and 80 (now available from a vegetal source) are examples of detergents that are widely used to reduce the rate of protein aggregation in high concentration antibody drug formulations. A precautionary note must be sounded, however, as detergents perform this function optimally at low concentrations (0.01% to 0.05%) and can act detrimentally to participate in protein unfolding at higher concentrations, e.g., 1%.

That antibody aggregation can be accelerated by several physical conditions provides the potential for multiple methods to determine if a particular antibody drug is prone to aggregation and to rapidly test formulations for their ability to impede aggregation. Agitation studies are done, in addition to thermal stability studies, to determine if aggregation can occur in a given formulation. Different test methods are used, employing a shaker or a stirring apparatus. In one study done on an IgG1 antibody found sizes of aggregates produced by the two methods were comparable [58]. They concluded that a higher throughput test could be constructed using stirring analyzed by absorbance measurement. In their work,

the stirred samples exhibited much higher absorbance and second particle species in DLS, indicating that stirring stress produces a higher amount of smaller protein aggregates. While Mahler found polysorbate 80 protects against aggregation, the stirred samples had an increase in turbidity and more aggregate products were detected by DLS as compared to a surfactant-free formulation. Polysorbate 80 stabilizes small aggregates and prevents further progress in the aggregation process.

4.4. Fragmentation

Intact, full-length antibodies are composed of several segments that have natural flexure sites. One site, in particular, exists at the flexure point between the Fc and Fv domain. Cleavage at this hinge region is a common concern when assessing antibody drug stability [25]. Molecular sizing methods such as sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) and size-exclusion high performance liquid chromatography (SE-HPLC) can be used to rapidly identify fragmentation events in antibody drugs [59]. Fragmentation of full-length antibody drugs is a common occurrence and invariably affects their function. In general, cleaved forms are present in such low amounts that it is likely that little change in efficacy would be seen [60]. At the very least, the antibody drug may have some small reduction in efficacy following fragmentation or may be more prone to proteases, degradation and clearance events that would limit the duration of its efficacy. At the worst, a fragmented antibody preparation may result in a different biodistribution and thus a different safety profile. This can be of particular concern if the antibody is being used to delivery a cytotoxic chemotherapeutic agent. Fortunately, the extent of fragmentation in an antibody can be easily limited in the formulated product.

5. Strategies to stabilize antibody formulations

While liquid antibody formulations are less expensive, faster to develop and generally easier to prepare for administration than alternative formulation approaches, liquid antibody formulations are prone to oxidation, deamidation, aggregation and fragmentation as discussed above. In each of these events, water is the common culprit: water mediates electron transfer during oxidation and deamidation events and its required addition across a peptide bond can be a critical step in fragmentation. The thermodynamic stresses that lead to protein aggregation are caused by hydrophobic protein surfaces being exposed to water and trying to find a lower energy state by non-native protein–protein interactions. Thus, water is a big problem for stabilizing antibody-based drugs. Lyophilization or introduction into hydrophobic polymer systems can reduce the impact of water on antibody drug formulations.

5.1. Lyophilization

Although some antibodies have demonstrated a propensity to undergo precipitation as they are cooled from 37 °C [53], antibodies are typically robust to freeze/thaw cycles [61]. Early studies reported that antibodies were stable to the freeze-drying (lyophilization) process in the absence of excipients that function as cryoprotectants [62], however, with the technical advancement of certain analytical methodologies, became evident that antibodies are generally damaged in some way as a result of lyophilization as demonstrated by extensive formation of insoluble aggregates [61]. More recently, studies have shown that freeze-drying antibodies to a specific percent of residual water (usually between 1 and 8%) allows for optimal stabilization in the dry state and stability during reconstitution [63]. Higher moisture content in lyophilized antibody preparations correlates with increased aggregation (as seen by SEC) and asparagine deamidation and isomerization (as measured by HIC). Studies have also been performed to identify optimized lyophilization schedules where the secondary drying phase is performed at an elevated temperature [64]. This technique allows the lyophylized cake to achieve optimum moisture content, allowing the final product to be conformationally stable (as measured by DSC) during extended storage. Solid-state structural studies can be used to monitor conformational changes and aggregation events during the storage of a lyophilized monoclonal antibody preparation [65]. Improved native-like structure and a reduction in aggregation can be obtained by incorporation of a carbohydrate excipient in sufficient

quantities to fulfill the hydrogen bonding requirements on the protein surface, suggesting a critical role for non-water molecules to act as placeholders for water molecules during drying and in the dry state. That the addition of excess carbohydrate failed to improve the stabilizing function of this excipient, reaffirms the conclusion that antibodies have a limited number of sites that must be protected in this fashion [65]. A variety of carbohydrates or polyol compounds such as sucrose, trehalose and mannitol have been shown to provide this stabilizing function [66,67].

The rate of rehydration when water is reintroduced during reconstitution of lyophilized formulations is a critical parameter. As water is removed during the different drying stages of the lyophilization cycle and replaced by a shell of non-water excipients, the antibody drug can undergo structural modifications that result in a non-native conformation as may be seen by differential scanning calorimetry [63]. If the rate of rehydration is sufficiently slow to allow recovery of native conformation as water replaces non-water excipient molecules, reconstitution will typically provide a satisfactory outcome for the antibody. If, however, the antibody does not have sufficient time or capacity to recover its native state during reconstitution, extensive aggregation can result. Efforts to protect monoclonal antibodies from the rigors of freeze-drying and reconstitution have been aided by a number of analytical methods that can examine protein modifications. In the solid state, circular dichroism (CD) and Fourier transform infrared (FTIR) spectroscopy may be used to evaluate the protein; after reconstitution in the liquid phase, SEC or SDS-PAGE have been utilized to gather information from lyophilization studies [68,69]. A microscopic apparatus to visually monitor freeze-drying events has even been described [70]. Excipients that have been reported to slow the reconstitution rate and thereby preventing such changes in the rehydrated antibody are glycerol [71,72] and polymeric materials such as polyethylene glycol [73].

Pharmaceutical scientists frequently use increased temperatures for accelerated formulation stability studies. Although such studies can be used to assess formulation parameters such as pH and ionic strength, antibodies lyophilized in the presence of a cryoprotective sugar excipient provide a more complicated picture. Lyophilized amorphous solids composed of a monoclonal antibody and a sugar cryoprotectant material such as sucrose or trehalose form glassy structures, liquids that are too viscous to flow. That antibody-excipient complexes exhibit a glass transition temperature (Tg) provides the basis for observations showing that these materials have unique properties above and below this value. Thus, in predicting shelf life in accelerated degradation studies, it is important to use testing temperatures that do not exceed the Tg threshold of the complex [67]. In general, lyophilized formulations containing trehalose may likely show less tendency toward antibody aggregation than those with sucrose, since trehalose preparations have a higher Tg [67]. With this in mind, a promising approach to assess secondary structural parameters in evaluating antibody formulation stability is the use of amide I band Raman spectroscopy. This method demonstrates a good correlation between structural protein perturbations immediately after lyophilization and the rate of aggregation during long-term storage under accelerated conditions [74].

5.2. Polymer delivery systems

Removal of water from antibody preparations, either by lyophilization or spray freeze-drying, provides a provides a starting point for incorporation of this dried material into a hydrophobic polymer matrix such as polylactide-co-glycolide (PLGA) that can be made into microspheres generated through a solid-in-oil-in-water (S/O/W) encapsulation process [75]. Although both mannitol and trehalose can stabilize human IgG during spray freeze-drying, the double-emulsion solvent evaporation method used to load spray freeze-dried human IgG into PLGA microspheres has been shown to produce extensive antibody aggregation [75]. Such an outcome is likely the result of thermodynamic stress experienced at the water/organic solvent interface and a variety of process methods and excipients can be use to minimize this concern [76].

One feature of PLGA microparticle preparations is their recognition by immune elements and their capacity to stimulate immunization against incorporated proteins [77–79]. While this has clear advantages for vaccines, it poses a serious concern for therapeutic protein delivery. Hydrophobic microparticles have been reported to incite local inflammation

at subcutaneous injection sites [80], events that may be partially mediated through macrophage recruitment [81]. Not only is the potential for antibody formation increased with local inflammation, the resulting injection site reaction may be clinically unacceptable.

In spite of some serious caveats, polymeric microspheres and delivery systems can be successful antibody formulations if administered to the appropriate sites, using certain types of polymers or preparing microspheres or polymeric formulations by methods that are more protective of the antibody. An example of a certain delivery site that may have less proclivity towards an inflammatory response is reported, where PLGA microspheres loaded with an anti-VEGF antibody were injected into the intravitreal humor of the eye, an immune-privileged site, for the treatment of age related macular degeneration (AMD) [82]. Resorbable polymers that show less potential to incite inflammation, e.g., have smoother surface characteristics, might be used to deliver antibodies in a sustained manner. Direct, local delivery of antibodies using carboxymethylcellulose aqueous gels can be an effective post-surgical anti-infective strategy [83]. Antibodies covalently coupled to a biodegradable hyaluronic acid hydrogel through a labile hydrazone linkage have been used for the sustained delivery of antibodies to sites within the central nervous system [84]. Introduction of dry powder IgG into ethylene–vinyl acetate copolymer (EVAc) has also been examined as a potential polymer-based antibody delivery system [85]. Similar to PLGA systems, EVAc microspheres can extend the time course of IgG release. This property makes polymers loaded with antibodies interesting opportunities for injectable sustained release delivery formats but also for topical application at mucosal surfaces. For example, long-term vaginal delivery of an antibody can be achieved in a mouse model using polymer vaginal rings [86,87]. Formulations of a biomedical grade polyurethane hydrogel with an antibody coating have also been prepared and shown to release bioactive protein [88]. It is important to note that one complicating aspect of many of these approaches is the requirement of a polymer solubilization step using a solvent, such as methylene chloride or isopropanol, which can compromise protein drug stability. Sustained release formulation approaches such as microspheres prepared using water, such as the PROMAXX microspheres (Epic Therapeutics) or crystallization of proteins [89] can bypass the use of solvents that are incompatible with proteins and antibodies.

6. Formulation issues for alternative forms of antibody delivery

To date, antibody development has focused primarily on injectable routes of administration: intravenous (IV), intramuscular (IM) and subcutaneous (SC). A long history of IV antibody infusions exists [90] and the advantages are clear for antibody-based drugs that are used in cancer treatments in order to reach tumor sites that may be diffuse or not otherwise accessible. In fact, the majority of the approved antibody-based drugs are administered by IV infusion (Table 1) with the total dose administered approaching one gram of protein per treatment in some cases. For many antibody-based therapies a critical safety concern involves the onset of acute or delayed systemic reactions following infusion [91,92]. Parameters and characteristics of the "infusion reaction" as well as treatment protocols have been well described with acute events commonly occurring within 10 min to 4 h and delayed events occurring 24 h to 4 days post dosing [93]. Although formation of antibodies to the administered antibody drug appear to be a risk factor for infusion reaction events [94], infusion reactions can occur following the initial exposure [93] and these reactions do not appear to be due to IgE responses or mast cell activation [95]. Most importantly for the patient, there appear to be treatment protocols to provide re-treatment of patients even after an infusion reaction event [93] with concomitant administration of immunomodulation molecules [94]. There are many unanswered questions about the mechanism and prevention of adverse infusion reaction events associated with IV infusion of antibody drugs. Certainly, one method is to explore IM and SC delivery when possible, although these delivery approaches may also have confounding aspects of tissue response and volume limitations.

Other routes are also amenable to antibody delivery. The increased number of antibody therapeutics on the market and the greater exploration of non-life threatening indications being treated by antibodies, drive efforts to deliver these agents by routes other than IV

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Table 1
Formulations of approved products

Antibody product; company	Generic name; description	Delivery route	Formulation concentration	Buffer components; pH[a]	*Excipients*
Othroclone OKT3®; J & J-Ortho Biotech	Muromonab-CD3; Murine IgG2a, anti-CD3	IV	1 mg/ml	Na,K phosphate; pH 7	NaCl, polysorbate 80
Reopro®; Centocor-Lilly	Abciximab; Chimeric IgG1, anti-GPIIb/IIIa, Fab	IV	2 mg/ml	Na phosphate; pH 7.2	NaCl, polysorbate 80
Rituxan®; Idec-Genentech	Rituximab; Chimeric IgG1, anti-CD20	IV	10 mg/ml	Na citrate; pH 6.5	NaCl, polysorbate 80
Zenapax®; Roche	Daclizimab; Humanized IgG1, anti-CD25	IV	5 mg/ml	Na phosphate; pH 6.9	NaCl, polysorbate 80
Simulect; Novartis[b]	Basilixamab; Chimeric IgG, anti-CD25	IV	4 mg/ml	Na,K phosphate, glycine	NaCl, sucrose, mannitol, polysorbate 80
Synagis®; MedImmune[b]	Palivizumab; Humanized IgG1, anti-RSV	IM	100 mg/ml	Histidine, glycine	Mannitol
Remicade®; Centocor[b]	Infliximab; Chimeric IgG1, anti-TNFα	IV	10 mg/ml	Na phosphate; pH 7.2	Sucrose, polysorbate 80
Herceptin®; Genectech[b]	Trastuzumab; Humanized IgG1, anti-HER2	IV	21 mg/ml	Histidine; pH 6	Trehalose, polysorbate 20, benzyl alcohol[c]
Mylotarg®; Wyeth[b]	Gemtuzumab ozogamicin; Humanized IgG4, anti-CD33, immunotoxin	IV	4 mg/ml	Na phosphate	NaCl, sucrose, dextran 40
Campath®-1H; Millennium-ILEX	Alemtuzumab; Humanized IgG1, anti-CD52	IV	Unclear — 30 mg /vial	Na,K-phosphate pH 7	NaCl, KCl, NaEDTA, polysorbate 80
Zevalin®; Biogen Idec	Ibritumomab tiuxetan; Murine IgG1, anti-CD20; radiolabeled (^{90}Y or ^{111}In)	IV[d]	1.6 mg/ml	Na Acetate, Na, K-phosphate pH 7	NaCl, human albumin
Humira®; Abbott	Adalimumab; Human IgG1, anti-TNFα	IV	50 mg/ml	Na phosphate, Na Citrate; pH 5.2	Mannitol, polysorbate 80
Xolair®; Genentech[b]	Omalizumab; Humanized IgG1, anti-IgE	SC	125 mg/ml	Histidine	Sucrose, polysorbate 20
Bexxar®; Corixam-GSK	Tositumomab-I131; Murine IgG2a, anti-CD20, radiolabeled (^{131}I)	IV	14 mg/ml	Na phosphate; pH 7.2	NaCl, maltose
Raptiva®; Genentech	Efalizumab; Humanized IgG1, anti-CD11a	SC	100 mg/ml	Histidine; pH 6.2	Sucrose, polysorbate 20
Erbitux®; Imclone Systems	Cetuximab; Chimeric IgG1, anti-EGFR	IV	2 mg/ml	Na phosphate; pH 7.2	NaCl
Avasatin®; Genentech	Bevacizumab; Humanized IgG1, anti-VEGF	IV	25 mg/ml	Na phosphate; pH 6.4	Trehalose, polysorbate 20
Tysabri; Biogen Idec	Natalizumab; Humanized IgG4, anti-4α-integrin	IV	20 g/ml	Na phosphate; pH 6.1	NaCl; polysorbate 80

Ordered by approval dates in the US.
Abbreviations: RSV=respiratory syncytial virus; TNFα=tumor necrosis factor alpha; EGFR=epidermal growth factor receptor; VEGF=vascular endothelial growth factor; NaEDTA=sodium edentate.
[a] Some lyophilized formulations do not stipulate a pH (or range) following reconstitution.
[b] Lyophlized product, concentration, pH, etc. values are obtained after reconstitution.
[c] Added as a preservative to generate a multi-dose vial configuration.
[d] Kit where components are mixed just prior to administation.

infusion. These routes may be more effective, less invasive, provide easier delivery, permit self-administration and thereby be more convenient and possibly have lower costs if less active agent can be used, as in the case where the alternate route of administration delivers the therapeutic agent to the intended site directly. Interestingly, some studies have suggested that antibodies administered by IV infusion are more

susceptible to proteolysis than via IM injection [59] and sucrose-stabilized immunoglobulins have been associated with acute renal failure following IV infusion [96]. The antibody used to protect neonates from respiratory syncytial viral (RSV) infection (Synagis®) is one example of an antibody administered by IM injection. For reasons discussed above, the majority of antibody-based drugs have moved toward SC delivery with formulations efforts being focused to this end. Based upon the desired actions for a number of antibody-based drugs, however, routes of administration other than IV, IM or SC may be desirable. These alternative routes can provide unique formulation and stability issues.

6.1. Oral

Uptake of antibodies from the intestinal lumen can occur through fetal Fc receptors (FcRn) expressed at the apical surface of enterocytes [97]. This natural antibody uptake mechanism was initially identified in the gastrointestinal (GI) tract of neonatal rodents and its expression shown to vanish following "closure" of the intestine after weaning. It was only recently that the continued expression of this receptor in the adult intestine was demonstrated and this finding has prompted efforts to examine this receptor system as a means of delivery antibodies after oral administration. Although this pathway appears to be a viable route for the delivery of therapeutic antibodies, issues associated with antibody stability in the GI tract [98] and competition from endogenous antibodies can dramatically reduce the efficiency of uptake after oral delivery. Outside of this specific mechanism, no other transcellular mechanism of efficient antibody transport across epithelial cell of the GI tract has been demonstrated to date. Topical application of antibodies to produce a desired clinical outcome have been shown, however, with the oral delivery of a chicken-derived (IgY) antibodies for treating and preventing infectious diseases of the GI tract [98–100]. It should be noted that IgY antibodies have been shown to not bind to (or be transported by) FcRn [97].

6.2. Respiratory tract

Intranasal and pulmonary administration of protein therapeutics has shown more promising clinical outcomes than oral delivery. While the surfaces of both the respiratory tract and the gastrointestinal tracts are readily accessible, the respiratory tract is a far less hostile environment for an administered protein therapeutic. Nonetheless there are physical clearance mechanisms in place to remove foreign particles which act to reduce residence time dramatically following administration. In the case of nasal administration the use of a cream emulsion and a polymer delivery system has been shown to significantly decrease the clearance rate for a monoclonal antibody when applied to the nasal mucosa [101]. This study provides one approach for the topical application of a therapeutic antibody designed to provide clinical benefit at the mucosal surface. It does not, however, suggest that an appreciable amount of an antibody might be absorbed into the systemic circulation from this site. The nasal mucosa affords only a small absorptive surface area compared to the epithelial linings of the lung.

Aerosol delivery of antibodies to the lung has been explored as either a liquid or dry powder formulation, where in both cases the droplets or particles must be of sufficiently small size that they are respirable perhaps to the level of the deep lung but large enough that they are not readily exhaled or just impact the back of the throat [102]. The sizes of particles that provide this performance have a mass mean aerodynamic diameter and density such that they enter the alveoli and remain in the lung. This size window has been reported to be between 1 to 5 μm depending on the formulation used and in one case, far larger, 20 μm where the particles are dense (<0.4 g/cm^3) and highly porous [102].

Formulation efforts were made for producing fine dry powder particles of an anti-IgE monoclonal antibody (E25) in the size range desired for delivery to the lung [103]. These studies showed that sodium phosphate was capable of extending the usefulness of mannitol as a protective excipient in spray-dried antibody formulations and that mannitol can play a role both in maintaining protein stability as well as producing a suitable aerosol preparation. Further studies to assess carbohydrate excipients for spray-dried aerosol E25 formulations showed that excipient to protein ratios were critical. Degradation issues involved not only protein aggregation but also protein glycation or lactosylation, a protein modification

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event where a reducing sugar can add covalently at a free amine [104]. The ability to formulate and delivery an antibody-based drug to the lung provides the potential for systemic delivery of that protein via uptake through the FcRn expressed at this mucosal surface. Elegant studies showing the distribution and function as well as the application of this transport route for systemic deliver of an Fc-containing protein chimera has been demonstrated [105,106]. Thus, the potential or systemic delivery of antibody-based drugs via the respiratory tract looks promising.

6.3. Miscellaneous delivery sites of the body

Unique aspects of antibody–polymer formulations designed for intravitreal injection [82] or topical vaginal delivery [86,87] have been discussed above. Additionally, antibody formulations using hyaluronic acid hydrogels for sustained brain delivery have been noted [84]. These methods focus on strategies to administer large amounts of an antibody at a specific site in order to provide a sustained level to improve efficacy and/or to minimize injection frequency. Other strategies have been described to deliver antibodies to miscellaneous sites throughout the body, For example, an anti-transferrin antibody (OX-26) has been described as a carrier for delivery of covalently attached therapeutic molecules across the blood–brain barrier following IV injection [107]. An anti-tumor necrosis factor antibody has been adsorbed onto cardiovascular stent wires for local neutralization of this cytokine in order to limit restenosis events following stent placement [108]. A CMC gel containing antibodies to prevent post-surgical infections has been administered to the intraperitoneal cavity [83].

6.4. Intracellular targeting

Some promising antibody drug targets are intracellular. Although techniques exist where a cell can synthesize an antibody and secrete it into the cell cytoplasm, successful use of this technology requires gene therapy. Instead, it is possible to chemically couple an antibody to a pH-sensitive polymer that functioned to disrupt membranes at acidic pH. Many antibodies are internalized by cells through a receptor-mediated uptake process that leads to their delivery into early and then late endosomes. During endosomal maturation after receptor–antibody internalization the pH of these vesicles will drop from near neutral to below pH 6. This approach was demonstrated in a format where the pH-responsive polymer poly(propylacrylic acid) was covalently attached to a monoclonal antibody to facilitate its delivery to the cytoplasm of target cells [12].

7. Other delivery issues

A wide range of novel drugs and drug conjugates are being developed using monoclonal antibodies and engineered antibody fragments [20]. For some of these novel therapeutic approaches to be successful, they require additional or non-traditional delivery strategies. A cursory discussion of some of these approaches as they relate to intracellular targeting, site placement and engineered antibodies fragments follows.

7.1. Antibody fragments

An entire spectrum of antibody fragments have been identified through protein engineering studies with many of these showing remarkable potential for unique and novel clinical opportunities [109]. These smaller recombinant antibody fragments, the monovalent antibody fragments, Fab and single chain Fv and the engineered variants, diabodies, triabodies, minibodies and single-domain antibodies are an emerging form of antibody therapy that are less costly to manufacture while still retaining the targeting specificity of full length antibodies. In fact some may have greater efficacy and more applications than whole monoclonal antibodies. It may be anticipated that this new subset of antibodies are posing new formulation challenges, however, to date, publications detailing stability studies and formulation development for these molecules are rare in the scientific literature so formulation data on antibody fragments is scant. The single V domains have been found to be poorly soluble and have a tendency to aggregate [109], but these problems are being overcome by the identification of mutants that minimize the hydrophobic interface and selected by phage display [110]. Five Fab molecules have been approved as of this writing with the one humanized

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Fab (ranibizumab rhFab) awaiting approval in the very near future, but many are in early clinical trials and most in preclinical development. One study has been described that focused on Fab fragments. In general, the binding of an antibody to an effector protein does not necessarily inactivate that target's function [111]. When an antibody is effectively inactivating, however, the Fab fragments in the absence of an Fc domain can frequently function as highly potent binding agents capable of masking binding sites or enzymatic elements on macromolecules. For example, Fab fragments prepared from sheep anti-snake venom antibodies (Digibind, from GSK) can be an effective anti-venom. Storage of liquid formulations of such anti-venoms in sub-tropical countries where refrigeration may not be possible provides a significant formulation challenge. Although lyophilized products can perform well under these conditions, a pH 4.0 (acetate buffer) formulation was found to also be stable and potent for at least one year at room temperature [112], presumably room temperatures characteristic of the tropical and subtropical regions where the material would be used. Strikingly, this stable formulation did not require the presence of a protective carbohydrate excipient. To improve drug delivery, antibody fragments have been fused to many types of molecules, such as radionuclides, cytotoxic drugs, toxins, peptides and proteins, enzymes and liposomes [113]. An immunoliposome made with a Mab fragment is reported to deliver drugs to the brain as such a molecule is able to cross the formidable barrier of the blood brain barrier [114].

7.2. Immunoconjugates

Arming antibodies with materials useful for detection or cell killing has become a prominent approach to increase the utility of these proteins, reviewed by Wu and Senter, [20]. Antibodies provide a useful format for the production of radiopharmaceuticals for site- or tissue-specific localization using gamma scintigraphy [10,115] or for enhanced cell killing. There are currently three approved antibody–radionuclide drugs: two are murine radiolabeled Ab for B cell lymphomas ibritumomab tuixetan (^{90}Y, Zevalin) and tositumomab (^{131}I Bexxar) and the third is a humanized, gemtuzumab ozogamicin (calicheamicin, Mylotarg) for leukemia. The presence of a high energy emitting radionuclide, however, will compromise long-term stability of any antibody formulation; not only would the released energies act to damage the protein but there is strong preference to use short half-life isotopes for these procedures [116]. Thus, in these instances, a stable formulation based upon the principles discussed above can provide a product that can be radiolabeled and then used soon after this step. One example of this approach is a lyophilized antibody formulation that is reconstituted and prepared by a kit method prior to patient dosing [117].

Antibodies coupled with cytotoxins for targeted cell killing [118] are particularly useful in antibody-based cancer therapies [119]. Beyond the identification of a stable formulation for the antibody, such materials have several additional problems for the formulation scientist to solve: stability issues of the attached agent and stability of the linker used to join the attached agent to the antibody. In the case of a monoclonal antibody-vinca alkaloid conjugate, a pH range of 4.5–5.5 in a phosphate buffer showed improved solution stability compared to material stored at pH 6.5–7.4 as evidenced by antibody aggregation and hydrolysis of the chemical linker used to conjoin the alkaloid to the antibody [120]. In most cases, cytotoxic materials are coupled to antibodies using reversible chemistries to provide a release mechanism for maximal activity at the target site. Many of these antibody conjugates use a disulfide bond linkage that can be reduced by a novel redox enzyme present in endosomes and lysosomes of target cells [121]. Slightly oxidizing conditions that would provide added stability of this linker in the formulation could, over time, act to cause detrimental oxidation events in the antibody and/or the linked compound. Other conjugates use an acid-labile linker [122]. In this case, formulation pH must be restricted to either neutral or alkaline conditions. Enzymatic separation of antibody and a cytotoxic material could also be achieved by coupling the two through an amino acid linker that is recognized as a substrate by a specific protease or peptidase [123]. Formulation instability of this linker sequences can be corrected to some extent by selective changes of the amino acids used.

Thus, the challenges of immunoconjugates include maintaining both drug and antibody potency and stability. While some antibodies are efficacious by

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themselves, many are much more therapeutically active after being armed with a toxin, drug and radionuclide [124]. These changes make the resulting product more difficult to prepare, stabilize and deliver. Yet, there is tremendous enthusiasm for these approaches as they provide the promise for some companies to transform their antibody into a potentially curative drug. For this reason many antibodies are combined with a generic delivery system, such as a liposome, that can be used to delivery a variety or even multiple agents simultaneously through antibody-directed targeting [125]. Examples of such an approach include studies performed using an antibody directed against the Her2/neu antigen to delivery liposomes containing a chemotherapeutic have been described [126], antibodies used to deliver cationic liposomes for the administration of nucleic acid material for gene therapy [127] and antibodies used in the targeted delivery of modified gelatin nanoparticles [128] that can be coupled through a disulfide linkage [129].

8. Conclusions — challenges and opportunities

As antibody-based drugs come to the forefront of therapeutics derived from biotechnology, they provide a range of new and exciting opportunities to treat a number of currently unmet medical needs. Successful clinical application of these novel agents requires the development of stable formulations that can be used for specific delivery methods. Antibodies, because of their endogenous nature, have built-in features that may pose problems for stability as biotherapeutics, that function in the normal clearance of these proteins from the body [40]. Thus, despite our best efforts to prepare stable antibody-based drug formulations, the ultimate stability of these products may be limited to inherent mechanisms of degradation pre-designed for the rate of clearance optimal for their function and turnover in the body. Protein engineering has led to significant advances in improving some of these parameters and the trend would predict that additional advances will be made in the near future (reviewed in [109]). Protein modifications can be engineered such that stability and efficacy can be improved in ways that cannot be achieved solely, if at all, with formulation alterations. While it is clear that more research is needed in the relatively new area of engineered antibody fragments for clinical use [109], they have great potential for diagnostic and therapeutic application.

In general, successful antibody formulation designs are simply the best compromise of minimizing several competing degradation pathways. One approach is to find a pH where the minimal amount of degradation events such as deamidation and oxidation will occur. Another is to identify a buffer system that can stabilize the formulation at that pH without damaging the antibody. One common tactic taken to reduce the rate of many of these chemical degradation events is to prepare lyophilized or freeze-dried antibody preparation but even these can be compromised by aggregation issues due to thermodynamic stress that occurs during freezing, drying and reconstitution. A number of protective excipients, mostly carbohydrates, can reduce the propensity of antibodies to aggregate during these stressful events. Another issue is to produce a formulation that is compatible with delivery — neither hypotonic — nor hypertonic solutions are well-tolerated upon injection. Added to this is the potential use of a surface active agent to help with liquid stability such as a non-ionic detergent at a low concentration [58] as well as the possible addition of preservatives required for multi-use systems [130].

The future of antibody based drugs is likely to include more complex systems than those currently approved for use in man. Possibly the most critical aspect of generating a pharmaceutically successful formulation for antibody based drugs is an understanding the critical aspects of stability for the protein or the materials associated with the protein. It has been known for some time that even a single amino acid change in the Fv region of an antibody can result in dramatic differences in antigen-binding specificity [31]. Also, alterations at specific amino acids in the Fc domain can dramatically change functional aspects of an antibody. Thus, these kinds of changes must be considered more important in the search for a successful formulation than those changes that do not appear to affect function. In the case of antibody or antibody-like agents being used to delivery a payload such as a toxin or chemotherapeutic, the stability of the material to be delivered and its continued association with the delivery antibody is crucial.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/19/2009, 09/01/2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-84* is/are pending in the application.

4a) Of the above claim(s) *75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-74, 76-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/21/2010*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *09/01/2010* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Examiner-Initiated Interview Summary	**Application No.** 12/621,792	**Applicant(s)** BELL ET AL.	
	Examiner Phillip Gambel	**Art Unit** 1644	

All Participants:

(1) *Phillip Gambel*.

(2) *Ryan Murphey*.

Status of Application: _____

(3) _____.

(4) _____.

Date of Interview: *1 September 2010*

Time: _____

Type of Interview:
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No
If Yes, provide a brief description: .

Part I.

Rejection(s) discussed:
n/a

Claims discussed:
pending

Prior art documents discussed:
n/a

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
examiner invited applicant to elect a species of "compound" from those claimed and/or disclosed in the specification. applicant elected "anti-C5a antibodies" as the "compound" for prosecution purposes

Part III.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.
☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

/Phillip Gambel/
Primary Examiner, Art Unit 1644

(Applicant/Applicant's Representative Signature – if appropriate)

DETAILED ACTION

1. Applicant's amendment, filed 11/19/2009, has been entered
Claims 1-71 and 85-171 have been canceled.

Claims 72-84 are pending.

2. This application is directed to the following species of administering a "compound" as set forth in claims 73 and 74 or as disclosed on pages 11-16 of the specification.

The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

These species of "compounds" are distinct because their structures, physicochemical properties and modes of action differ action to such an extent and require non-coextensive searches to such an extent that they are considered patentable distinct. Further, these "compounds" do not share a substantial structural feature essential to a common utility do not have common structure to a common utility. Therefore, they are separate and patentably distinct species.

Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species of "compound" (e.g., *anti-C5 antibody or anti-C5a receptor antibody)* if elected herein for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. For example, claim 72 is generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

3. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

4. During a telephone conversation with Ryan Murphey on 09/01/2010, a provisional election was made with traverse to prosecute the species of "anti-C5a antibodies".

Affirmation of this election must be made by applicant in responding to this Office action.

Claims 72-74 and 76-84 are under consideration as they read on the elected species.

Claim 75 has been withdrawn from consideration as being drawn to a non-elected species.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected. Appropriate corrections are required.

Trademarks should be capitalized or accompanied by the ® or ™ symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Appropriate corrections are required

8. Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 74 is indefinite in the recitation of "functional fragment of h5G1.1" in that while applicant's intent may be directed to "antigen-binding fragments thereof / C5-binding fragments thereof", the claims are no so limited and can read on any fragment.

For example, immunoglobulin Fc fragments comprised immunoglobulin effector function capabilities and often employed in therapeutic agents; however this does not appear to be applicant's intent for the claimed invention herein.

The claim is indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant is invited to amend the claims to recite the appropriate "fragments thereof".

9. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 74: h5G1.1.

It is apparent that h5G1.1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell line / hybridoma which produce this antibody. See 37 CFR 1.801-1.809.

Given the disclosure on pages 17-18 of the instant specification and the claims of U.S. Patent 6,355,245 (1449) encompassing the instant 5G1.1 antibody produced by the hybridoma designated ATCC HB 11625; the conditions for the deposit of biological materials under 35 USC 112, first paragraph, with respect to h5G1.1 has been satisfied.

Note that Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449) indicates that 5G1.1 and 5G1.1 are synonyms (see entire document, including page box on the top of page 1017, column 2).

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title,if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(f) or (g) prior art under 35 U.S.C. § 103(a).

13. Claims 72-74 and 76-84 are rejected under 35 U.S.C. § 102(a) as being anticipated by Hillmen et al. (Blood 102: 1858, 2003) (1449) (see entire document)
and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Hillmen et al. teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), intravascular hemolysis and venous thrombosis, with an anti-C5 antibody (eculizumab) and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH and PNH type III cells (see entire document).

Eculizumab is derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.
Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobulnuria (PNH) (e.g., see claims 76-84),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same PNH patients are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., reticulocyte numbers and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

14. Claims 72-74 and 76-84 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexion Pharmaceuticals Signs Agreement with Lonza Biologics for Commercial Manufacturing (01/06/2003) (1449) (see entire document)
and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Alexion Pharmaceuticals Signs Agreement with Lonza Biologics For Commercial Manufacturing describes the commercial manufacture, commercialization and clinical studies of evaluating and treating patients with paroxysmal nocturnal hemoglobinuria with eculizumab, an antibody that binds C5.

Note, too, that Alexion is treating patents with coronary artery bypass graft surgery patients undergoing cardiopulmonary bypass as well as patients with acute myocardial infarction patients with pexelizumab, a single chain antibody that binds C5.

Both eculizumab and pexelizumab are derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.

Although the reference is silent about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobinuria (PNH) (e.g., see claims 76-84),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same PNH patients are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., platelet counts, reticulocyte counts and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

15. Claims 72-74 and 76-84 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexion Announces Results of Clinical Trial in Paroxysmal Nocturnal Hemoglobinuria Presented at the American Society of Hematology Annual Meeting (12/02/2002) (1449) (see entire document)
and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Alexion Announces Results of Clinical Trail in Paroxysmal Nocturnal Hemoglobinuria Presented at the American Society of Hematology Annual Meeting describes the use of eculizumab in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), showing a reduction in biochemical parameters of hemolysis, including the increase of Type III PNH red blood cells. Also, this announcement describes the complications of deficiencies of other blood cell types and inappropriate blood clotting known as thrombosis in patients with PNH.

Eculizumab is derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.

Although the reference is silent or not specific about certain specific claimed limitations per se of a patient having paroxysmal nocturnal hemoglobinuria (PNH) (e.g., see claims 76-84),
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same PNH patients are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters (e.g., platelet counts, reticulocyte counts and PNH type III cells) in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat PNH patients.

16. Claims 72-74 are rejected under 35 U.S.C. § 102(e) as being anticipated by Bell (U.S. Patent No. 7,361,339) (see entire document)
and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Bell teaches and claims methods of treat acute myocardial infarction, including reducing the mortality of patients as well as treating patients in connection with angioplasty with anti-C5 antibodies, including h5G1.1 anti-C5 antibodies (see entire document, including Background, Summary and Detailed Description of Preferred Embodiments and Claims).
Note that Bell describes the advent of thrombolysis and angioplasty to restore blood flow and the role of complement activation in the formation of pro-thrombotic microparticles in the Background of the Invention (e.g., see column 1, paragraph 3 and column 2, paragraph 1)

Eculizumab is derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.

Although the reference is not specific about reducing thrombosis per se,
it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable". In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

On this record, it is reasonable to conclude that the same patients with thrombotic conditions are being administered the active agent anti-C5 antibodies by the same mode of administration in the same amount to achieve the same or nearly the same improvement in biochemical and biological parameters associated with myocardial infarction in both the instant claims and the prior art reference. The fact that applicant may have discovered yet another beneficial effect from the method set forth in the prior art does not mean that they are entitled to receive a patent on that method.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to administer anti-C5 antibodies to treat patients with myocardial infarction undergoing angioplasty.

17. Claims 72-74 and 76-84 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillmen et al. (Blood 102: 1858, 2003) (1449) AND/OR Alexion Announces Results of Clinical Trial in Paroxysmal Nocturnal Hemoglobinuria Presented at the American Society of ematology Annual Meeting (12/02/2002) (1449) in view of Meyers et al. (Int. J. Hematol. 77: 125-132, 2003) and Evans et al. (U.S. Patent No. 6,355,245) and in further evidence by Kaplan (Curr. Opin. Investig. Drugs 3: 1017-1023, 2002) (1449).

Hillmen et al. (2003) teach methods of treating paroxysmal nocturnal hemoglobulinuria (PNH), which is characterized by intravascular hemolysis and venous thrombosis with an anti-C5 antibody and in certain instances with erythropoietin as well, including improvement in biochemical / biological parameters associated with LDH and PNH type III cells (see entire document).

Alexion Announces Results of Clinical Trail in Paroxysmal Nocturnal Hemoglobinuria Presented at the American Society of Hematology Annual Meeting describes the use of eculizumab in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), showing a reduction in biochemical parameters of hemolysis, including the increase of Type III PNH red blood cells. Also, this announcement describes the complications of deficiencies of other blood cell types and inappropriate blood clotting known as thrombosis in patients with PNH.

Eculizumab is derived from the h5G1.1 anti-C5 antibody, as evidenced by Kaplan.

With respect to the 5G1.1 antibody itself,
Evans et al. teaches making and using the h5G1.1. anti-C5 antibody and antigen-binding fragments for therapeutic utilities associated with blocking the complement hemolytic activity and C5a generation associated undesirable inflammatory conditions (see entire document, including Field of the Invention, Background of the Invention, Summary of the Invention, Background Physiology and Pathology, Description of the Preferred "Embodiments, Examples and Claims.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

Meyers et al. teach management issues in the treatment of paroxysmal nocturnal hemoglobinuria (see entire document), including the hallmarks of hemolysis and anemia (e.g., see pages 125-128) as well as the treatment of this syndrome with complement inhibitors such as anti-C5 antibodies particularly for the hemolysis of PNH (see Section 2.5, Complement Inhibitors), erythropoietin (see Section 2.6, Management of Nonhemolytic Anemia) and Thrombosis (see Section 3) and Bone Marrow Failure (e.g., see Section 4).

Given the nature of the clinical manifestations of PNH such as hemolysis and anemia, one of ordinary skill in the art at the time the invention was made would have been motivated to select anti-C5 antibodies to address and manage the clinical manifestations of PNH over time with an expectation of success in increase type II red blood cells, platelet counts and reticulocytes. One would have been motivated to combine these therapies with a reasonable expectation of success because each treats a different aspect of the hemolytic disease in the patient and could be reasonably expected to improve the prognosis of the patient more rapidly than either therapy alone. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdiqital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 72-74 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 7,361,339.

Given that thrombosis is characteristic of treating patients with myocardial infarction undergoing angioplasty (e.g., see Background of U.S. Patent No. 7,361,339),
the patented claims of treating acute myocardial infarction, including reducing the mortality of patients as well as treating patients in connection with angioplasty with anti-C5 antibodies, including h5G1.1 anti-C5 antibodies, anticipate the instant claims.

20. Claims 72-74 are directed to an invention not patentably distinct from claims 1-23 of commonly assigned U.S. Patent No. 7,361,339 for the reasons above in Section 19.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No., discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.
A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

21. Claims 72-74 and 76-84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-48, 50-89, 91-129, 130, 132-163 and 168-191 of USSN 11/595,118.

The instant and copending claims are drawn to the same or nearly the same therapeutic endpoints of treating / reducing thrombosis encompassing the treatment of paroxysmal nocturnal hemoglobinuria (PNH) with the same anti-C5 antibodies to achieve the same or nearly same effects on hemopoietic elements.

While the copending claims include combination therapy, one of ordinary skill in the art would have employed conventional therapy to treat the same patients with thrombosis or PNH at the time the invention was made. Such combination therapy would anticipate the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Given copending applications encompassing similar subject matter and the restriction set forth therein,
applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/

Primary Examiner
Technology Center 1600
Art Unit 1644
September 20, 2010

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: August 24, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/642,096 Confirmation No.: 7606

Filed: July 5, 2017 Art Unit: 1662

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

Examiner: Not Yet Assigned

MS Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND PRELIMINARY AMENDMENT AND RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

Dear Sir:

In response to the Notice to File Corrected Application Papers issued by the United States Patent and Trademark Office on July 28, 2017, please amend the above-identified U.S. Patent application as follows:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks begin on page 5 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please replace the Specification as originally filed with the Substitute Specification submitted herewith. A marked-up copy and a clean copy of the substitute specification are enclosed, pursuant to 37 CFR §1.52, 1.121(b)(3) and 1.125(b). *No new matter has been added.*

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AMENDMENTS TO THE CLAIMS

1-51. (Canceled)

52. **(New)** 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.

53. **(New)** The method of claim 52, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

54. **(New)** The method of claim 53, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

55. **(New)** The method of claim 54, wherein the patient is treated with the antibody for at least 26 weeks.

56. **(New)** 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.

57. **(New)** The method of claim 56, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

58. **(New)** The method of claim 57, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

59. **(New)** The method of claim 58, wherein the patient is treated with the antibody for at least 26 weeks.

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REMARKS

Claims 1-51 were pending in this application. Claims 1-51 have been canceled, without prejudice or disclaimer. New claims 52-59 have been added. Support for the new claims can be found throughout the claims and specification as originally filed. *No new matter has been added.*

Objections to the Specification

The United States Patent and Trademark Office ("PTO") issued a Notice to File Corrected Application Papers on July 28, 2017 indicating that page 36 of the specification contains text that is "unreadable or of insufficient clarity." In response, Applicant respectfully submits the present Preliminary Amendment, a clean Substitute Specification, and a marked-up Substitute Specification (*i.e.*, which has been marked to show the changes entered from the previously submitted Preliminary Amendment of July 5, 2017), as required by 37 C.F.R. §1.821-1.825. *No new matter has been added.*

Request for Refund

Applicant submits herewith a Request for Refund in the amount of $2,900, which was debited at the time of filing due to the inadvertent inclusion of language in Applicant's First Preliminary Amendment authorizing the PTO to debit and/or credit any additional fees or overpayments.

CONCLUSION

If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 217-4630.

Dated: August 24, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Electronic Acknowledgement Receipt

EFS ID:	30171513
Application Number:	15642096
International Application Number:	
Confirmation Number:	7606
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Danielle Gamache
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN5
Receipt Date:	24-AUG-2017
Filing Date:	05-JUL-2017
Time Stamp:	14:05:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Specification	AXJ_114BUSCN5_SubSpec_Marked.pdf	540973 751198f9891c789369ee56e0c9ebc0fba87f006f	no	52

Warnings:

Information:					
2	Specification	AXJ_114BUSCN5_SubSpec_Clean.pdf	540968 f3f2e6ca528a3a04ddfd238e04a78688d126c547	no	52
Warnings:					
Information:					
3	Request for Corrected Filing Receipt	AXJ_114BUSCN5_Request_Corrected_FR.pdf	168928 5bb222a812f76cb29917cb99b43ff142d8553823	no	2
Warnings:					
Information:					
4	Refund Request	AXJ_114BUSCN5_Request_for_Refund.pdf	172135 d85c9e3ab402220083ee9dd73ae783d5c4938eac	no	2
Warnings:					
Information:					
5		AXJ_114BUSCN5_Prelim_Amdt.pdf	215636 c52a9c92b56534a9486d2e56345bad17278d94c9	yes	6

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	4
Applicant Arguments/Remarks Made in an Amendment	5	6

Warnings:	
Information:	
Total Files Size (in bytes):	1638640

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 15/284,015, filed October 3, 2016, which is a continuation of U.S. Patent Application No. 15/260,888, filed September 9, 2016, which is a continuation of U.S. Patent Application No. 15/148,839, filed May 6, 2016, which is a continuation of U.S. Patent Application No. 13/426,973, filed March 22, 2012, which is a continuation of U.S. Patent Application No. 12/225,040, filed on May 13, 2009, which is a 35 U.S.C. 371 national stage filing of International Application No. PCT/US2007/006606, filed March 15, 2007. The contents of the aforementioned applications are hereby incorporated by reference in their entireties.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 5, 2017, is named AXJ_114BUSCN5_SL.txt and is 10,376 bytes in size.

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disease that results from clonal expansion of hematopoietic stem cells with somatic mutations in the X-linked gene called PIG-A.[1,2] Mutations in PIG-A lead to an early block in the synthesis of glycosylphosphatidylinositol (GPI)-anchors, which are required to tether many proteins to the cell surface. Consequently, PNH blood cells have a partial (type II) or complete (type III) deficiency of GPI-anchored proteins.

Intravascular hemolysis is a prominent feature of PNH and a direct result of the absence of the GPI-anchored complement regulatory protein CD59.[3,4] Under normal circumstances, CD59 blocks the formation of the terminal complement complex (also called the membrane attack complex) on the cell surface, thereby preventing erythrocyte lysis and platelet activation.[5-8]

Excessive or persistent intravascular hemolysis in PNH patients not only results in anemia (normal ranges of hemoglobin are 14-18 g/dL for men and 12-16 g/dL for women, and persons with lower levels are considered to be anemic), but also hemoglobinuria and clinical sequelae related to the release of the erythrocyte contents into the circulation: fatigue, thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9,10,21,22] Indeed, impaired quality of life in PNH is disproportionate to the degree of anemia. Many PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels. There have been no therapies that effectively reduce intravascular hemolysis and improve the associated clinical morbidities in PNH.

Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5.[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

SUMMARY

The present pivotal, phase III study, Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH), evaluated the effect of eculizumab on the stabilization of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of 87 transfusion-dependent PNH patients. Measures of intravascular hemolysis and quality of life were also assessed. This is the first placebo controlled study of a PNH patient population to control hemolysis and to differentiate between the effects due to hemolysis and the effects due to anemia.

It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role

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functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method of prolonging the health-adjusted life expectancy of a patient comprising administering to said

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patient in need thereof a compound which inhibits formation of C5b-9. In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman. In certain embodiments, said patient suffers from paroxysmal nocturnal hemoglobinuria.

In certain aspects, the application provides a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria by administering a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers,

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tubing, etc.

In certain embodiments, said quality of life is measured by a FACIT-Fatigue score. In certain embodiments, the FACIT-Fatigue score increases by at least 3 points. In certain embodiments, the FACIT-Fatigue score increases by ≥ 4 points.

In certain embodiments, said quality of life is measured by an EORTC QLQ-C30 score. In certain embodiments, said EORTC QLQ-C30 score improves by $\geq 10\%$ of the pretreatment score. In certain embodiments, said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia. In certain embodiments, said aspect of quality of life is fatigue.

In certain embodiments, said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. In certain embodiments, said compound is a steroid that suppresses complement.

In certain embodiments, said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors. In certain embodiments, said compound is an antibody or an active antibody fragment. In certain embodiments, said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

In certain embodiments, said antibody or an active antibody fragment thereof binds C5. In certain embodiments, said antibody or active antibody fragment blocks C5 cleavage. In certain embodiments, said antibody or active antibody fragment inhibits the formation of C5b-9. In certain embodiments, said

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antibody is eculizumab. In certain embodiments, said antibody or active antibody fragment is administered for at least 6 months. In certain embodiments, said patient has aplastic anemia or myelodysplastic syndrome.

In certain embodiments, said antibody that binds C5 or an active antibody fragment thereof is administered in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the single unit dosage form is lyophilized. In certain embodiments, the single unit dosage form is a sterile solution. In certain embodiments, the single unit dosage form is a preservative free formulation. In certain embodiments, the 300 mg single-use dosage form comprises 30 ml of a 10 mg/ml sterile, preservative free solution.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises an altered constant region, wherein said antibody or antigen-binding fragment exhibits decreased effector function relative to an anti-CDCP1 antibody with a native constant region. In certain embodiments, decreased effector function comprises one or more properties of the following group: a) decreased antibody-dependent cell-mediated cytotoxicity (ADCC), and b) decreased complement dependent cytotoxicity (CDC), compared to an anti-CDCP1 antibody with a native constant region. In certain embodiments, the altered constant region comprises a G2/G4 construct in place of the G1 domain.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 1 and the light chain variable region consists of SEQ ID NO: 3. In certain embodiments, the pharmaceutical

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composition comprises eculizumab. In certain embodiments, the pharmaceutical composition comprises pexelizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ ID NO: 4.

In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

In certain embodiments, said health-adjusted life expectancy is measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one day. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least week. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one month. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one year.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the pharmaceutical composition comprises an antibody that binds C5 or an active antibody fragment thereof.

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BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-B show that eculizumab treatment decreases intravascular hemolysis and increases PNH type III erythrocytes. Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels. Figure 1B shows the mean proportion of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients.

Figure 2 shows the effect of eculizumab treatment on transfusion requirements in PNH patients. This is a Kaplan-Meier plot of time to first transfusion for eculizumab- and placebo-treated patients from baseline through week 26. The P value is from the log rank analysis.

Figure 3 shows the effect of eculizumab on fatigue assessed by the FACIT-Fatigue Instrument. Quality of Life scores were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. Values for change from baseline to 26 weeks represent least-square means. A positive change indicates an improvement and a negative change indicates deterioration in the FACIT-Fatigue measures of quality of life.

DETAILED DESCRIPTION

I. Definitions

The term "derived from" means "obtained from" or "produced by" or "descending from".

The term "genetically altered antibodies" means antibodies wherein the amino acid sequence has been varied from that of a native antibody. Because of the relevance of recombinant DNA techniques to this application, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. The possible variations are many and range from the changing of just one or a few amino acids to the complete redesign of, for example, the variable or constant region. Changes in the constant region will, in general, be made in order to improve or alter characteristics, such as complement fixation, interaction with membranes and other effector functions. Changes in the variable region will be

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made in order to improve the antigen binding characteristics.

The term "an antigen-binding fragment of an antibody" refers to any portion of an antibody that retains the binding utility to the antigen. An exemplary antigen-binding fragment of an antibody is the heavy chain and/or light chain CDR, or the heavy and/or light chain variable region.

The term "homologous," in the context of two nucleic acids or polypeptides refers to two or more sequences or subsequences that have at least about 85%, at least 90%, at least 95%, or higher nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using the following sequence comparison method and/or by visual inspection. In certain embodiments, the "homolog" exists over a region of the sequences that is about 50 residues in length, at least about 100 residues, at least about 150 residues, or over the full length of the two sequences to be compared.

Methods of determining percent identity are known in the art. "Percent (%) sequence identity" with respect to a specified subject sequence, or a specified portion thereof, may be defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul et al., J. Mol. Biol. 215:403-410 (1997); http://blast.wustl.edu/blast/README.htm- 1) with search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A "% identity value" is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported.

II. Overview

The present disclosure relates to a method of treating paroxysmal nocturnal hemoglobinuria ("PNH"), more specifically to improving certain

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aspects of quality of life which are impaired in PNH patients, and other hemolytic diseases in mammals. Specifically, the methods of treating hemolytic diseases, which are described herein, involve using compounds which bind to or otherwise block the generation and/or activity of one or more complement components. The present methods have been found to provide surprising results. For instance, hemolysis rapidly ceases upon administration of the compound which binds to or otherwise blocks the generation and/or activity of one or more complement components, with hemoglobinuria being significantly reduced after treatment. Also, hemolytic patients can be rendered less dependent on transfusions or transfusion- independent for extended periods (twelve months or more), well beyond the 120 day life cycle of red blood cells. In addition, type III red blood cell count can be increased dramatically in the midst of other mechanisms of red blood cell lysis (non-complement mediated and/or earlier complement component mediated e.g., Cb3). Another example of a surprising result is that symptoms resolved, indicating that NO serum levels were increased enough even in the presence of other mechanisms of red blood cell lysis. These and other results reported herein are unexpected and could not be predicted from prior treatments of hemolytic diseases.

III. The Complement System

The complement system, useful complement inhibitors, and use of these inhibitors to treat PNH and other patients are more fully described in PCT Patent Application PCT/US2005/003225 filed February 3, 2005 and published as International Publication Number WO 2005/074607 A2 on August 18, 2005, the contents of which are incorporated herein by reference in their entirety.

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting

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complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3

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percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment (Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b- 8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

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As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction.

IV Measures of Quality of Life

Various measurements exist to assess quality of life .and the effect of medical interventions on quality of life for example the Mini-Mental State Examination (MMSE), the Short Test of Mental Status, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the FACIT questionnaires and subscales including fatigue and anemia, the Likert Scale, and Borg Scale (Tombaugh, et al., J. Am. Geriatr. Soc. 40:922, 1992; Cummings, JAMA. 269(18):2420, 1993; Crum, et al., JAMA. 269(18):2386, 1993; Folstein, et al., J. Psychiat. Res. 12:189,1975; Kokmen, et al., Mayo Clin. Proc. 62:281, 1987; Tang-Wai, et al., Arch. Neurol. 60:1777, 2003; Tamburini, Ann. Oncol. 12(Suppl. 3):S7, 2001; Webster et al., Health and Quality of Life Outcomes. 1:79, 2003, www.hqlo.com/content/I/I/79; Grant, et al., Chest. 116:1208, 1999; and www.qolid.org). Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by the Functional Assessment of Chronic

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Illness Therapy (FACIT) Measurement System. In certain embodiments, improvement in quality of life is measured by: a) full scales; b) stand-alone subscales; and c) symptom indices.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by a European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. In certain embodiments, the EORTC questionnaire is the QLQ-C30.

In certain embodiments, improvement in quality of life is measured by the health- adjusted life expectancy (HALE) index as described in Wilkins, R. and Adams, OB., Am J Public Health, 73: 1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein MC and Stason WB, N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

In certain embodiments, improvement in quality of life is measured by the following instruments: Years of potential life lost, Disability-free life expectancy, Health- adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, and Years of healthy life. These measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods improve the quality of life of a patient for at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years, or the duration of treatment.

In certain embodiments, the symptoms used to measure quality of life

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are scaled for intensity. In certain embodiments, the symptoms are scaled for frequency. In certain embodiments, the symptoms are scaled for intensity and frequency.

In certain aspects, the application provides a method for prolonging the health-adjusted life expectancy of a subject comprising administering to the subject a compound which inhibits complement or inhibits formation of C5b-9. The above measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality-adjusted life expectancy due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods prolong the health-adjusted life expectancy in a subject by at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years as measured by the health-adjusted life expectancy (HALE) index as described in Wilkins et al. Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein et al., N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

V Inhibitors of the Complement Cascade

In certain embodiments, any compound which binds to or otherwise blocks the generation and/or activity of one or more complement components can be used in the present methods. In certain embodiments, a complement inhibitor may be a small molecule (up to 6,000 Da in molecular weight), a nucleic acid or nucleic acid analog, a peptidomimetic, or a macromolecule that is not a nucleic acid, a serine protease inhibitor, or a

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protein. These agents include, but are not limited to, small organic molecules, RNA aptamers including ARC187 (which is commercially available from Archemix Corp., Cambridge, Mass.), L-RNA aptamers, Spiegelmers, antisense compounds, molecules which may be utilized in RNA interference (RNAi) such as double stranded RNA including small interfering RNA (siRNA), locked nucleic acid (LNA) inhibitors, peptide nucleic acid (PNA) inhibitors.

In certain embodiments, a complement inhibitor may be a protein or protein fragment. Proteins are known which inhibit the complement cascade, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated neural injury, and C3a and C5a production. In certain embodiments, a complement inhibitor may be naturally occurring or soluble forms of complement inhibitory compounds such as CR1, LEX-CR1 , MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

In certain embodiments, a complement inhibitor may be an antibody capable of inhibiting complement, such as an antibody that can block the formation of MAC. For example, an antibody complement inhibitor may include an antibody that binds C5. Such anti-C5 antibodies may directly interact with C5 and/or C5b, so as to inhibit the formation of and/or physiologic function of C5b.

Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

The concentration and/or physiologic activity of C5a and C5b in a body

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fluid can be measured by methods well known in the art. For C5a such methods include chemotaxis assays, RIAs, or ELISAs (see, for example, Ward and Zvaifler, J Clin Invest. 1971 Mar;50(3):606-16; Wurzner, et al., Complement Inflamm. 8:328-340, 1991). For C5b, hemolytic assays or assays for soluble C5b-9 as discussed herein can be used. Other assays known in the art can also be used. Using assays of these or other suitable types, candidate antibodies capable of inhibiting complement such as anti-C5 antibodies, now known or subsequently identified, can be screened in order to 1) identify compounds that are useful in the practice of the application and 2) determine the appropriate dosage levels of such compounds.

An antibody capable of inhibiting complement such as an antibody that binds C5 affecting C5b is preferably used at concentrations providing substantial reduction (i.e., reduction by at least about 25% as compared to that in the absence of the antibody that binds C5) in the C5b levels present in at least one blood-derived fluid of the patient following activation of complement within the fluid. Such concentrations can be conveniently determined by measuring the cell-lysing ability (e.g., hemolytic activity) of complement present in the fluid or the levels of soluble C5b-9 present in the fluid. Accordingly, a specific concentration for an antibody that affects C5b is one that results in a substantial reduction (i.e., a reduction by at least about 25%) in the cell-lysing ability of the complement present in at least one of the patient's blood-derived fluids. Reductions of the cell-lysing ability of complement present in the patient's body fluids can be measured by methods well known in the art such as, for example, by a conventional hemolytic assay such as the hemolysis assay described by Kabat and Mayer (eds), "Experimental Immunochemistry, 2d Edition", 135-240, Springfield, IL, CC Thomas (1961), pages 135- 139, or a conventional variation of that assay such as the chicken erythrocyte hemolysis method described below.

Specific antibodies capable of inhibiting complement, such as an antibody that binds C5, are relatively specific and do not block the functions of early complement components. In particular, such specific agents will not substantially impair the opsonization functions associated with complement component C3b, which functions provide a means for clearance of foreign

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particles and substances from the body.

C3b is generated by the cleavage of C3, which is carried out by classical and/or alternative C3 convertases and results in the generation of both C3a and C3b. Therefore, in order not to impair the opsonization functions associated with C3b, specific antibodies capable of inhibiting complement such as an antibody that binds C5 do not substantially interfere with the cleavage of complement component C3 in a body fluid of the patient (e.g., serum) into C3a and C3b. Such interference with the cleavage of C3 can be detected by measuring body fluid levels of C3a and/or C3b, which are produced in equimolar ratios by the actions of the C3 convertases. Such measurements are informative because C3a and C3b levels will be reduced (compared to a matched sample without the antibody capable of inhibiting complement such as an antibody that binds C5) if cleavage is interfered with by an antibody capable of inhibiting complement such as an antibody that binds C5.

In practice, the quantitative measurement of such cleavage is generally more accurate when carried out by the measurement of body fluid C3a levels rather than of body fluid C3b levels, since C3a remains in the fluid phase whereas C3b is rapidly cleared. C3a levels in a body fluid can be measured by methods well known in the art such as, for example, by using a commercially available C3a EIA kit, e.g., that sold by Quidel Corporation, San Diego, Calif., according to the manufacturer's specifications. Particularly specific antibodies capable of inhibiting complement such as an antibody that binds C5 produce essentially no reduction in body fluid C3a levels following complement activation when tested in such assays.

Certain antibodies of the disclosure will prevent the cleavage of C5 to form C5a and C5b, thus preventing the generation of the anaphylatoxic activity associated with C5a and preventing the assembly of the membrane attack complex associated with C5b. As discussed above, in a particular embodiment, these anti-C5 antibodies will not impair the opsonization function associated with the action of C3b.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage.

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This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include a preferred whole antibody (now named eculizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)). Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, single-chain antibody, and Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., Nature 321:522-5 (1986)), chimerized, or deimmunized. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies.

In specific embodiments, a therapeutic agent of the disclosure comprises an antibody or antibody fragment. Antibodies and fragments thereof may be made by any conventional method, such as those methods described herein. Antibodies are found in multiple forms, e.g., IgA, IgG, IgM, etc. Additionally, antibodies can be engineered in numerous ways. They can be made as single-chain antibodies (including small modular immunopharmaceuticals or SMIPs™), Fab and $F(ab')_2$ fragments, etc. Antibodies can be humanized, chimerized, deimmunized, or fully human. Numerous publications set forth the many types of antibodies and the methods of engineering such antibodies. For example, see U.S. Patent Nos. 6,355,245; 6,180,370; 5,693,762; 6,407,213; 6,548,640; 5,565,332; 5,225,539; 6,103,889; and 5,260,203.

This invention provides fragments of anti-C5 antibodies, which may comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8:1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding

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fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fe" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment of an antibody yields an F(ab')2 fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" refers to the minimum antibody fragment that contains a complete antigen- recognition and -binding site. This region consists of a dimer of one heavy- and one light- chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although likely at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the scFv to form the desired structure for antigen binding. For a review of scFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

SMIPs are a class of single-chain peptide engineered to include a target binding region, effector domain (CH2 and CH3 domains). *See, e.g.,* U.S. Patent Application Publication No. 20050238646. The target binding region may be derived from the variable region or CDRs of an antibody, e.g.,

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an antibody that binds C5 of the application. Alternatively, the target binding region is derived from a protein that binds C5.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light- chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen- binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

It is well known that the binding to a molecule (or a pathogen) of antibodies with an Fe region assists in the processing and clearance of the molecule (or pathogen). The Fe portions of antibodies are recognized by specialized receptors expressed by immune effector cells. The Fe portions of lgG1 and lgG3 antibodies are recognized by Fe receptors present on the surface of phagocytic cells such as macrophages and neutrophils, which can thereby bind and engulf the molecules or pathogens coated with antibodies of these isotypes (C. A. Janeway et al., Immunobiology 5th edition, page 147, Garland Publishing (New York, 2001)).

This disclosure also provides monoclonal anti-C5 antibodies. A monoclonal antibody can be obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are often synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. Monoclonal antibodies may also be produced in transfected cells, such as CHO cells and NS0 cells. The modifier

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"monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and does not require production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler et al., Nature 256:495-497 (1975), or may be made by recombinant DNA methods *(see, e.g.,* U.S. Patent Nos. 4,816,567 and 6,331,415). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature 352:624-628 (1991) and Marks et al., J. Mol. Biol. 222:581-597 (1991), for example.

A description of the preparation of a mouse anti-human-C5 monoclonal antibody with specific binding characteristics is presented in U.S. Patent Application Publication No. 20050226870. Wurzner et al., Complement Inflamm. 8:328-340 (1991), describe the preparation of other mouse anti-human-C5 monoclonal antibodies referred to as N19-8 and N20-9.

Other antibodies specifically contemplated are "oligoclonal" antibodies. As used herein, the term "oligoclonal" antibodies" refers to a predetermined mixture of distinct monoclonal antibodies. *See, e.g.,* PCT publication WO 95/20401; U.S. Patent Nos. 5,789,208 and 6,335,163. In one embodiment, oligoclonal antibodies consisting of a predetermined mixture of antibodies against one or more epitopes are generated in a single cell. In other embodiments, oligoclonal antibodies comprise a plurality of heavy chains capable of pairing with a common light chain to generate antibodies with multiple specificities *(e.g.,* PCT publication WO 04/009618). Oligoclonal antibodies are particularly useful when it is desired to target multiple epitopes on a single target molecule *(e.g.,* C5). In view of the assays and epitopes disclosed herein, those skilled in the art can generate or select antibodies or mixtures of antibodies that are applicable for an intended purpose and desired need.

In certain embodiments that include a humanized and/or chimeric antibody, one or more of the CDRs are derived from an anti-human C5 antibody. In a specific embodiment, all of the CDRs are derived from an anti-human C5 antibody. In another specific embodiment, the CDRs from more

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than one anti-human C5 antibody are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first anti-human C5 antibody combined with CDR2 and CDR3 from the light chain of a second anti-human C5 antibody, and the CDRs from the heavy chain may be derived from a third anti-human C5 antibody. Further, the framework regions may be derived from one of the same anti-human C5 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. Human or humanized antibodies are specific for administration to human patients.

In certain embodiments, single chain antibodies, and chimeric, humanized or primatized (CDR-grafted) antibodies, as well as chimeric or CDR-grafted single chain antibodies, comprising portions derived from different species, are also encompassed by the present disclosure as antigen-binding fragments of an antibody. The various portions of these antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, nucleic acids encoding a chimeric or humanized chain can be expressed to produce a contiguous protein. See, e.g., U.S. Pat. Nos. 4,816,567 and 6,331,415; U.S. Pat. No. 4,816,397; European Patent No. 0,120,694; WO 86/01533; European Patent No. 0,194,276 B1; U.S. Pat. No. 5,225,539; and European Patent No. 0,239,400 B1. See also, Newman et al., BioTechnology 10:1455-1460 (1992), regarding primatized antibody. See, e.g., Ladner et al., U.S. Pat. No. 4,946,778; and Bird et al., Science 242:423-426 (1988), regarding single chain antibodies.

In addition, functional fragments of antibodies, including fragments of chimeric, humanized, primatized or single chain antibodies, can also be produced. Functional fragments of the subject antibodies retain at least one binding function and/or modulation function of the full-length antibody from which they are derived. Preferred functional fragments retain an antigen-binding function of a corresponding full-length antibody (such as for example, ability of antibody that binds C5 to bind C5).

General methods for the immunization of animals (in this case with C5 and/or C5b, etc.), isolation of antibody producing cells, fusion of such cells

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with immortal cells (e.g., myeloma cells) to generate hybridomas secreting monoclonal antibodies, screening of hybridoma supernatants for reactivity of secreted monoclonal antibodies with a desired antigen (in this case the immunogen or a molecule containing the immunogen), the preparation of quantities of such antibodies in hybridoma supernatants or ascites fluids, and for the purification and storage of such monoclonal antibodies, can be found in numerous publications. These include: Coligan, et al., eds. Current Protocols In Immunology, John Wiley & Sons, New York, 1992; Harlow and Lane, Antibodies. A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Liddell and Cryer, A Practical Guide To Monoclonal Antibodies, John Wiley & Sons, Chichester, West Sussex, England, 1991; Montz et al., Cellular Immunol. 127:337-351 (1990); Wurzner et al., Complement Inflamm. 8:328-340 (1991); and Mollnes et al., Scand. J. Immunol. 28:307-312 (1988).

VI Methods of Treatment

Methods of the application may be used to treat paroxysmal nocturnal hemoglobinuria associated symptoms. Methods of the application may be used to treat anemia associated symptoms. Treatment of paroxysmal nocturnal hemoglobinuria and/or anemia may be administered by standard means. Treatments of the application may be used in combination with other treatments of the application or known treatments for paroxysmal nocturnal hemoglobinuria and/or anemia. Treatments of the application may be co-administered with other treatments that treat symptoms of paroxysmal nocturnal hemoglobinuria and/or anemia.

VII Pharmaceutical Formulations and Uses

Methods of administration of small molecules, proteins, and nucleic acids are well- known to those of skill in the art. Methods of administration of antibodies are well-known to those of skill in the art. To achieve the desired inhibition, the antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab fragments will also require differing dosages than the

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equivalent intact immunoglobulins, as they are of considerably smaller mass than intact immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood. The dose will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician. Dosage levels of the antibodies for human subjects are generally between about 1 mg per kg and about 100 mg per kg per patient per treatment, and preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment. In terms of plasma concentrations, the antibody concentrations are preferably in the range from about 25 μg/mL to about 500 μg/mL. However, greater amounts may be required for extreme cases and smaller amounts may be sufficient for milder cases.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the antibody is administered according to the following protocol: 600 mg via 25 to 45 minute IV infusion every 7 ± 2 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 ± 2 days later, then 900 mg every 14 ± 2 days thereafter. Antibody is administered via IV infusion over 25 to 45 minute.

Administration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection. Other routes of administration may be used if desired but an intravenous route will be the most preferable. Formulations suitable for injection are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985). Such formulations must be sterile and non-pyrogenic, and generally will include a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The

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formulations may contain pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like. In certain embodiments, complement inhibitors such as eculizumab may be administered via IV infusion and diluted to a final concentration of 5 mg/ml prior to administration.

Administration of the antibodies capable of inhibiting complement such as an antibody that binds C5 will generally be performed by a parenteral route, typically via injection such as intra-articular or intravascular injection (e.g., intravenous infusion) or intramuscular injection. Other routes of administration, e.g., oral (p.o.), may be used if desired and practicable for the particular antibody capable of inhibiting complement to be administered. Antibodies capable of inhibiting complement such as an antibody that binds C5 can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and in vivo half-life of the particular antibody capable of inhibiting complement being administered. Doses of antibodies capable of inhibiting complement such as an antibody that binds C5 will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

In certain embodiments, a typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints with the dosage levels adjusted as needed to achieve the desired clinical outcome. In certain embodiments, treatment is administered in multiple dosages over at least a week. In certain embodiments, treatment is administered in multiple dosages over at least a month. In certain embodiments, treatment is administered in multiple dosages over at least a year. In certain embodiments, treatment is administered in multiple dosages over the remainder of the patient's life.

The frequency of administration may also be adjusted according to various parameters. These include the clinical response, the plasma half-life of the therapeutic of the disclosure, and the levels of the antibody in a body fluid, such as, blood, plasma, serum, or synovial fluid. To guide adjustment of the frequency of administration, levels of the therapeutic of the disclosure in the

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body fluid may be monitored during the course of treatment.

In certain embodiments, the frequency of administration may be adjusted according to an assay measuring cell-lysing ability of complement present in one or more of the patient's body fluids. The cell-lysing ability can be measured as percent hemolysis in hemolytic assays of the types described herein. A 10% or 25% or 50% reduction in the cell-lysing ability of complement present in a body fluid after treatment with the antibody capable of inhibiting complement used in the practice of the application means that the percent hemolysis after treatment is 90, 75, or 50 percent, respectively, of the percent hemolysis before treatment.

For the treatment of hemolytic diseases such as PNH by systemic administration of an antibody capable of inhibiting complement such as an antibody that binds C5 (as opposed to local administration), administration of a large initial dose is specific, i.e., a single initial dose sufficient to yield a substantial reduction, and more preferably an at least about 50% reduction, in the hemolytic activity of the patient's serum. Such a large initial dose is preferably followed by regularly repeated administration of tapered doses as needed to maintain substantial reductions of serum hemolytic titer. In another embodiment, the initial dose is given by both local and systemic routes, followed by repeated systemic administration of tapered doses as described above.

Formulations particularly useful for antibody-based therapeutic agents are also described in U.S. Patent App. Publication Nos. 20030202972, 20040091490 and 20050158316. In certain embodiments, the liquid formulations of the application are substantially free of surfactant and/or inorganic salts. In another specific embodiment, the liquid formulations have a pH ranging from about 5.0 to about 7.0. In yet another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from about 1 mM to about 100 mM. In still another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from 1 mM to 100 mM. It is also contemplated that the liquid formulations may further comprise one or more excipients such as a saccharide, an amino acid (e.g., arginine, lysine, and methionine) and a polyol. Additional descriptions and

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methods of preparing and analyzing liquid formulations can be found, for example, in PCT publications WO 03/106644, WO 04/066957, and WO 04/091658.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the application.

In certain embodiments, formulations of the subject antibodies are pyrogen-free formulations which are substantially free of endotoxins and/or related pyrogenic substances. Endotoxins include toxins that are confined inside microorganisms and are released when the microorganisms are broken down or die. Pyrogenic substances also include fever-inducing, thermostable substances (glycoproteins) from the outer membrane of bacteria and other microorganisms. Both of these substances can cause fever, hypotension and shock if administered to humans. Due to the potential harmful effects, it is advantageous to remove even low amounts of endotoxins from intravenously administered pharmaceutical drug solutions. The Food & Drug Administration ("FDA") has set an upper limit of 5 endotoxin units (EU) per dose per kilogram body weight in a single one hour period for intravenous drug applications (The United States Pharmacopeial Convention, Pharmacopeial Forum 26 (1):223 (2000)). When therapeutic proteins are administered in amounts of several hundred or thousand milligrams per kilogram body weight, as can be the case with monoclonal antibodies, it is advantageous to remove even trace amounts of endotoxin.

Formulations of the subject antibodies include those suitable for oral, dietary, topical, parenteral (e.g., intravenous, intraarterial, intramuscular, subcutaneous injection), ophthalmologic (e.g., topical or intraocular), inhalation (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops), rectal, and/or intravaginal administration. Other suitable methods of administration can also include rechargeable or biodegradable devices and controlled release polymeric devices. Stents, in particular, may be coated with a controlled release polymer mixed with an agent of the application. The

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pharmaceutical compositions of this disclosure can also be administered as part of a combinatorial therapy with other agents (either in the same formulation or in a separate formulation).

The amount of the formulation which will be therapeutically effective can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. The dosage of the compositions to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. For example, the actual patient body weight may be used to calculate the dose of the formulations in milliliters (mL) to be administered. There may be no downward adjustment to "ideal" weight. In such a situation, an appropriate dose may be calculated by the following formula: Dose (mL) = [patient weight (kg) x dose level (mg/kg)/ drug concentration (mg/mL)]

To achieve the desired treatment results, anti-C5 antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab' fragments or single chain antibodies will also require differing dosages than the equivalent native immunoglobulins, as they are of considerably smaller mass than native immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood.

Other therapeutics of the disclosure can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and *in vivo* half-life of the particular therapeutic being administered.

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Doses of therapeutics of the disclosure will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

The formulations of the application can be distributed as articles of manufacture comprising packaging material and a pharmaceutical agent which comprises the antibody capable of inhibiting complement and a pharmaceutically acceptable carrier as appropriate to the mode of administration. The packaging material may include a label which indicates that the formulation is for use in the treatment of hemolytic diseases such as PNH. Although antibodies are preferred, especially anti-C5 antibodies which have already been shown to be safe and effective at decreasing the accumulation of downstream complement components in persons, the use of other complement inhibitors is also contemplated by this disclosure. The pharmaceutical formulations and uses of the disclosure may be combined with- any known complement inhibitors or hemolytic diseases treatments known in the art.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

EXEMPLIFICATION

METHODS

Patient Selection

The TRIUMPH trial consisted of a 2-week screening period, an observation period of up to 3 months duration, and a 26-week treatment period.

During the screening period, patients were evaluated with respect to inclusion and exclusion criteria. Men and women, 18 years or older,

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diagnosed as having PNH with a type III erythrocyte population of ≥10%, and who had received at least 4 transfusions in the previous 12 months were eligible. Concomitant administration of erythropoietin, immunosuppressants, corticosteroids, coumadin, low molecular weight heparin, iron supplements, and folic acid were not reasons for exclusion, provided the doses were steady prior to the first visit and throughout the duration of the study. Because of the increased frequency of neisserial infections in individuals genetically deficient in terminal complement proteins, all patients were vaccinated against *Neisseria meningitides*. Patients were to avoid conception. The protocol was approved by an Investigational Review Board at each clinical site and written informed consent was obtained from all patients enrolled.

Patients transfused with a mean pre-transfusion hemoglobin level > 10.5 g/dL over the previous 12 months, and those who showed evidence of having a suppressed immune response, complement deficiency, or active bacterial infection, including any history of meningococcal disease, were excluded from the study. Patients were also not eligible if they had previously received a bone marrow transplant or if they had participated in another trial or received another investigational drug within 30 days of the first visit. An individualized transfusion algorithm was calculated for each patient based on their prior 12-month transfusion history; the written algorithm documented the number of packed red blood cell (PRBC) units transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during observation and treatment periods.

Each patient considered eligible entered an observation period of up to 13 weeks in order to confirm their PBRC transfusion dependence. At least one transfusion --termed the "qualifying" transfusion-- during the 13-week observation period at a hemoglobin value at or below 9 g/dL with symptoms, or at or below 7 g/dL with or without symptoms, in accordance with the transfusion algorithm indicated for each patient, was a requirement to proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set point" for that individual for the purpose of the primary efficacy variable. A platelet count ≥100,000/mL and a LDH level ≥1.5 times the upper limit of the normal

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range were also required either at screening or during the observation period for eligibility.

Study Design

Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Measures of Clinical Efficacy

There were two co-primary endpoints in the study: (1) stabilization of hemoglobin levels, defined as a hemoglobin value maintained above the individual hemoglobin set point in the absence of transfusions for the entire 26-week treatment period, and (2) reduction in units of PRBCs transfused during the 26-week treatment phase of the study. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia and reached their individualized, pre-determined "set point". Pre-specified secondary endpoints included transfusion avoidance, hemolysis as measured by LDH area under the curve from baseline to 26 weeks, and QoL changes as measured from baseline to 26 weeks using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.[13] Pre-specified exploratory analyses included assessment of the EORTC QLQ-C30 instrument,[14] the change in LDH from baseline through week 26, and thrombosis. Other pre-specified measurements included pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. Time to first transfusion during the 26-week treatment phase and the proportion of PNH type III blood cells were also assessed.

Safety Assessments

Treatment-emergent adverse events, clinical laboratory tests (e.g., serum

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chemical analyses and complete blood counts), electrocardiogram data, and vital signs were assessed. Adverse events were defined using the MedDRA preferred terms and tabulated as incidence rates per treatment group.

Statistical Analysis

For co-primary endpoints, analyses were performed according to the intention to treat using the data from all patients who were randomized and received study drug; stabilization of hemoglobin levels was analyzed using the Fisher's exact test and total PRBC units transfused were analyzed with the Wilcoxon's rank sum test. For comparison of treatment effect on transfusion avoidance, the Fisher's exact test was used on the incidence and the log rank test was used for time to first transfusion. For LDH area under the curve the Wilcoxon's rank sum test was used.

Quality of life measure of fatigue was assessed using the scoring guidelines for the FACIT-Fatigue instrument. [15] Assessment of quality of life measures based on the EORTC QLQ-C30 instrument was conducted in accordance with the appropriate scoring guidelines.[16] The changes of FACIT-Fatigue and EORTC QLQ-C30 scores from baseline through 26 weeks were analyzed using a mixed model, with baseline as covariate, treatment and time as fixed effects, and patient as a random effect. Changes in LDH levels and PNH type III erythrocytes from baseline through 26 weeks were analyzed using the same mixed model. Two-sided tests were used for all analyses. The adverse events and long-term safety checklist were tabulated separately and compared between treatments using the Fisher's exact test. A p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

Characteristics of Patients

A total of 115 PNH patients were screened. Six patients did not meet the inclusion/exclusion criteria during the screening period. Twenty-one other patients did not receive a qualifying transfusion and were not randomized into the treatment phase. One patient who did not meet the inclusion criteria was inadvertently randomized, but did not receive study medication. Thus 87 hemolytic PNH patients (35 men and 52 women) were enrolled and randomized

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to receive either eculizumab (N=43) or placebo (N=44), exceeding the original target of 75 randomized patients.

Patient characteristics were similar in the eculizumab- and placebo-treated cohorts: median age, 41 (range 20-85) and 35 (range 18-78) years; median duration of PNH, 4.2 (range 0.8 to 29.7) and 9.2 (range 0.4 to 38.3) years; patients with history of aplastic anemia, 4 and 11; history of myelodysplastic syndrome, 1 and 0; and history of thrombosis, 9 (16 events) and 8 (11 events). Stable usage of concomitant medications at baseline in the eculizumab- and placebo-treated groups included the following: erythropoietin, 3 patients and 0 patients; cyclosporine, 1 and 1; anticoagulants (coumarins or heparins) 21 and 11; and steroids (glucocorticoids or androgenic steroids), 12 and 12, respectively.

Of the 87 patients randomized, 85 completed the trial. Two patients who did not complete the trial had been randomized to the eculizumab arm: one patient discontinued due to the inconvenience of travel to the study site and the second patient became pregnant. Ten patients in the placebo-treatment group discontinued infusions, in all cases due to perceived lack of efficacy, but they remained in the study for monitoring purposes.

Pharmacokinetics/Pharmacodynamics

In 42 of the 43 eculizumab-treated patients the levels of drug during the maintenance period (900 mg every 2 weeks±2 days) were sufficient to completely block serum hemolytic activity (mean trough value at week 26 of 101.8 μg/mL). A single patient did not sustain therapeutic trough levels of eculizumab and demonstrated a breakthrough in complement blockade during the last few days of each dosing interval. These breakthroughs were clinically manageable and quickly resolved following the next dose.

Hemolytic Efficacy Variables

The impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an immediate (one week) and sustained decrease in mean levels of LDH (Figure I A). The median LDH area under the curve during the 26-week study period was reduced 85.8% in eculizumab- relative to placebo-treated patients ($P<0.001$). The mean LDH level decreased from 2199.7±157.7 IU/L at baseline to 327.3±67.6 IU/L by 26 weeks in eculizumab-treated patients while levels in

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placebo-treated patients remained consistently elevated with values of 2259.0±158.5 IU/L at baseline and 2418.9±140.3 IU/L at 26 weeks (P<0.001, for eculizumab versus placebo). A second biochemical measure of hemolysis, serum aspartate aminotransferase (AST), also showed a statistically significant improvement following eculizumab- versus placebo-treatment (data not shown). Haptoglobin levels were statistically significantly increased in eculizumab- as compared to placebo-treated patients but mean levels of haptoglobin were still below normal levels in eculizumab-treated patients (data not shown).

Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels (±standard error) from baseline (study week 0) to week 26 for both eculizumab- and placebo-treated patient populations. Screening occurred up to 3 months prior to study week 0. The upper limit of the normal range (103-223 IU/L) for LDH is indicated by a dashed line. LDH was reduced to a mean level just above the upper limit of normal at week 26 for eculizumab-treated patients; 15 of 41 patients who completed the study demonstrated LDH levels within the normal range. All placebo-treated patients remained at least 5 times above the upper limit of normal at week 26. The P value is based on a mixed model analysis from baseline through week 26. Figure 1B shows the mean proportion (±standard error) of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients. The screening visit occurred up to 3 months prior to study week 0. The P value is based on a mixed model analysis from baseline through week 26.

A corollary to the reduction in intravascular hemolysis during eculizumab treatment was an observed increase in the PNH type III erythrocyte population (Figure 1B). The mean proportions of type III erythrocytes increased from 28.1±2.0% at baseline to 56.9±3.6% by week 26 for eculizumab-treated patients while proportions in the placebo group remained constant with mean values of 35.7±2.8% before treatment to 35.5±2.8% at 26 weeks (P<0.001, for eculizumab versus placebo). By contrast, the proportions of PNH type III granulocytes and monocytes did not change significantly between the treatment groups during the treatment period and were greater than 90% at week 26.

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CLINICAL EFFICACY

Co-primary endpoints

The co-primary efficacy endpoints in the TRIUMPH trial were stabilization of hemoglobin levels and reduction in PRBC units transfused. At the end of the treatment period, 48.8% of eculizumab-treated patients had maintained levels of hemoglobin above the pre-specified set-point (median set-point value of 7.7 g/dL for both treatment groups) in the absence of transfusions, whereas stabilization of hemoglobin did not occur in any of the patients in the placebo group ($P<0.001$; Table 1). By week 26, the median of PRBC units transfused per patient was 0 in the eculizumab group and 10.0 in the placebo cohort ($P<0.001$), while the mean of PRBC units transfused was 3.0 and 11.0 in the eculizumab and placebo cohorts, respectively. In the 6-month period prior to the study, the median of PRBC units transfused per patient was 9.0 in the eculizumab cohort and 8.5 in placebo patients while the mean of PRBC units transfused was 9.6±0.6 and 9.7±0.7, respectively. Mean hemoglobin levels were similar between the treatment groups at baseline (10.0±1.8 g/dL in eculizumab-treated patients and 9.7±1.8 g/dL in placebo-treated patients) and did not substantially change by week 26 (10.1±2.5 g/dL and 8.9±2.2 g/dL in eculizumab and placebo cohorts; respectively).

The median time to first transfusion was not reached during the study period in eculizumab-treated patients (it was greater than 26 weeks) while the placebo group reached the median time to first transfusion in only 4 weeks ($P<0.001$; Figure 2). Transfusion avoidance was achieved in 51.2% and 0% of the eculizumab and placebo cohorts, respectively ($P<0.001$). By the end of the 26-week treatment period, the total PRBC units transfused were 131 in eculizumab-treated patients versus 482 in the placebo group (Table 1). By contrast, in the 6-month period prior to the study, total PRBC units transfused in the eculizumab- and placebo-cohorts were 413 and 417, respectively.

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Table 1

Stabilization of Hemoglobin Levels and Reduction

in Transfusion Requirements during Eculizumab Treatment

	PRE-TREATMENT HISTORY*		TREATMENT PERIOD		
	Placebo	Eculizumab	Placebo	Eculizumab	P Value
†Stabilization of Hemoglobin Levels in the absence of transfusions (percent of patients)	NA	NA	0	48.8	<0.001ǂ
†Units Transfused per Patient					
Median	8.5	9.0	10	0	<0.001§
Mean± SE	9.7±0.7	9.6±0.6	11.0±0.83	3.0±0.67	
Total Units Transfused per Group	417	413	482	131	

*Twelve month historical transfusion data normalized to 6 months

†Co-primary endpoints

ǂBase on 2-sided Fisher's exact test

§Based on Wilcoxon's rank sum test NA, not applicable

Improvements in quality of life measures

Assessments of quality of life in PNH patients during eculizumab treatment were performed using two different instruments; FACIT-Fatigue and the EORTC QLQ-C30. Eculizumab-treated patients showed a mean increase (improvement) in the FACIT-Fatigue score of 6.4±1.2 points from baseline to 26-weeks while the mean score in placebo patients decreased by 4.0±1.7 points, a total difference between the treatment groups of 10.4 points (Figure 3). Mixed model analysis of covariance demonstrated a statistically significant difference between treatment groups (P<0.001).

For the EORTC instrument, improvements were observed with eculizumab- treatment in each subscale. Statistically significant improvements with eculizumab- compared with placebo-treated groups were observed in the following quality of life subscales (Table 2): global health status (P<0.001), physical

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functioning (P<0.001), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P<0.001), social functioning (P=0.003), fatigue (P<0.001), pain (P=0.002), dyspnea (P<0.001), appetite loss (P<0.001), and insomnia (P=0.014). The improvements with eculizumab treatment in the other scales, including nausea and vomiting, diarrhea, constipation, and financial difficulties, did not reach statistical significance.

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Table 2

Effect of Eculizumab Treatment on
Quality of Life Assessed by the EORTC QLQ-C30 Instrument

	Mean Change from Baseline to Week 26*			
	Placebo	Eculizumab	Absolute Difference	P Value†
Global Health Status	-8.5	10.9	19.4	<0.001
Functional				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.6	=0.003
Cognitive	-6.1	7.9	14.0	=0.002
Physical	-3.5	9.4	13.0	<0.001
Emotional	-3.7	7.5	11.2	=0.008
Symptoms/Single Items				
Fatigue	10.0	-16.9	27.0	<0.001
Pain	5.3	-12.3	17.6	=0.002
Dyspnea	8.9	-7.9	16.9	<0.001
Appetite Loss	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	=0.014
Financial Difficulties	0.0	-10.3	10.3	=0.186
Constipation	0.0	-6.3	6.3	=0.199
Nausea/vomiting	2.8	-0.4	3.2	=0.056
Diarrhea	5.7	4.8	0.9	=0.147

*A positive change indicates an improvement in global health status and functional scales and a negative change indicates an improvement in symptom and single item scales.

†Based on a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect and baseline as a covariate.

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Relationship between FACIT-Fatigue quality of life and intravascular hemolysis

In order to determine if there was a treatment independent relationship between the FACIT-Fatigue quality of life instrument and intravascular hemolysis, an analysis was performed whereby the mean LDH level (through the 26 week study period) for each TRIUMPH patient was analyzed as a function of the patient's respective mean change in FACIT-Fatigue score from baseline (through the 26 week study period) (see Table 3). For this analysis, mean levels of LDH were divided into 4 groups that included: normal levels, 1-2 times the upper limit of normal (ULN), 2-10 times the upper limit of normal, and greater than 10 times the upper limit of normal. The analysis demonstrated that patients who maintained normal LDH levels throughout the study experienced significant improvements in fatigue when compared to patients who had incrementally higher levels of LDH throughout the study (p=0.0048). These data establish a clear link between increasing intravascular hemolysis as measured by LDH levels and decreased quality of life as measured by the FACIT-Fatigue quality of life instrument.

Table 3

Relationship between FACIT-Fatigue and Intravascular Hemolysis

		Change of FACIT from Baseline		
Treatment Group	**LDH Category**	**<4**	**>=4**	**P Value**
Combined	Normal	4 (30.77%)	9 (69.23%)	.0048
	1-2 X ULN	16 (61.54%)	10 (38.46%)	
	2 - 10 X ULN	18 (72.00%)	7 (28.00%)	
	> 10 X ULN	16 (80.00%)	4 (20.00%)	

Safety

There were no deaths in the study. Serious adverse events (SAEs) were reported for 13 patients, of which 4 occurred in the eculizumab-treated cohort and 9 were in the placebo-treated cohort (see Table 4). All patients recovered without sequelae.

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The most common AEs reported for eculizumab-treated patients were headache, nasopharyngitis, back pain, and upper respiratory tract infection. Headache and back pain occurred more commonly in the eculizumab-treatment group compared with the placebo group. However, the increase in headaches was limited to the first 2 weeks of therapy and was mild to moderate. There were no statistically significant differences in incidents rates between treatment groups for any AEs reported.

One episode of thrombosis (Budd-Chiari) occurred m a placebo-treated patient. There were no thromboses in eculizumab-treated patients.

Only one patient showed a detectable level of anti-eculizumab antibodies in the eculizumab-treated cohort; this response was weak (did not titrate), occurred at only one time point and did not result in a disruption of complement blockade.

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Table 4

Adverse Event Reporting

SERIOUS ADVERSE EVENTS*	Placebo Patients n (percent)	Eculizumab Patients n (percent)
Total	9 (20.5)	4 (9.3)
Eculizumab treatment emergent		
Exacerbation of PNH	3 (6.8)	1 (2.3)
Renal colic	0	1 (2.3)
Lumbar sacral disc prolapse	0	1 (2.3)
Alpha streptococcal bacteremia	0	1 (2.3)
Central line infection and UTI	1 (2.3)	0 (0)
Upper respiratory tract infection	1 (2.3)	0 (0)
Probable viral infection	1 (2.3)	0 (0)
Neutropenia	1 (2.3)	0 (0)
Cellulitis / folliculitis / neutropemia	1 (2.3)	0 (0)
Anemia and pyrexia	1 (2.3)	0 (0)
MOST FREQUENT ADVERSE EVENTS*†		
Headache§	12 (27.3)	19ǂ (44.2)
Nasopharyngitis	8 (18.2)	10 (23.3)
Upper respiratory tract infection	10 (22.7)	6 (14)
Back pain	4 (9.1)	8 (18.6)
Nausea	5 (11.4)	7 (16.3)
Cough	4 (9.1)	5 (11.6)
Diarrhea	5 (11.4)	4 (9.3)
Arthralgia	5 (11.4)	3 (7.0)
Abdominal pain	5 (11.4)	2 (4.7)
Dizziness	5 (11.4)	2 (4.7)
Vomiting	5 (11.4)	2 (4.7)
Fatigue	1 (2.3)	5 (11.6)
Viral infection	5 (11.4)	1 (2.3)

*By preferred terms

†Occurring in 10% or more of patients

ǂSixteen of 19 patients experienced headache within 48 hours of infusion

§Following the first 2 weeks of dosing, 20.9% of eculizumab- and 22.7%

of placebo-treated patients experienced headache

DISCUSSION

Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44%. reduction in the rate of transfusion (data now shown).

Lactate dehydrogenase, a biochemical marker of hemolysis in PNH,[9] was immediately and consistently decreased in all eculizumab-treated patients, while patients in the placebo cohort continued to hemolyze with levels of LDH exceeding 5 times the upper limit of the normal range in all patients at the study end. Levels of LDH were reduced into the normal range in approximately one-third of eculizumab-treated patients, while the remainder stabilized at a level just above the upper limit of normal suggesting residual low level hemolysis in some patients. Levels of haptoglobin, a more sensitive marker of the presence of cell free hemoglobin in the circulation, were undetectable in most patients. Low level hemolysis in a subset of eculizumab-treated patients is possibly due to an inherent decrease in survival of these cells or C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.[17]

Before eculizumab treatment, hemoglobin levels in study patients were artificially maintained by frequent transfusion. Therefore, stabilization of hemoglobin levels with a concomitant cessation of or reduction in

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transfusions represents a net increase in endogenous hemoglobin levels. Our data suggest that resolution of hemolysis with eculizumab results in a new steady state hemoglobin level determined by a balance between the extent of the underlying bone marrow dysfunction, the number of PNH erythrocytes that are preserved by eculizumab therapy and the new level (if any) of transfusion requirement.

Patients with PNH generally experience markedly impaired quality of life characterized by fatigue, anemia, thrombosis, and pulmonary hypertension as well as smooth muscle dystonia including abdominal pain, dysphagia, and erectile dysfunction.[9,10,18] These symptoms have been attributed to both excessive intravascular hemolysis and downstream scavenging of nitric oxide by cell free hemoglobin in plasma. The reduction of intravascular hemolysis in eculizumab-treated patients in the current study was associated with significant improvements in the fatigue component of quality of life relative to placebo-treated patients as assessed via the FACIT-Fatigue instrument. Further, eculizumab therapy was associated with a median increase of 6.4 points over baseline values established before treatment. It has previously been demonstrated that an increase of 3 or more points from baseline represents a clinically important difference in this quality of life instrument. [19] Patients who received eculizumab also experienced a significant improvement in most domains of the EORTC QLQ-30 relative to the placebo-treated cohort including global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and insomnia. Improvement in the fatigue component of the EORTC QLQ-30 provides support for the improvement demonstrated in the FACIT-Fatigue instrument during eculizumab therapy. Importantly, these improvements in quality of life in the eculizumab-treated patients occurred despite similar levels of erythrocyte hemoglobin in the two treatment groups, further supporting the contribution of hemolysis per se, as opposed to anemia, in mediating the poor quality of life in PNH patients. Clinical assessment of additional life quality-related symptoms of PNH, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[20]

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Eculizumab was safe and well-tolerated. There were no deaths in the study and only a single thrombotic event which occurred in a placebo patient in a site (the hepatic veins) which is typical of the thrombosis in PNH. The relative brief duration of this study was not sufficient to address the relevant issue of a possible protection from thrombosis by terminal complement inhibition with eculizumab.

Adverse events were generally mild with headache occurring at increased frequency in the eculizumab-treated patients; however, this increased frequency did not persist following the first two doses of therapy. There were 4 SAEs in the eculizumab treatment group and 9 SAEs in the placebo group. There was no evidence of increased infection risk in eculizumab-treated patients during the study period. One eculizumab-treated patient showed a low level of anti-eculizumab antibodies at one time point during the study which did not persist and did not result in a disruption of complement blockade. There were no AEs associated with eculizumab withdrawal in the 2 eculizumab-treated patients who did not complete the trial. Additional safety assessments, as well as efficacy measures, are being examined in an ongoing multi-center, open-label Phase III safety trial of eculizumab (SHEPHERD) in approximately 95 patients with PNH.

Results from the current randomized, double-blind, placebo-controlled, global study show that terminal complement inhibition with eculizumab appears to be a safe and effective therapy for patients with the rare disorder PNH. Treatment with eculizumab reduced intravascular hemolysis, and stabilized hemoglobin levels despite a reduction of transfusions, to the point where most PNH patients were rendered transfusion independent. Substantial and clinically meaningful improvements in fatigue and other key quality of life parameters were also demonstrated. All of the 85 patients who completed the study elected to receive eculizumab in an open-label extension study and all currently remain on drug. The results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency.

The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to

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those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

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SEQUENCES

SEQ ID NO: 1 -Eculizumab V_H

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMG
EILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFF
GSSPNWYFDVWGQGTLVTVSSA

SEQ ID NO: 2 -Eculizumab Heavy chain

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMG
EILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFF
GSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYT
CNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO: 3 -Eculizumab V_L

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASE
NIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQ
PEDFATYYCQNVLNTPLTFGQGTKVEIKRT

SEQ ID NO: 4 -Eculizumab Light chain

~~MDMRVPAQLLGLLLLWLRGARC~~DIQMTQSPSSLSASVGDRVTITCGASE
NIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 5 -Eculizumab CDRH1

NYWIQ

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SEQ ID NO: 6 -Eculizumab CDRH2
EILPGSGSTEYTENFKD

SEQ ID NO: 7 -Eculizumab CDRH3
YFFGSSPNWYFDV

SEQ ID NO: 8 -Eculizumab CDRL1
GASENIYGALN

SEQ ID NO: 9 -Eculizumab CDRL2
GATNLAD

SEQ ID NO: 10 -Eculizumab CDRL3
QNVLNTPLT

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TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 15/284,015, filed October 3, 2016, which is a continuation of U.S. Patent Application No. 15/260,888, filed September 9, 2016, which is a continuation of U.S. Patent Application No. 15/148,839, filed May 6, 2016, which is a continuation of U.S. Patent Application No. 13/426,973, filed March 22, 2012, which is a continuation of U.S. Patent Application No. 12/225,040, filed on May 13, 2009, which is a 35 U.S.C. 371 national stage filing of International Application No. PCT/US2007/006606, filed March 15, 2007. The contents of the aforementioned applications are hereby incorporated by reference in their entireties.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on July 5, 2017, is named AXJ_114BUSCN5_SL.txt and is 10,376 bytes in size.

BACKGROUND

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematologic disease that results from clonal expansion of hematopoietic stem cells with somatic mutations in the X-linked gene called PIG-A.[1,2] Mutations in PIG-A lead to an early block in the synthesis of glycosylphosphatidylinositol (GPI)-anchors, which are required to tether many proteins to the cell surface. Consequently, PNH blood cells have a partial (type II) or complete (type III) deficiency of GPI-anchored proteins.

Intravascular hemolysis is a prominent feature of PNH and a direct result of the absence of the GPI-anchored complement regulatory protein CD59.[3,4] Under normal circumstances, CD59 blocks the formation of the terminal complement complex (also called the membrane attack complex) on the cell surface, thereby preventing erythrocyte lysis and platelet activation.[5-8]

Excessive or persistent intravascular hemolysis in PNH patients not only results in anemia (normal ranges of hemoglobin are 14-18 g/dL for men and 12-16 g/dL for women, and persons with lower levels are considered to be anemic), but also hemoglobinuria and clinical sequelae related to the release of the erythrocyte contents into the circulation: fatigue, thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.[9,10,21,22] Indeed, impaired quality of life in PNH is disproportionate to the degree of anemia. Many PNH patients depend on blood transfusions to maintain adequate erythrocyte hemoglobin levels. There have been no therapies that effectively reduce intravascular hemolysis and improve the associated clinical morbidities in PNH.

Eculizumab is a humanized monoclonal antibody directed against the terminal complement protein C5.[11] In a preliminary, 12-week, open-label clinical study in 11 PNH patients, eculizumab was shown to reduce intravascular hemolysis and transfusion requirements.[12] However, this unblinded study involved a small number of patients with no control arm and without protocol-driven transfusion standards.

SUMMARY

The present pivotal, phase III study, Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria (TRIUMPH), evaluated the effect of eculizumab on the stabilization of hemoglobin levels and transfusion requirements during 6 months of treatment in a cohort of 87 transfusion-dependent PNH patients. Measures of intravascular hemolysis and quality of life were also assessed. This is the first placebo controlled study of a PNH patient population to control hemolysis and to differentiate between the effects due to hemolysis and the effects due to anemia.

It has been surprisingly discovered that certain aspects of quality of life were unexpectedly improved by the treatment of PNH patients with eculizumab. Furthermore, these improvements in the quality of life were independent of transfusion. The improved aspects include, e.g., global health status, physical functioning, emotional functioning, cognitive functioning, role

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functioning, social functioning, fatigue, pain, dyspnea, appetite loss and insomnia. Improvement was also seen in nausea and vomiting, diarrhea, constipation, and financial difficulties but did not reach the level of statistical significance. Because the treated patients remained anemic throughout their treatment, it was unexpected that all of these improvements would have been seen because they were previously thought to be a result of the patient being anemic. Although not wishing to be bound by any theory, it appears that some of the symptoms are likely due, at least in part, to hemolysis and release of hemoglobin into the bloodstream and do not result solely from the patient being anemic. The treatment with eculizumab decreases the amount of lysis thereby limiting hemoglobin release into the bloodstream, thereby apparently resulting in the improvements seen in the treated patients' quality of life. The results presented herein indicate that any treatment that decreases hemolysis in a patient will result in an improvement in the quality of life of said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits complement or inhibits formation of C5b-9.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of a patient suffering from paroxysmal nocturnal hemoglobinuria, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method to improve at least one aspect of the quality of life of an anemic patient whose anemia results at least in part from hemolysis, said method comprising administering to said patient in need thereof a compound which inhibits intravascular hemolysis, wherein said patient remains anemic. In certain embodiments, said method results in a greater than 30% reduction in LDH in said patient.

In certain aspects, the application provides a method of prolonging the health-adjusted life expectancy of a patient comprising administering to said

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patient in need thereof a compound which inhibits formation of C5b-9. In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman. In certain embodiments, said patient suffers from paroxysmal nocturnal hemoglobinuria.

In certain aspects, the application provides a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides a method of treating a patient suffering from paroxysmal nocturnal hemoglobinuria by administering a pharmaceutical composition comprising an antibody that binds C5 or an active antibody fragment thereof. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is eculizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof is pexelizumab. In certain embodiments, the pharmaceutical formulations of the application may be administered to a subject, particularly a subject having PNH.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers,

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tubing, etc.

In certain embodiments, said quality of life is measured by a FACIT-Fatigue score. In certain embodiments, the FACIT-Fatigue score increases by at least 3 points. In certain embodiments, the FACIT-Fatigue score increases by ≥ 4 points.

In certain embodiments, said quality of life is measured by an EORTC QLQ-C30 score. In certain embodiments, said EORTC QLQ-C30 score improves by $\geq 10\%$ of the pretreatment score. In certain embodiments, said aspect of the quality of life as measured by an EORTC QLQ-C30 score is selected from the group consisting of a) global health status, b) physical functioning, c) emotional functioning, d) cognitive functioning, e) role functioning, f) social functioning, g) fatigue, h) pain, i) dyspnea, j) appetite loss, and k) insomnia. In certain embodiments, said aspect of quality of life is fatigue.

In certain embodiments, said compound is selected from the group consisting of CR1, LEX-CR1, MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. In certain embodiments, said compound is a steroid that suppresses complement.

In certain embodiments, said compound is selected from the group consisting of antibodies, active antibody fragments, soluble complement inhibitory compounds, proteins, soluble complement inhibitors with a lipid tail, protein fragments, peptides, small organic compounds, RNA aptamers, L-RNA aptamers, spiegelmers, antisense compounds, serine protease inhibitors, double stranded RNA, small interfering RNA, locked nucleic acid inhibitors, and peptide nucleic acid inhibitors. In certain embodiments, said compound is an antibody or an active antibody fragment. In certain embodiments, said antibody or active antibody fragment is selected from the group consisting of a) polyclonal antibodies, b) monoclonal antibodies, c) single chain antibodies, d) chimeric antibodies, e) humanized antibodies, f) Fabs, g) F(ab')s, h) $F(ab')_2$s, i) Fvs, j) diabodies, and k) human antibodies.

In certain embodiments, said antibody or an active antibody fragment thereof binds C5. In certain embodiments, said antibody or active antibody fragment blocks C5 cleavage. In certain embodiments, said antibody or active antibody fragment inhibits the formation of C5b-9. In certain embodiments, said

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antibody is eculizumab. In certain embodiments, said antibody or active antibody fragment is administered for at least 6 months. In certain embodiments, said patient has aplastic anemia or myelodysplastic syndrome.

In certain embodiments, said antibody that binds C5 or an active antibody fragment thereof is administered in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the single unit dosage form is lyophilized. In certain embodiments, the single unit dosage form is a sterile solution. In certain embodiments, the single unit dosage form is a preservative free formulation. In certain embodiments, the 300 mg single-use dosage form comprises 30 ml of a 10 mg/ml sterile, preservative free solution.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises an altered constant region, wherein said antibody or antigen-binding fragment exhibits decreased effector function relative to an anti-CDCP1 antibody with a native constant region. In certain embodiments, decreased effector function comprises one or more properties of the following group: a) decreased antibody-dependent cell-mediated cytotoxicity (ADCC), and b) decreased complement dependent cytotoxicity (CDC), compared to an anti-CDCP1 antibody with a native constant region. In certain embodiments, the altered constant region comprises a G2/G4 construct in place of the G1 domain.

In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, and wherein the light chain variable region comprises one or more CDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region consists of SEQ ID NO: 1 and the light chain variable region consists of SEQ ID NO: 3. In certain embodiments, the pharmaceutical

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composition comprises eculizumab. In certain embodiments, the pharmaceutical composition comprises pexelizumab. In certain embodiments, the antibody that binds C5 or an active antibody fragment thereof comprises a heavy chain and a light chain, wherein the heavy chain consists of SEQ ID NO: 2 and the light chain consists of SEQ ID NO: 4.

In certain embodiments, said patient is anemic. In certain embodiments, said patient remains anemic following treatment. In certain embodiments, said patient has a hemoglobin level less than i) 14 g/dL if a man or ii) 12 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 13 g/dL if a man or ii) 11 g/dL if a woman. In certain embodiments, said patient has a hemoglobin level less than i) 12 g/dL if a man or ii) 10 g/dL if a woman.

In certain embodiments, said health-adjusted life expectancy is measured according to a unit selected from the group consisting of Years of potential life lost, Disability-free life expectancy, Health-adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, or Years of healthy life.

In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one day. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least week. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one month. In certain embodiments, the health-adjusted life expectancy in a subject is prolonged by at least one year.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the pharmaceutical composition comprises an antibody that binds C5 or an active antibody fragment thereof.

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BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-B show that eculizumab treatment decreases intravascular hemolysis and increases PNH type III erythrocytes. Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels. Figure 1B shows the mean proportion of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients.

Figure 2 shows the effect of eculizumab treatment on transfusion requirements in PNH patients. This is a Kaplan-Meier plot of time to first transfusion for eculizumab- and placebo-treated patients from baseline through week 26. The P value is from the log rank analysis.

Figure 3 shows the effect of eculizumab on fatigue assessed by the FACIT-Fatigue Instrument. Quality of Life scores were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument. Values for change from baseline to 26 weeks represent least-square means. A positive change indicates an improvement and a negative change indicates deterioration in the FACIT-Fatigue measures of quality of life.

DETAILED DESCRIPTION

I. Definitions

The term "derived from" means "obtained from" or "produced by" or "descending from".

The term "genetically altered antibodies" means antibodies wherein the amino acid sequence has been varied from that of a native antibody. Because of the relevance of recombinant DNA techniques to this application, one need not be confined to the sequences of amino acids found in natural antibodies; antibodies can be redesigned to obtain desired characteristics. The possible variations are many and range from the changing of just one or a few amino acids to the complete redesign of, for example, the variable or constant region. Changes in the constant region will, in general, be made in order to improve or alter characteristics, such as complement fixation, interaction with membranes and other effector functions. Changes in the variable region will be

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made in order to improve the antigen binding characteristics.

The term "an antigen-binding fragment of an antibody" refers to any portion of an antibody that retains the binding utility to the antigen. An exemplary antigen-binding fragment of an antibody is the heavy chain and/or light chain CDR, or the heavy and/or light chain variable region.

The term "homologous," in the context of two nucleic acids or polypeptides refers to two or more sequences or subsequences that have at least about 85%, at least 90%, at least 95%, or higher nucleotide or amino acid residue identity, when compared and aligned for maximum correspondence, as measured using the following sequence comparison method and/or by visual inspection. In certain embodiments, the "homolog" exists over a region of the sequences that is about 50 residues in length, at least about 100 residues, at least about 150 residues, or over the full length of the two sequences to be compared.

Methods of determining percent identity are known in the art. "Percent (%) sequence identity" with respect to a specified subject sequence, or a specified portion thereof, may be defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul et al., J. Mol. Biol. 215:403-410 (1997); http://blast.wustl.edu/blast/README.htm- 1) with search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A "% identity value" is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported.

II. Overview

The present disclosure relates to a method of treating paroxysmal nocturnal hemoglobinuria ("PNH"), more specifically to improving certain

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aspects of quality of life which are impaired in PNH patients, and other hemolytic diseases in mammals. Specifically, the methods of treating hemolytic diseases, which are described herein, involve using compounds which bind to or otherwise block the generation and/or activity of one or more complement components. The present methods have been found to provide surprising results. For instance, hemolysis rapidly ceases upon administration of the compound which binds to or otherwise blocks the generation and/or activity of one or more complement components, with hemoglobinuria being significantly reduced after treatment. Also, hemolytic patients can be rendered less dependent on transfusions or transfusion- independent for extended periods (twelve months or more), well beyond the 120 day life cycle of red blood cells. In addition, type III red blood cell count can be increased dramatically in the midst of other mechanisms of red blood cell lysis (non-complement mediated and/or earlier complement component mediated e.g., Cb3). Another example of a surprising result is that symptoms resolved, indicating that NO serum levels were increased enough even in the presence of other mechanisms of red blood cell lysis. These and other results reported herein are unexpected and could not be predicted from prior treatments of hemolytic diseases.

III. The Complement System

The complement system, useful complement inhibitors, and use of these inhibitors to treat PNH and other patients are more fully described in PCT Patent Application PCT/US2005/003225 filed February 3, 2005 and published as International Publication Number WO 2005/074607 A2 on August 18, 2005, the contents of which are incorporated herein by reference in their entirety.

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. There are at least 25 complement proteins, which are found as a complex collection of plasma proteins and membrane cofactors. The plasma proteins make up about 10% of the globulins in vertebrate serum. Complement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting

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complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions.

The complement cascade progresses via the classical pathway or the alternative pathway. These pathways share many components and, while they differ in their initial steps, they converge and share the same "terminal complement" components (C5 through C9) responsible for the activation and destruction of target cells.

The classical complement pathway is typically initiated by antibody recognition of and binding to an antigenic site on a target cell. The alternative pathway is usually antibody independent and can be initiated by certain molecules on pathogen surfaces. Both pathways converge at the point where complement component C3 is cleaved by an active protease (which is different in each pathway) to yield C3a and C3b. Other pathways activating complement attack can act later in the sequence of events leading to various aspects of complement function.

C3a is an anaphylatoxin. C3b binds to bacterial and other cells, as well as to certain viruses and immune complexes, and tags them for removal from the circulation. C3b in this role is known as opsonin. The opsonic function of C3b is considered to be the most important anti-infective action of the complement system. Patients with genetic lesions that block C3b function are prone to infection by a broad variety of pathogenic organisms, while patients with lesions later in the complement cascade sequence, i.e., patients with lesions that block C5 functions, are found to be more prone only to Neisseria infection, and then only somewhat more prone (Fearon, 1983).

C3b also forms a complex with other components unique to each pathway to form classical or alternative C5 convertase, which cleaves C5 into C5a and C5b. C3 is thus regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways (Wurzner et al., 1991). This property of C3b is regulated by the serum protease Factor I, which acts on C3b to produce iC3b. While still functional as opsonin, iC3b cannot form an active C5 convertase.

C5 is a 190 kDa beta globulin found in normal serum at approximately 75 μg/mL (0.4 μM). C5 is glycosylated, with about 1.5-3

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percent of its mass attributed to carbohydrate. Mature C5 is a heterodimer of a 999 amino acid 115 kDa alpha chain that is disulfide linked to a 656 amino acid 75 kDa beta chain. C5 is synthesized as a single chain precursor protein product of a single copy gene (Haviland et al., 1991). The cDNA sequence of the transcript of this gene predicts a secreted pro-C5 precursor of 1659 amino acids along with an 18 amino acid leader sequence.

The pro-C5 precursor is cleaved after amino acid 655 and 659, to yield the beta chain as an amino terminal fragment (amino acid residues +1 to 655) and the alpha chain as a carboxyl terminal fragment (amino acid residues 660 to 1658), with four amino acids deleted between the two.

C5a is cleaved from the alpha chain of C5 by either alternative or classical C5 convertase as an amino terminal fragment comprising the first 74 amino acids of the alpha chain (i.e., amino acid residues 660-733). Approximately 20 percent of the 11 kDa mass of C5a is attributed to carbohydrate. The cleavage site for convertase action is at or immediately adjacent to amino acid residue 733. A compound that would bind at or adjacent to this cleavage site would have the potential to block access of the C5 convertase enzymes to the cleavage site and thereby act as a complement inhibitor.

C5 can also be activated by means other than C5 convertase activity. Limited trypsin digestion (Minta and Man, 1977; Wetsel and Kolb, 1982) and acid treatment (Yamamoto and Gewurz, 1978; Vogt et al., 1989) can also cleave C5 and produce active C5b.

C5a is another anaphylatoxin. C5b combines with C6, C7, and C8 to form the C5b- 8 complex at the surface of the target cell. Upon binding of several C9 molecules, the membrane attack complex (MAC, C5b-9, terminal complement complex-TCC) is formed. When sufficient numbers of MACs insert into target cell membranes the openings they create (MAC pores) mediate rapid osmotic lysis of the target cells. Lower, non-lytic concentrations of MACs can produce other effects. In particular, membrane insertion of small numbers of the C5b-9 complexes into endothelial cells and platelets can cause deleterious cell activation. In some cases activation may precede cell lysis.

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As mentioned above, C3a and C5a are anaphylatoxins. These activated complement components can trigger mast cell degranulation, which releases histamine and other mediators of inflammation, resulting in smooth muscle contraction, increased vascular permeability, leukocyte activation, and other inflammatory phenomena including cellular proliferation resulting in hypercellularity. C5a also functions as a chemotactic peptide that serves to attract pro-inflammatory granulocytes to the site of complement activation.

The beneficial effect of anti-C5 mAb has previously been reported in several experimental models including myocardial reperfusion (Vakeva et al., 1998), systemic lupus erythematosus (Wang et al., 1996) and rheumatoid arthritis (Wang et al., 1995); as well as in human clinical trials (Kirschfink, 2001) of autoimmune disease, cardiopulmonary bypass and acute myocardial infarction.

IV Measures of Quality of Life

Various measurements exist to assess quality of life .and the effect of medical interventions on quality of life for example the Mini-Mental State Examination (MMSE), the Short Test of Mental Status, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the FACIT questionnaires and subscales including fatigue and anemia, the Likert Scale, and Borg Scale (Tombaugh, et al., J. Am. Geriatr. Soc. 40:922, 1992; Cummings, JAMA. 269(18):2420, 1993; Crum, et al., JAMA. 269(18):2386, 1993; Folstein, et al., J. Psychiat. Res. 12:189,1975; Kokmen, et al., Mayo Clin. Proc. 62:281, 1987; Tang-Wai, et al., Arch. Neurol. 60:1777, 2003; Tamburini, Ann. Oncol. 12(Suppl. 3):S7, 2001; Webster et al., Health and Quality of Life Outcomes. 1:79, 2003, www.hqlo.com/content/I/I/79; Grant, et al., Chest. 116:1208, 1999; and www.qolid.org). Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by the Functional Assessment of Chronic

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Illness Therapy (FACIT) Measurement System. In certain embodiments, improvement in quality of life is measured by: a) full scales; b) stand-alone subscales; and c) symptom indices.

In certain embodiments, improvement in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9 is measured by a European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire. In certain embodiments, the EORTC questionnaire is the QLQ-C30.

In certain embodiments, improvement in quality of life is measured by the health- adjusted life expectancy (HALE) index as described in Wilkins, R. and Adams, OB., Am J Public Health, 73: 1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein MC and Stason WB, N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

In certain embodiments, improvement in quality of life is measured by the following instruments: Years of potential life lost, Disability-free life expectancy, Health- adjusted life year, Quality adjusted life year, Healthy years equivalents, Healthy days gained, Episode-free day, Q-TWiST, Health Utilities Index, and Years of healthy life. These measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality of life due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods improve the quality of life of a patient for at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years, or the duration of treatment.

In certain embodiments, the symptoms used to measure quality of life

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are scaled for intensity. In certain embodiments, the symptoms are scaled for frequency. In certain embodiments, the symptoms are scaled for intensity and frequency.

In certain aspects, the application provides a method for prolonging the health-adjusted life expectancy of a subject comprising administering to the subject a compound which inhibits complement or inhibits formation of C5b-9. The above measurements account for both changes in mortality as well as changes in morbidity and disability. Any of these measurements may be used to assess the change in quality-adjusted life expectancy due to administration of a compound which inhibits complement or inhibits formation of C5b-9.

In one embodiment, the disclosed methods prolong the health-adjusted life expectancy in a subject by at least one day, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least 6 months, at least one year, at least 18 months, at least two years, at least 30 months, or at least three years as measured by the health-adjusted life expectancy (HALE) index as described in Wilkins et al. Am J Public Health, 73:1073-1080 (1983). Health-adjusted life expectancy is an average of the quality-adjusted life years (QALY) for a given population and can be used to evaluate the therapeutic value of a medical intervention. Quality-adjusted life years is a health index that weighs each year of life on a scale from 1 to 0 (Weinstein et al., N Engl J Med, 296:716-721 (1977)). Perfect health is rated as 1, death is rated as 0, and disability and pain are rated based on severity. QALY is determined by multiplying the number of years at each health status.

V Inhibitors of the Complement Cascade

In certain embodiments, any compound which binds to or otherwise blocks the generation and/or activity of one or more complement components can be used in the present methods. In certain embodiments, a complement inhibitor may be a small molecule (up to 6,000 Da in molecular weight), a nucleic acid or nucleic acid analog, a peptidomimetic, or a macromolecule that is not a nucleic acid, a serine protease inhibitor, or a

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protein. These agents include, but are not limited to, small organic molecules, RNA aptamers including ARC187 (which is commercially available from Archemix Corp., Cambridge, Mass.), L-RNA aptamers, Spiegelmers, antisense compounds, molecules which may be utilized in RNA interference (RNAi) such as double stranded RNA including small interfering RNA (siRNA), locked nucleic acid (LNA) inhibitors, peptide nucleic acid (PNA) inhibitors.

In certain embodiments, a complement inhibitor may be a protein or protein fragment. Proteins are known which inhibit the complement cascade, including CD59, CD55, CD46 and other inhibitors of C8 and C9 (see, e.g., U.S. Patent 6,100,443). Proteins known as complement receptors and which bind complement are also known (see, Published PCT Patent Application WO 92/10205 and U.S. Patent 6,057,131). Use of soluble forms of complement receptors, e.g., soluble CR1, can inhibit the consequences of complement activation such as neutrophil oxidative burst, complement mediated neural injury, and C3a and C5a production. In certain embodiments, a complement inhibitor may be naturally occurring or soluble forms of complement inhibitory compounds such as CR1, LEX-CR1 , MCP, DAF, CD59, Factor H, cobra venom factor, FUT-175, complestatin, and K76 COOH. Those of skill in the art recognize the above as some, but not all, of the known methods of inhibiting complement and its activation.

In certain embodiments, a complement inhibitor may be an antibody capable of inhibiting complement, such as an antibody that can block the formation of MAC. For example, an antibody complement inhibitor may include an antibody that binds C5. Such anti-C5 antibodies may directly interact with C5 and/or C5b, so as to inhibit the formation of and/or physiologic function of C5b.

Suitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Patent 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Patent 5,660,825). U.S. Patent 6,355,245 teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

The concentration and/or physiologic activity of C5a and C5b in a body

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fluid can be measured by methods well known in the art. For C5a such methods include chemotaxis assays, RIAs, or ELISAs (see, for example, Ward and Zvaifler, J Clin Invest. 1971 Mar;50(3):606-16; Wurzner, et al., Complement Inflamm. 8:328-340, 1991). For C5b, hemolytic assays or assays for soluble C5b-9 as discussed herein can be used. Other assays known in the art can also be used. Using assays of these or other suitable types, candidate antibodies capable of inhibiting complement such as anti-C5 antibodies, now known or subsequently identified, can be screened in order to 1) identify compounds that are useful in the practice of the application and 2) determine the appropriate dosage levels of such compounds.

An antibody capable of inhibiting complement such as an antibody that binds C5 affecting C5b is preferably used at concentrations providing substantial reduction (i.e., reduction by at least about 25% as compared to that in the absence of the antibody that binds C5) in the C5b levels present in at least one blood-derived fluid of the patient following activation of complement within the fluid. Such concentrations can be conveniently determined by measuring the cell-lysing ability (e.g., hemolytic activity) of complement present in the fluid or the levels of soluble C5b-9 present in the fluid. Accordingly, a specific concentration for an antibody that affects C5b is one that results in a substantial reduction (i.e., a reduction by at least about 25%) in the cell-lysing ability of the complement present in at least one of the patient's blood-derived fluids. Reductions of the cell-lysing ability of complement present in the patient's body fluids can be measured by methods well known in the art such as, for example, by a conventional hemolytic assay such as the hemolysis assay described by Kabat and Mayer (eds), "Experimental Immunochemistry, 2d Edition", 135-240, Springfield, IL, CC Thomas (1961), pages 135- 139, or a conventional variation of that assay such as the chicken erythrocyte hemolysis method described below.

Specific antibodies capable of inhibiting complement, such as an antibody that binds C5, are relatively specific and do not block the functions of early complement components. In particular, such specific agents will not substantially impair the opsonization functions associated with complement component C3b, which functions provide a means for clearance of foreign

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particles and substances from the body.

C3b is generated by the cleavage of C3, which is carried out by classical and/or alternative C3 convertases and results in the generation of both C3a and C3b. Therefore, in order not to impair the opsonization functions associated with C3b, specific antibodies capable of inhibiting complement such as an antibody that binds C5 do not substantially interfere with the cleavage of complement component C3 in a body fluid of the patient (e.g., serum) into C3a and C3b. Such interference with the cleavage of C3 can be detected by measuring body fluid levels of C3a and/or C3b, which are produced in equimolar ratios by the actions of the C3 convertases. Such measurements are informative because C3a and C3b levels will be reduced (compared to a matched sample without the antibody capable of inhibiting complement such as an antibody that binds C5) if cleavage is interfered with by an antibody capable of inhibiting complement such as an antibody that binds C5.

In practice, the quantitative measurement of such cleavage is generally more accurate when carried out by the measurement of body fluid C3a levels rather than of body fluid C3b levels, since C3a remains in the fluid phase whereas C3b is rapidly cleared. C3a levels in a body fluid can be measured by methods well known in the art such as, for example, by using a commercially available C3a EIA kit, e.g., that sold by Quidel Corporation, San Diego, Calif., according to the manufacturer's specifications. Particularly specific antibodies capable of inhibiting complement such as an antibody that binds C5 produce essentially no reduction in body fluid C3a levels following complement activation when tested in such assays.

Certain antibodies of the disclosure will prevent the cleavage of C5 to form C5a and C5b, thus preventing the generation of the anaphylatoxic activity associated with C5a and preventing the assembly of the membrane attack complex associated with C5b. As discussed above, in a particular embodiment, these anti-C5 antibodies will not impair the opsonization function associated with the action of C3b.

A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage.

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This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Patent 6,355,245). These antibodies disclosed in U.S. Patent 6,355,245 include a preferred whole antibody (now named eculizumab). A similar antibody against mouse C5 is called BB5.1 (Frei et al., Mol. Cell. Probes. 1:141-149 (1987)). Antibodies to inhibit complement activity need not be monoclonal antibodies. They can be, e.g., polyclonal antibodies. They may additionally be antibody fragments. An antibody fragment includes, but is not limited to, an Fab, F(ab'), $F(ab')_2$, single-chain antibody, and Fv. Furthermore, it is well known by those of skill in the art that antibodies can be humanized (Jones et al., Nature 321:522-5 (1986)), chimerized, or deimmunized. The antibodies to be used in the present disclosure may be any of these. It is preferable to use humanized antibodies.

In specific embodiments, a therapeutic agent of the disclosure comprises an antibody or antibody fragment. Antibodies and fragments thereof may be made by any conventional method, such as those methods described herein. Antibodies are found in multiple forms, e.g., IgA, IgG, IgM, etc. Additionally, antibodies can be engineered in numerous ways. They can be made as single-chain antibodies (including small modular immunopharmaceuticals or SMIPs™), Fab and $F(ab')_2$ fragments, etc. Antibodies can be humanized, chimerized, deimmunized, or fully human. Numerous publications set forth the many types of antibodies and the methods of engineering such antibodies. For example, see U.S. Patent Nos. 6,355,245; 6,180,370; 5,693,762; 6,407,213; 6,548,640; 5,565,332; 5,225,539; 6,103,889; and 5,260,203.

This invention provides fragments of anti-C5 antibodies, which may comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata et al., Protein Eng. 8:1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding

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fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fe" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment of an antibody yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" refers to the minimum antibody fragment that contains a complete antigen- recognition and -binding site. This region consists of a dimer of one heavy- and one light- chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although likely at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the scFv to form the desired structure for antigen binding. For a review of scFv see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

SMIPs are a class of single-chain peptide engineered to include a target binding region, effector domain (CH2 and CH3 domains). *See, e.g.,* U.S. Patent Application Publication No. 20050238646. The target binding region may be derived from the variable region or CDRs of an antibody, e.g.,

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an antibody that binds C5 of the application. Alternatively, the target binding region is derived from a protein that binds C5.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light- chain variable domain (V_L) in the same polypeptide chain (V_H-V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen- binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

It is well known that the binding to a molecule (or a pathogen) of antibodies with an Fe region assists in the processing and clearance of the molecule (or pathogen). The Fe portions of antibodies are recognized by specialized receptors expressed by immune effector cells. The Fe portions of lgG1 and lgG3 antibodies are recognized by Fe receptors present on the surface of phagocytic cells such as macrophages and neutrophils, which can thereby bind and engulf the molecules or pathogens coated with antibodies of these isotypes (C. A. Janeway et al., Immunobiology 5th edition, page 147, Garland Publishing (New York, 2001)).

This disclosure also provides monoclonal anti-C5 antibodies. A monoclonal antibody can be obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are often synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. Monoclonal antibodies may also be produced in transfected cells, such as CHO cells and NS0 cells. The modifier

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"monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and does not require production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler et al., Nature 256:495-497 (1975), or may be made by recombinant DNA methods *(see, e.g.,* U.S. Patent Nos. 4,816,567 and 6,331,415). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature 352:624-628 (1991) and Marks et al., J. Mol. Biol. 222:581-597 (1991), for example.

A description of the preparation of a mouse anti-human-C5 monoclonal antibody with specific binding characteristics is presented in U.S. Patent Application Publication No. 20050226870. Wurzner et al., Complement Inflamm. 8:328-340 (1991), describe the preparation of other mouse anti-human-C5 monoclonal antibodies referred to as N19-8 and N20-9.

Other antibodies specifically contemplated are "oligoclonal" antibodies. As used herein, the term "oligoclonal" antibodies" refers to a predetermined mixture of distinct monoclonal antibodies. *See, e.g.,* PCT publication WO 95/20401; U.S. Patent Nos. 5,789,208 and 6,335,163. In one embodiment, oligoclonal antibodies consisting of a predetermined mixture of antibodies against one or more epitopes are generated in a single cell. In other embodiments, oligoclonal antibodies comprise a plurality of heavy chains capable of pairing with a common light chain to generate antibodies with multiple specificities *(e.g.,* PCT publication WO 04/009618). Oligoclonal antibodies are particularly useful when it is desired to target multiple epitopes on a single target molecule *(e.g.,* C5). In view of the assays and epitopes disclosed herein, those skilled in the art can generate or select antibodies or mixtures of antibodies that are applicable for an intended purpose and desired need.

In certain embodiments that include a humanized and/or chimeric antibody, one or more of the CDRs are derived from an anti-human C5 antibody. In a specific embodiment, all of the CDRs are derived from an anti-human C5 antibody. In another specific embodiment, the CDRs from more

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than one anti-human C5 antibody are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first anti-human C5 antibody combined with CDR2 and CDR3 from the light chain of a second anti-human C5 antibody, and the CDRs from the heavy chain may be derived from a third anti-human C5 antibody. Further, the framework regions may be derived from one of the same anti-human C5 antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. Human or humanized antibodies are specific for administration to human patients.

In certain embodiments, single chain antibodies, and chimeric, humanized or primatized (CDR-grafted) antibodies, as well as chimeric or CDR-grafted single chain antibodies, comprising portions derived from different species, are also encompassed by the present disclosure as antigen-binding fragments of an antibody. The various portions of these antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous protein using genetic engineering techniques. For example, nucleic acids encoding a chimeric or humanized chain can be expressed to produce a contiguous protein. See, e.g., U.S. Pat. Nos. 4,816,567 and 6,331,415; U.S. Pat. No. 4,816,397; European Patent No. 0,120,694; WO 86/01533; European Patent No. 0,194,276 B1; U.S. Pat. No. 5,225,539; and European Patent No. 0,239,400 B1. See also, Newman et al., BioTechnology 10:1455-1460 (1992), regarding primatized antibody. See, e.g., Ladner et al., U.S. Pat. No. 4,946,778; and Bird et al., Science 242:423-426 (1988), regarding single chain antibodies.

In addition, functional fragments of antibodies, including fragments of chimeric, humanized, primatized or single chain antibodies, can also be produced. Functional fragments of the subject antibodies retain at least one binding function and/or modulation function of the full-length antibody from which they are derived. Preferred functional fragments retain an antigen-binding function of a corresponding full-length antibody (such as for example, ability of antibody that binds C5 to bind C5).

General methods for the immunization of animals (in this case with C5 and/or C5b, etc.), isolation of antibody producing cells, fusion of such cells

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with immortal cells (e.g., myeloma cells) to generate hybridomas secreting monoclonal antibodies, screening of hybridoma supernatants for reactivity of secreted monoclonal antibodies with a desired antigen (in this case the immunogen or a molecule containing the immunogen), the preparation of quantities of such antibodies in hybridoma supernatants or ascites fluids, and for the purification and storage of such monoclonal antibodies, can be found in numerous publications. These include: Coligan, et al., eds. Current Protocols In Immunology, John Wiley & Sons, New York, 1992; Harlow and Lane, Antibodies. A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988; Liddell and Cryer, A Practical Guide To Monoclonal Antibodies, John Wiley & Sons, Chichester, West Sussex, England, 1991; Montz et al., Cellular Immunol. 127:337-351 (1990); Wurzner et al., Complement Inflamm. 8:328-340 (1991); and Mollnes et al., Scand. J. Immunol. 28:307-312 (1988).

VI Methods of Treatment

Methods of the application may be used to treat paroxysmal nocturnal hemoglobinuria associated symptoms. Methods of the application may be used to treat anemia associated symptoms. Treatment of paroxysmal nocturnal hemoglobinuria and/or anemia may be administered by standard means. Treatments of the application may be used in combination with other treatments of the application or known treatments for paroxysmal nocturnal hemoglobinuria and/or anemia. Treatments of the application may be co-administered with other treatments that treat symptoms of paroxysmal nocturnal hemoglobinuria and/or anemia.

VII Pharmaceutical Formulations and Uses

Methods of administration of small molecules, proteins, and nucleic acids are well- known to those of skill in the art. Methods of administration of antibodies are well-known to those of skill in the art. To achieve the desired inhibition, the antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab fragments will also require differing dosages than the

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equivalent intact immunoglobulins, as they are of considerably smaller mass than intact immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood. The dose will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician. Dosage levels of the antibodies for human subjects are generally between about 1 mg per kg and about 100 mg per kg per patient per treatment, and preferably between about 5 mg per kg and about 50 mg per kg per patient per treatment. In terms of plasma concentrations, the antibody concentrations are preferably in the range from about 25 μg/mL to about 500 μg/mL. However, greater amounts may be required for extreme cases and smaller amounts may be sufficient for milder cases.

In certain embodiments, the pharmaceutical composition is in a single unit dosage form. In certain embodiments, the single unit dosage form is a 300 mg unit dosage form. In certain embodiments, the pharmaceutical composition is lyophilized. In certain embodiments, the pharmaceutical composition is a sterile solution. In certain embodiments, the pharmaceutical composition is a preservative free formulation. In certain embodiments, the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. In certain embodiments, the antibody is administered according to the following protocol: 600 mg via 25 to 45 minute IV infusion every 7 ± 2 days for the first 4 weeks, followed by 900 mg for the fifth dose 7 ± 2 days later, then 900 mg every 14 ± 2 days thereafter. Antibody is administered via IV infusion over 25 to 45 minute.

Administration of the anti-C5 antibodies will generally be performed by an intravascular route, e.g., via intravenous infusion by injection. Other routes of administration may be used if desired but an intravenous route will be the most preferable. Formulations suitable for injection are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed. (1985). Such formulations must be sterile and non-pyrogenic, and generally will include a pharmaceutically effective carrier, such as saline, buffered (e.g., phosphate buffered) saline, Hank's solution, Ringer's solution, dextrose/saline, glucose solutions, and the like. The

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formulations may contain pharmaceutically acceptable auxiliary substances as required, such as, tonicity adjusting agents, wetting agents, bactericidal agents, preservatives, stabilizers, and the like. In certain embodiments, complement inhibitors such as eculizumab may be administered via IV infusion and diluted to a final concentration of 5 mg/ml prior to administration.

Administration of the antibodies capable of inhibiting complement such as an antibody that binds C5 will generally be performed by a parenteral route, typically via injection such as intra-articular or intravascular injection (e.g., intravenous infusion) or intramuscular injection. Other routes of administration, e.g., oral (p.o.), may be used if desired and practicable for the particular antibody capable of inhibiting complement to be administered. Antibodies capable of inhibiting complement such as an antibody that binds C5 can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and in vivo half-life of the particular antibody capable of inhibiting complement being administered. Doses of antibodies capable of inhibiting complement such as an antibody that binds C5 will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

In certain embodiments, a typical therapeutic treatment includes a series of doses, which will usually be administered concurrently with the monitoring of clinical endpoints with the dosage levels adjusted as needed to achieve the desired clinical outcome. In certain embodiments, treatment is administered in multiple dosages over at least a week. In certain embodiments, treatment is administered in multiple dosages over at least a month. In certain embodiments, treatment is administered in multiple dosages over at least a year. In certain embodiments, treatment is administered in multiple dosages over the remainder of the patient's life.

The frequency of administration may also be adjusted according to various parameters. These include the clinical response, the plasma half-life of the therapeutic of the disclosure, and the levels of the antibody in a body fluid, such as, blood, plasma, serum, or synovial fluid. To guide adjustment of the frequency of administration, levels of the therapeutic of the disclosure in the

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body fluid may be monitored during the course of treatment.

In certain embodiments, the frequency of administration may be adjusted according to an assay measuring cell-lysing ability of complement present in one or more of the patient's body fluids. The cell-lysing ability can be measured as percent hemolysis in hemolytic assays of the types described herein. A 10% or 25% or 50% reduction in the cell-lysing ability of complement present in a body fluid after treatment with the antibody capable of inhibiting complement used in the practice of the application means that the percent hemolysis after treatment is 90, 75, or 50 percent, respectively, of the percent hemolysis before treatment.

For the treatment of hemolytic diseases such as PNH by systemic administration of an antibody capable of inhibiting complement such as an antibody that binds C5 (as opposed to local administration), administration of a large initial dose is specific, i.e., a single initial dose sufficient to yield a substantial reduction, and more preferably an at least about 50% reduction, in the hemolytic activity of the patient's serum. Such a large initial dose is preferably followed by regularly repeated administration of tapered doses as needed to maintain substantial reductions of serum hemolytic titer. In another embodiment, the initial dose is given by both local and systemic routes, followed by repeated systemic administration of tapered doses as described above.

Formulations particularly useful for antibody-based therapeutic agents are also described in U.S. Patent App. Publication Nos. 20030202972, 20040091490 and 20050158316. In certain embodiments, the liquid formulations of the application are substantially free of surfactant and/or inorganic salts. In another specific embodiment, the liquid formulations have a pH ranging from about 5.0 to about 7.0. In yet another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from about 1 mM to about 100 mM. In still another specific embodiment, the liquid formulations comprise histidine at a concentration ranging from 1 mM to 100 mM. It is also contemplated that the liquid formulations may further comprise one or more excipients such as a saccharide, an amino acid (e.g., arginine, lysine, and methionine) and a polyol. Additional descriptions and

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methods of preparing and analyzing liquid formulations can be found, for example, in PCT publications WO 03/106644, WO 04/066957, and WO 04/091658.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the application.

In certain embodiments, formulations of the subject antibodies are pyrogen-free formulations which are substantially free of endotoxins and/or related pyrogenic substances. Endotoxins include toxins that are confined inside microorganisms and are released when the microorganisms are broken down or die. Pyrogenic substances also include fever-inducing, thermostable substances (glycoproteins) from the outer membrane of bacteria and other microorganisms. Both of these substances can cause fever, hypotension and shock if administered to humans. Due to the potential harmful effects, it is advantageous to remove even low amounts of endotoxins from intravenously administered pharmaceutical drug solutions. The Food & Drug Administration ("FDA") has set an upper limit of 5 endotoxin units (EU) per dose per kilogram body weight in a single one hour period for intravenous drug applications (The United States Pharmacopeial Convention, Pharmacopeial Forum 26 (1):223 (2000)). When therapeutic proteins are administered in amounts of several hundred or thousand milligrams per kilogram body weight, as can be the case with monoclonal antibodies, it is advantageous to remove even trace amounts of endotoxin.

Formulations of the subject antibodies include those suitable for oral, dietary, topical, parenteral (e.g., intravenous, intraarterial, intramuscular, subcutaneous injection), ophthalmologic (e.g., topical or intraocular), inhalation (e.g., intrabronchial, intranasal or oral inhalation, intranasal drops), rectal, and/or intravaginal administration. Other suitable methods of administration can also include rechargeable or biodegradable devices and controlled release polymeric devices. Stents, in particular, may be coated with a controlled release polymer mixed with an agent of the application. The

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pharmaceutical compositions of this disclosure can also be administered as part of a combinatorial therapy with other agents (either in the same formulation or in a separate formulation).

The amount of the formulation which will be therapeutically effective can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. The dosage of the compositions to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms. For example, the actual patient body weight may be used to calculate the dose of the formulations in milliliters (mL) to be administered. There may be no downward adjustment to "ideal" weight. In such a situation, an appropriate dose may be calculated by the following formula: Dose (mL) = [patient weight (kg) x dose level (mg/kg)/ drug concentration (mg/mL)]

To achieve the desired treatment results, anti-C5 antibodies can be administered in a variety of unit dosage forms. The dose will vary according to the particular antibody. For example, different antibodies may have different masses and/or affinities, and thus require different dosage levels. Antibodies prepared as Fab' fragments or single chain antibodies will also require differing dosages than the equivalent native immunoglobulins, as they are of considerably smaller mass than native immunoglobulins, and thus require lower dosages to reach the same molar levels in the patient's blood.

Other therapeutics of the disclosure can also be administered in a variety of unit dosage forms and their dosages will also vary with the size, potency, and *in vivo* half-life of the particular therapeutic being administered.

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Doses of therapeutics of the disclosure will also vary depending on the manner of administration, the particular symptoms of the patient being treated, the overall health, condition, size, and age of the patient, and the judgment of the prescribing physician.

The formulations of the application can be distributed as articles of manufacture comprising packaging material and a pharmaceutical agent which comprises the antibody capable of inhibiting complement and a pharmaceutically acceptable carrier as appropriate to the mode of administration. The packaging material may include a label which indicates that the formulation is for use in the treatment of hemolytic diseases such as PNH. Although antibodies are preferred, especially anti-C5 antibodies which have already been shown to be safe and effective at decreasing the accumulation of downstream complement components in persons, the use of other complement inhibitors is also contemplated by this disclosure. The pharmaceutical formulations and uses of the disclosure may be combined with- any known complement inhibitors or hemolytic diseases treatments known in the art.

In certain aspects, the application provides kits comprising a pharmaceutical composition of the application. In some embodiments, the kit further comprises at least one component of a closed sterile system. Components of the closed sterile system include, but are not limited to, needles, syringes, catheter based syringes, needle based injection devices, needle-less injection devices, filters, tubing, valves and cannulas. In a related embodiment, the kit comprise components for the removal of a preservative from the composition. Such components include filters, syringes, vials, containers, tubing, etc.

EXEMPLIFICATION

METHODS

Patient Selection

The TRIUMPH trial consisted of a 2-week screening period, an observation period of up to 3 months duration, and a 26-week treatment period.

During the screening period, patients were evaluated with respect to inclusion and exclusion criteria. Men and women, 18 years or older,

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diagnosed as having PNH with a type III erythrocyte population of ≥10%, and who had received at least 4 transfusions in the previous 12 months were eligible. Concomitant administration of erythropoietin, immunosuppressants, corticosteroids, coumadin, low molecular weight heparin, iron supplements, and folic acid were not reasons for exclusion, provided the doses were steady prior to the first visit and throughout the duration of the study. Because of the increased frequency of neisserial infections in individuals genetically deficient in terminal complement proteins, all patients were vaccinated against *Neisseria meningitides*. Patients were to avoid conception. The protocol was approved by an Investigational Review Board at each clinical site and written informed consent was obtained from all patients enrolled.

Patients transfused with a mean pre-transfusion hemoglobin level > 10.5 g/dL over the previous 12 months, and those who showed evidence of having a suppressed immune response, complement deficiency, or active bacterial infection, including any history of meningococcal disease, were excluded from the study. Patients were also not eligible if they had previously received a bone marrow transplant or if they had participated in another trial or received another investigational drug within 30 days of the first visit. An individualized transfusion algorithm was calculated for each patient based on their prior 12-month transfusion history; the written algorithm documented the number of packed red blood cell (PRBC) units transfused for given hemoglobin values and served as a prospectively determined guide for transfusion during observation and treatment periods.

Each patient considered eligible entered an observation period of up to 13 weeks in order to confirm their PBRC transfusion dependence. At least one transfusion --termed the "qualifying" transfusion-- during the 13-week observation period at a hemoglobin value at or below 9 g/dL with symptoms, or at or below 7 g/dL with or without symptoms, in accordance with the transfusion algorithm indicated for each patient, was a requirement to proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set point" for that individual for the purpose of the primary efficacy variable. A platelet count ≥100,000/mL and a LDH level ≥1.5 times the upper limit of the normal

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range were also required either at screening or during the observation period for eligibility.

Study Design

Patients were randomly assigned on a one-on-one basis to receive either placebo or eculizumab (Soliris™, Alexion Pharmaceuticals, Inc.) within 10 days of the qualifying transfusion. Study medication was dosed in a blinded fashion as follows: 600 mg eculizumab for patients randomly assigned to active drug, or placebo for those patients randomly assigned to placebo, respectively via IV infusion every 7±1 days for 4 doses; followed by 900 mg eculizumab, or placebo, respectively, via IV infusion 7±1 day later; followed by a maintenance dose of 900 mg eculizumab, or placebo, respectively, via IV infusion every 14±2 days for a total of 26 weeks of treatment.

Measures of Clinical Efficacy

There were two co-primary endpoints in the study: (1) stabilization of hemoglobin levels, defined as a hemoglobin value maintained above the individual hemoglobin set point in the absence of transfusions for the entire 26-week treatment period, and (2) reduction in units of PRBCs transfused during the 26-week treatment phase of the study. The trigger for transfusion during the study period remained unchanged for each patient, as compared with their care before entry into the study: patients received blood transfusions when they had symptoms resulting from anemia and reached their individualized, pre-determined "set point". Pre-specified secondary endpoints included transfusion avoidance, hemolysis as measured by LDH area under the curve from baseline to 26 weeks, and QoL changes as measured from baseline to 26 weeks using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) instrument.[13] Pre-specified exploratory analyses included assessment of the EORTC QLQ-C30 instrument,[14] the change in LDH from baseline through week 26, and thrombosis. Other pre-specified measurements included pharmacokinetics, pharmacodynamics, and immunogenicity of eculizumab. Time to first transfusion during the 26-week treatment phase and the proportion of PNH type III blood cells were also assessed.

Safety Assessments

Treatment-emergent adverse events, clinical laboratory tests (e.g., serum

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chemical analyses and complete blood counts), electrocardiogram data, and vital signs were assessed. Adverse events were defined using the MedDRA preferred terms and tabulated as incidence rates per treatment group.

Statistical Analysis

For co-primary endpoints, analyses were performed according to the intention to treat using the data from all patients who were randomized and received study drug; stabilization of hemoglobin levels was analyzed using the Fisher's exact test and total PRBC units transfused were analyzed with the Wilcoxon's rank sum test. For comparison of treatment effect on transfusion avoidance, the Fisher's exact test was used on the incidence and the log rank test was used for time to first transfusion. For LDH area under the curve the Wilcoxon's rank sum test was used.

Quality of life measure of fatigue was assessed using the scoring guidelines for the FACIT-Fatigue instrument. [15] Assessment of quality of life measures based on the EORTC QLQ-C30 instrument was conducted in accordance with the appropriate scoring guidelines.[16] The changes of FACIT-Fatigue and EORTC QLQ-C30 scores from baseline through 26 weeks were analyzed using a mixed model, with baseline as covariate, treatment and time as fixed effects, and patient as a random effect. Changes in LDH levels and PNH type III erythrocytes from baseline through 26 weeks were analyzed using the same mixed model. Two-sided tests were used for all analyses. The adverse events and long-term safety checklist were tabulated separately and compared between treatments using the Fisher's exact test. A p-value ≤ 0.05 was considered to be statistically significant.

RESULTS

Characteristics of Patients

A total of 115 PNH patients were screened. Six patients did not meet the inclusion/exclusion criteria during the screening period. Twenty-one other patients did not receive a qualifying transfusion and were not randomized into the treatment phase. One patient who did not meet the inclusion criteria was inadvertently randomized, but did not receive study medication. Thus 87 hemolytic PNH patients (35 men and 52 women) were enrolled and randomized

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to receive either eculizumab (N=43) or placebo (N=44), exceeding the original target of 75 randomized patients.

Patient characteristics were similar in the eculizumab- and placebo-treated cohorts: median age, 41 (range 20-85) and 35 (range 18-78) years; median duration of PNH, 4.2 (range 0.8 to 29.7) and 9.2 (range 0.4 to 38.3) years; patients with history of aplastic anemia, 4 and 11; history of myelodysplastic syndrome, 1 and 0; and history of thrombosis, 9 (16 events) and 8 (11 events). Stable usage of concomitant medications at baseline in the eculizumab- and placebo-treated groups included the following: erythropoietin, 3 patients and 0 patients; cyclosporine, 1 and 1; anticoagulants (coumarins or heparins) 21 and 11; and steroids (glucocorticoids or androgenic steroids), 12 and 12, respectively.

Of the 87 patients randomized, 85 completed the trial. Two patients who did not complete the trial had been randomized to the eculizumab arm: one patient discontinued due to the inconvenience of travel to the study site and the second patient became pregnant. Ten patients in the placebo-treatment group discontinued infusions, in all cases due to perceived lack of efficacy, but they remained in the study for monitoring purposes.

Pharmacokinetics/Pharmacodynamics

In 42 of the 43 eculizumab-treated patients the levels of drug during the maintenance period (900 mg every 2 weeks±2 days) were sufficient to completely block serum hemolytic activity (mean trough value at week 26 of 101.8 μg/mL). A single patient did not sustain therapeutic trough levels of eculizumab and demonstrated a breakthrough in complement blockade during the last few days of each dosing interval. These breakthroughs were clinically manageable and quickly resolved following the next dose.

Hemolytic Efficacy Variables

The impact of terminal complement inhibition with eculizumab on chronic intravascular hemolysis in PNH patients was demonstrated in this study by an immediate (one week) and sustained decrease in mean levels of LDH (Figure I A). The median LDH area under the curve during the 26-week study period was reduced 85.8% in eculizumab- relative to placebo-treated patients ($P<0.001$). The mean LDH level decreased from 2199.7±157.7 IU/L at baseline to 327.3±67.6 IU/L by 26 weeks in eculizumab-treated patients while levels in

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placebo-treated patients remained consistently elevated with values of 2259.0±158.5 IU/L at baseline and 2418.9±140.3 IU/L at 26 weeks (P<0.001, for eculizumab versus placebo). A second biochemical measure of hemolysis, serum aspartate aminotransferase (AST), also showed a statistically significant improvement following eculizumab- versus placebo-treatment (data not shown). Haptoglobin levels were statistically significantly increased in eculizumab- as compared to placebo-treated patients but mean levels of haptoglobin were still below normal levels in eculizumab-treated patients (data not shown).

Figure 1A shows the degree of intravascular hemolysis in PNH patients, demonstrated by mean lactate dehydrogenase (LDH) levels (±standard error) from baseline (study week 0) to week 26 for both eculizumab- and placebo-treated patient populations. Screening occurred up to 3 months prior to study week 0. The upper limit of the normal range (103-223 IU/L) for LDH is indicated by a dashed line. LDH was reduced to a mean level just above the upper limit of normal at week 26 for eculizumab-treated patients; 15 of 41 patients who completed the study demonstrated LDH levels within the normal range. All placebo-treated patients remained at least 5 times above the upper limit of normal at week 26. The P value is based on a mixed model analysis from baseline through week 26. Figure 1B shows the mean proportion (±standard error) of PNH type III erythrocytes assessed for placebo- and eculizumab-treated patients. The screening visit occurred up to 3 months prior to study week 0. The P value is based on a mixed model analysis from baseline through week 26.

A corollary to the reduction in intravascular hemolysis during eculizumab treatment was an observed increase in the PNH type III erythrocyte population (Figure 1B). The mean proportions of type III erythrocytes increased from 28.1±2.0% at baseline to 56.9±3.6% by week 26 for eculizumab-treated patients while proportions in the placebo group remained constant with mean values of 35.7±2.8% before treatment to 35.5±2.8% at 26 weeks (P<0.001, for eculizumab versus placebo). By contrast, the proportions of PNH type III granulocytes and monocytes did not change significantly between the treatment groups during the treatment period and were greater than 90% at week 26.

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CLINICAL EFFICACY

Co-primary endpoints

The co-primary efficacy endpoints in the TRIUMPH trial were stabilization of hemoglobin levels and reduction in PRBC units transfused. At the end of the treatment period, 48.8% of eculizumab-treated patients had maintained levels of hemoglobin above the pre-specified set-point (median set-point value of 7.7 g/dL for both treatment groups) in the absence of transfusions, whereas stabilization of hemoglobin did not occur in any of the patients in the placebo group ($P<0.001$; Table 1). By week 26, the median of PRBC units transfused per patient was 0 in the eculizumab group and 10.0 in the placebo cohort ($P<0.001$), while the mean of PRBC units transfused was 3.0 and 11.0 in the eculizumab and placebo cohorts, respectively. In the 6-month period prior to the study, the median of PRBC units transfused per patient was 9.0 in the eculizumab cohort and 8.5 in placebo patients while the mean of PRBC units transfused was 9.6±0.6 and 9.7±0.7, respectively. Mean hemoglobin levels were similar between the treatment groups at baseline (10.0±1.8 g/dL in eculizumab-treated patients and 9.7±1.8 g/dL in placebo-treated patients) and did not substantially change by week 26 (10.1±2.5 g/dL and 8.9±2.2 g/dL in eculizumab and placebo cohorts; respectively).

The median time to first transfusion was not reached during the study period in eculizumab-treated patients (it was greater than 26 weeks) while the placebo group reached the median time to first transfusion in only 4 weeks ($P<0.001$; Figure 2). Transfusion avoidance was achieved in 51.2% and 0% of the eculizumab and placebo cohorts, respectively ($P<0.001$). By the end of the 26-week treatment period, the total PRBC units transfused were 131 in eculizumab-treated patients versus 482 in the placebo group (Table 1). By contrast, in the 6-month period prior to the study, total PRBC units transfused in the eculizumab- and placebo-cohorts were 413 and 417, respectively.

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Table 1

Stabilization of Hemoglobin Levels and Reduction

in Transfusion Requirements during Eculizumab Treatment

	PRE-TREATMENT HISTORY*		TREATMENT PERIOD		
	Placebo	Eculizumab	Placebo	Eculizumab	P Value
†Stabilization of Hemoglobin Levels in the absence of transfusions (percent of patients)	NA	NA	0	48.8	<0.001‡
†Units Transfused per Patient					
Median	8.5	9.0	10	0	<0.001§
Mean± SE	9.7±0.7	9.6±0.6	11.0±0.83	3.0±0.67	
Total Units Transfused per Group	417	413	482	131	

*Twelve month historical transfusion data normalized to 6 months

†Co-primary endpoints

‡Base on 2-sided Fisher's exact test

§Based on Wilcoxon's rank sum test NA, not applicable

Improvements in quality of life measures

Assessments of quality of life in PNH patients during eculizumab treatment were performed using two different instruments; FACIT-Fatigue and the EORTC QLQ-C30. Eculizumab-treated patients showed a mean increase (improvement) in the FACIT-Fatigue score of 6.4±1.2 points from baseline to 26-weeks while the mean score in placebo patients decreased by 4.0±1.7 points, a total difference between the treatment groups of 10.4 points (Figure 3). Mixed model analysis of covariance demonstrated a statistically significant difference between treatment groups (P<0.001).

For the EORTC instrument, improvements were observed with eculizumab- treatment in each subscale. Statistically significant improvements with eculizumab- compared with placebo-treated groups were observed in the following quality of life subscales (Table 2): global health status (P<0.001), physical

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functioning (P<0.001), emotional functioning (P=0.008), cognitive functioning (P=0.002), role functioning (P<0.001), social functioning (P=0.003), fatigue (P<0.001), pain (P=0.002), dyspnea (P<0.001), appetite loss (P<0.001), and insomnia (P=0.014). The improvements with eculizumab treatment in the other scales, including nausea and vomiting, diarrhea, constipation, and financial difficulties, did not reach statistical significance.

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Table 2

Effect of Eculizumab Treatment on
Quality of Life Assessed by the EORTC QLQ-C30 Instrument

	Mean Change from Baseline to Week 26*			
	Placebo	Eculizumab	Absolute Difference	P Value†
Global Health Status	-8.5	10.9	19.4	<0.001
Functional				
Role	-6.9	17.9	24.8	<0.001
Social	2.0	16.7	14.6	=0.003
Cognitive	-6.1	7.9	14.0	=0.002
Physical	-3.5	9.4	13.0	<0.001
Emotional	-3.7	7.5	11.2	=0.008
Symptoms/Single Items				
Fatigue	10.0	-16.9	27.0	<0.001
Pain	5.3	-12.3	17.6	=0.002
Dyspnea	8.9	-7.9	16.9	<0.001
Appetite Loss	3.3	-10.3	13.6	<0.001
Insomnia	4.9	-7.9	12.8	=0.014
Financial Difficulties	0.0	-10.3	10.3	=0.186
Constipation	0.0	-6.3	6.3	=0.199
Nausea/vomiting	2.8	-0.4	3.2	=0.056
Diarrhea	5.7	4.8	0.9	=0.147

*A positive change indicates an improvement in global health status and functional scales and a negative change indicates an improvement in symptom and single item scales.

†Based on a mixed analysis-of-covariance model with visit as a fixed effect, patient as a random effect and baseline as a covariate.

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Relationship between FACIT-Fatigue quality of life and intravascular hemolysis

In order to determine if there was a treatment independent relationship between the FACIT-Fatigue quality of life instrument and intravascular hemolysis, an analysis was performed whereby the mean LDH level (through the 26 week study period) for each TRIUMPH patient was analyzed as a function of the patient's respective mean change in FACIT-Fatigue score from baseline (through the 26 week study period) (see Table 3). For this analysis, mean levels of LDH were divided into 4 groups that included: normal levels, 1-2 times the upper limit of normal (ULN), 2-10 times the upper limit of normal, and greater than 10 times the upper limit of normal. The analysis demonstrated that patients who maintained normal LDH levels throughout the study experienced significant improvements in fatigue when compared to patients who had incrementally higher levels of LDH throughout the study (p=0.0048). These data establish a clear link between increasing intravascular hemolysis as measured by LDH levels and decreased quality of life as measured by the FACIT-Fatigue quality of life instrument.

Table 3

Relationship between FACIT-Fatigue and Intravascular Hemolysis

		Change of FACIT from Baseline		
Treatment Group	LDH Category	<4	>=4	P Value
Combined	Normal	4 (30.77%)	9 (69.23%)	.0048
	1-2 X ULN	16 (61.54%)	10 (38.46%)	
	2 - 10 X ULN	18 (72.00%)	7 (28.00%)	
	> 10 X ULN	16 (80.00%)	4 (20.00%)	

Safety

There were no deaths in the study. Serious adverse events (SAEs) were reported for 13 patients, of which 4 occurred in the eculizumab-treated cohort and 9 were in the placebo-treated cohort (see Table 4). All patients recovered without sequelae.

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The most common AEs reported for eculizumab-treated patients were headache, nasopharyngitis, back pain, and upper respiratory tract infection. Headache and back pain occurred more commonly in the eculizumab-treatment group compared with the placebo group. However, the increase in headaches was limited to the first 2 weeks of therapy and was mild to moderate. There were no statistically significant differences in incidents rates between treatment groups for any AEs reported.

One episode of thrombosis (Budd-Chiari) occurred m a placebo-treated patient. There were no thromboses in eculizumab-treated patients.

Only one patient showed a detectable level of anti-eculizumab antibodies in the eculizumab-treated cohort; this response was weak (did not titrate), occurred at only one time point and did not result in a disruption of complement blockade.

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Table 4

Adverse Event Reporting

SERIOUS ADVERSE EVENTS*	Placebo Patients n (percent)	Eculizumab Patients n (percent)
Total	9 (20.5)	4 (9.3)
Eculizumab treatment emergent		
Exacerbation of PNH	3 (6.8)	1 (2.3)
Renal colic	0	1 (2.3)
Lumbar sacral disc prolapse	0	1 (2.3)
Alpha streptococcal bacteremia	0	1 (2.3)
Central line infection and UTI	1 (2.3)	0 (0)
Upper respiratory tract infection	1 (2.3)	0 (0)
Probable viral infection	1 (2.3)	0 (0)
Neutropenia	1 (2.3)	0 (0)
Cellulitis / folliculitis / neutropemia	1 (2.3)	0 (0)
Anemia and pyrexia	1 (2.3)	0 (0)
MOST FREQUENT ADVERSE EVENTS*†		
Headache§	12 (27.3)	19ǂ (44.2)
Nasopharyngitis	8 (18.2)	10 (23.3)
Upper respiratory tract infection	10 (22.7)	6 (14)
Back pain	4 (9.1)	8 (18.6)
Nausea	5 (11.4)	7 (16.3)
Cough	4 (9.1)	5 (11.6)
Diarrhea	5 (11.4)	4 (9.3)
Arthralgia	5 (11.4)	3 (7.0)
Abdominal pain	5 (11.4)	2 (4.7)
Dizziness	5 (11.4)	2 (4.7)
Vomiting	5 (11.4)	2 (4.7)
Fatigue	1 (2.3)	5 (11.6)
Viral infection	5 (11.4)	1 (2.3)

*By preferred terms

†Occurring in 10% or more of patients

ǂSixteen of 19 patients experienced headache within 48 hours of infusion

§Following the first 2 weeks of dosing, 20.9% of eculizumab- and 22.7%

of placebo-treated patients experienced headache

DISCUSSION

Chronic intravascular hemolysis with periods of acute exacerbation are the classical manifestations of PNH, frequently resulting in anemia, the need for transfusions to sustain hemoglobin levels, and deterioration in quality of life. In the phase III pivotal TRIUMPH study, we examined the effect of terminal complement inhibition with eculizumab on hemoglobin levels and transfusion requirements in patients with PNH. Forty-nine percent of patients treated with eculizumab over the 6-month period demonstrated stabilization of hemoglobin in the absence of transfusions compared to no patients in the placebo arm of the trial. Over 50% of eculizumab-treated patients were transfusion independent during the entire study compared to none in the placebo arm, and the overall mean transfusion rate was reduced by 73%. Moreover, even in patients who did not achieve transfusion independence, eculizumab treatment was associated with a 44%. reduction in the rate of transfusion (data now shown).

Lactate dehydrogenase, a biochemical marker of hemolysis in PNH,[9] was immediately and consistently decreased in all eculizumab-treated patients, while patients in the placebo cohort continued to hemolyze with levels of LDH exceeding 5 times the upper limit of the normal range in all patients at the study end. Levels of LDH were reduced into the normal range in approximately one-third of eculizumab-treated patients, while the remainder stabilized at a level just above the upper limit of normal suggesting residual low level hemolysis in some patients. Levels of haptoglobin, a more sensitive marker of the presence of cell free hemoglobin in the circulation, were undetectable in most patients. Low level hemolysis in a subset of eculizumab-treated patients is possibly due to an inherent decrease in survival of these cells or C3b-mediated, extravascular clearance of PNH erythrocytes through the reticuloendothelial system.[17]

Before eculizumab treatment, hemoglobin levels in study patients were artificially maintained by frequent transfusion. Therefore, stabilization of hemoglobin levels with a concomitant cessation of or reduction in

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transfusions represents a net increase in endogenous hemoglobin levels. Our data suggest that resolution of hemolysis with eculizumab results in a new steady state hemoglobin level determined by a balance between the extent of the underlying bone marrow dysfunction, the number of PNH erythrocytes that are preserved by eculizumab therapy and the new level (if any) of transfusion requirement.

Patients with PNH generally experience markedly impaired quality of life characterized by fatigue, anemia, thrombosis, and pulmonary hypertension as well as smooth muscle dystonia including abdominal pain, dysphagia, and erectile dysfunction.[9,10,18] These symptoms have been attributed to both excessive intravascular hemolysis and downstream scavenging of nitric oxide by cell free hemoglobin in plasma. The reduction of intravascular hemolysis in eculizumab-treated patients in the current study was associated with significant improvements in the fatigue component of quality of life relative to placebo-treated patients as assessed via the FACIT-Fatigue instrument. Further, eculizumab therapy was associated with a median increase of 6.4 points over baseline values established before treatment. It has previously been demonstrated that an increase of 3 or more points from baseline represents a clinically important difference in this quality of life instrument. [19] Patients who received eculizumab also experienced a significant improvement in most domains of the EORTC QLQ-30 relative to the placebo-treated cohort including global health status, physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, fatigue, pain, dyspnea, appetite loss, and insomnia. Improvement in the fatigue component of the EORTC QLQ-30 provides support for the improvement demonstrated in the FACIT-Fatigue instrument during eculizumab therapy. Importantly, these improvements in quality of life in the eculizumab-treated patients occurred despite similar levels of erythrocyte hemoglobin in the two treatment groups, further supporting the contribution of hemolysis per se, as opposed to anemia, in mediating the poor quality of life in PNH patients. Clinical assessment of additional life quality-related symptoms of PNH, including abdominal pain, dysphagia, and erectile dysfunction, have also been reported to improve during eculizumab therapy.[20]

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Eculizumab was safe and well-tolerated. There were no deaths in the study and only a single thrombotic event which occurred in a placebo patient in a site (the hepatic veins) which is typical of the thrombosis in PNH. The relative brief duration of this study was not sufficient to address the relevant issue of a possible protection from thrombosis by terminal complement inhibition with eculizumab.

Adverse events were generally mild with headache occurring at increased frequency in the eculizumab-treated patients; however, this increased frequency did not persist following the first two doses of therapy. There were 4 SAEs in the eculizumab treatment group and 9 SAEs in the placebo group. There was no evidence of increased infection risk in eculizumab-treated patients during the study period. One eculizumab-treated patient showed a low level of anti-eculizumab antibodies at one time point during the study which did not persist and did not result in a disruption of complement blockade. There were no AEs associated with eculizumab withdrawal in the 2 eculizumab-treated patients who did not complete the trial. Additional safety assessments, as well as efficacy measures, are being examined in an ongoing multi-center, open-label Phase III safety trial of eculizumab (SHEPHERD) in approximately 95 patients with PNH.

Results from the current randomized, double-blind, placebo-controlled, global study show that terminal complement inhibition with eculizumab appears to be a safe and effective therapy for patients with the rare disorder PNH. Treatment with eculizumab reduced intravascular hemolysis, and stabilized hemoglobin levels despite a reduction of transfusions, to the point where most PNH patients were rendered transfusion independent. Substantial and clinically meaningful improvements in fatigue and other key quality of life parameters were also demonstrated. All of the 85 patients who completed the study elected to receive eculizumab in an open-label extension study and all currently remain on drug. The results of the TRIUMPH study indicate that terminal complement inhibition with eculizumab safely and effectively addresses an important consequence of the underlying genetic defect in PNH hematopoietic stem cells by providing a therapeutic replacement for the terminal complement inhibitor deficiency.

The present invention provides among other things treatment with an inhibitor of complement. Many variations of the invention will become apparent to

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those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

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Ref Type: Abstract

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Page 1031

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SEQUENCES

SEQ ID NO: 1 -Eculizumab V_H

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMG
EILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFF
GSSPNWYFDVWGQGTLVTVSSA

SEQ ID NO: 2 -Eculizumab Heavy chain

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMG
EILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFF
GSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYT
CNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
RLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO: 3 -Eculizumab V_L

MDMRVPAQLLGLLLLWLRGARCDIQMTQSPSSLSASVGDRVTITCGASE
NIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQ
PEDFATYYCQNVLNTPLTFGQGTKVEIKRT

SEQ ID NO: 4 -Eculizumab Light chain

DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIY
GATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFG
QGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV
THQGLSSPVTKSFNRGEC

SEQ ID NO: 5 -Eculizumab CDRH1

NYWIQ

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SEQ ID NO: 6 -Eculizumab CDRH2
EILPGSGSTEYTENFKD

SEQ ID NO: 7 -Eculizumab CDRH3
YFFGSSPNWYFDV

SEQ ID NO: 8 -Eculizumab CDRL1
GASENIYGALN

SEQ ID NO: 9 -Eculizumab CDRL2
GATNLAD

SEQ ID NO: 10 -Eculizumab CDRL3
QNVLNTPLT

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Page 1034

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: August 24, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/642,096 Confirmation No.: 7606

Filed: July 5, 2017 Art Unit: 1662

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

Examiner: Not Yet Assigned

Office of Initial Patent Examination's Filing Receipt Corrections
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED FILING RECEIPT

Dear Sir:

Applicant hereby requests that a corrected Filing Receipt be issued in the above-identified patent application to correct an omission found in the Inventor information.

Please correct the Inventor(s) information from:

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;
~~Mark EVANS, Radnor, PA~~

to:

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;
Mark J. EVANS, Radnor, PA;

Applicant additionally requests that all pertinent U.S. Patent and Trademark Office records relating to the subject application be changed to reflect this correction.

Dated: August 24, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Samsung Bioepis Exhibit No. 1002
Page 1036

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: August 24, 2017
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/642,096 Confirmation No.: 7606

Filed: July 5, 2017 Art Unit: 1662

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

Examiner: Not Yet Assigned

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR REFUND

Dear Sir:

Applicant respectfully requests a refund of the following fees charged to our Deposit Account No. 12-0080 on July 27, 2017, against the above-referenced patent application:

Each independent claim in excess of 3	(Fee Code: 1201)	$420.00
Each claim in excess of 20	(Fee Code: 1202)	$2,480.00
Total Refund Being Requested:		**$2,900.00**

Applicant respectfully asserts that the above-referenced fees were debited at the time of filing due to the inadvertent inclusion of language in Applicant's First Preliminary Amendment authorizing the PTO to debit and/or credit any additional fees or overpayments.

Applicant respectfully requests that the fees outlined above in the amount of **$2,900.00** be refunded to our Deposit Account No. 12-0080, under Order No. AXJ-114BUSCN5.

Dated: August 24, 2017

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/642,096	07/05/2017	1662	4500	AXJ-114BUSCN5	8	2

CONFIRMATION NO. 7606

CORRECTED FILING RECEIPT

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

OC000000093726478

Date Mailed: 08/29/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;
Mark J. EVANS, Radnor, PA;

Applicant(s)

Alexion Pharmaceuticals, Inc., New Haven, CT;

Power of Attorney: The patent practitioners associated with Customer Number 133485

Domestic Priority data as claimed by applicant

This application is a CON of 15/284,015 10/03/2016 PAT 9732149
which is a CON of 15/260,888 09/09/2016 PAT 9725504
which is a CON of 15/148,839 05/06/2016 PAT 9718880
which is a CON of 13/426,973 03/22/2012 ABN
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 07/19/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/642,096**

Projected Publication Date: Perfected

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

800

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/642,096

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	8 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5

CONFIRMATION NO. 7606

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

IMPROPER CFR REQUEST

OC000000093728480

Date Mailed: 08/29/2017

RESPONSE TO REQUEST FOR CORRECTED FILING RECEIPT

Power of Attorney, Claims, Fees, System Limitations, and Miscellaneous

In response to your request for a corrected Filing Receipt, the Office is unable to comply with your request because:

- The number of claims reflected on the filing receipt is correct. Upon review of the claims, it was found that there was a miscalculation by the applicant. This may be due to improperly presented multiple dependent claims, typographical error, misnumbering of the claims, or other oversight. An amendment may be necessary to correct the problem.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ggasgedom/

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/642,096	07/05/2017	1662	4500	AXJ-114BUSCN5	8	2

CONFIRMATION NO. 7606

UPDATED FILING RECEIPT

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

OC000000093728227

Date Mailed: 08/29/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Leonard BELL, Woodbridge, CT;
Russell P. ROTHER, Oklahoma City, OK;
Mark J. EVANS, Radnor, PA;

Applicant(s)

Alexion Pharmaceuticals, Inc., New Haven, CT;

Power of Attorney: The patent practitioners associated with Customer Number 133485

Domestic Priority data as claimed by applicant

This application is a CON of 15/284,015 10/03/2016 PAT 9732149
which is a CON of 15/260,888 09/09/2016 PAT 9725504
which is a CON of 15/148,839 05/06/2016 PAT 9718880
which is a CON of 13/426,973 03/22/2012 ABN
which is a CON of 12/225,040 05/13/2009 ABN
which is a 371 of PCT/US2007/006606 03/15/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 07/19/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/642,096**

Projected Publication Date: 12/07/2017

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

800

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Samsung Bioepis Exhibit No. 1002
Page 1048

To: chris.schlauch@nelsonmullins.com,ipqualityassuranceboston@nelsonmullins.com,ipboston.docketing@nel
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 133485

Aug 29, 2017 07:33:48 AM

Dear PAIR Customer:

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 133485 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

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Application	Document	Mailroom Date	Attorney Docket No.
15642096	APP.FILE.REC	08/29/2017	AXJ-114BUSCN5
	M327	08/29/2017	AXJ-114BUSCN5
	APP.FILE.REC	08/29/2017	AXJ-114BUSCN5

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Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 15/642,096	Filing Date 07/05/2017	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**0**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**0**

APPLICATION AS AMENDED – PART II

AMENDMENT	08/24/2017	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0	X $0 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $0 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
GLORIA J. TRAMMELL

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5

CONFIRMATION NO. 7606

133485
Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square
30th Floor
Boston, MA 02109-2127

PUBLICATION NOTICE

OC00000095939166

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

Publication No.US-2017-0349652-A1
Publication Date:12/07/2017

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

To: chris.schlauch@nelsonmullins.com,ipqualityassuranceboston@nelsonmullins.com,ipboston.docketing@nel
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 133485

Dec 08, 2017 04:01:34 AM

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Application	Document	Mailroom Date	Attorney Docket No.
15642096	NTC.PUB	12/07/2017	AXJ-114BUSCN5

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PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15642096
Filing Date	2017-07-05
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN5

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	1	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14 February 1999 (1999-02-14), retrieved from STN Database accession no. 219685-50-4, 2 pages.	☐
	2	European Examination Report, European Application No. 16172335.8, dated November 23, 2017, 8 pages.	☐
	3	European Examination Report, European Application No. 16195355.9, dated November 17, 2017, 30 pages.	☐
	4	Third Party Observation, European Application No. 16195355.9, dated December 12, 2017, 40 pages.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2018-03-28
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	32177079
Application Number:	15642096
International Application Number:	
Confirmation Number:	7606
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Anita Costa
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN5
Receipt Date:	28-MAR-2018
Filing Date:	05-JUL-2017
Time Stamp:	12:46:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Database_Registry.pdf	78870 2aa0d8ae24f85da4cd0f2ab5c5fc840ed5b3ded9	no	2

Warnings:

Information:					
2	Non Patent Literature	EESR.pdf	254123 dff89f9aae90f61e7b0bddabbd0f2c9d96f8ae6b	no	8
Warnings:					
Information:					
3	Non Patent Literature	Examination_report_dated_11-20-2017.pdf	1568330 e69e16ff0551b5434892dd6f40b5c53cb8737911	no	30
Warnings:					
Information:					
4	Non Patent Literature	Submission_third_party.pdf	2640014 31ea8bbcbd8e8a6371c5185c87211ca2b4bb7835	no	41
Warnings:					
Information:					
5	Transmittal Letter	2018-03-28_IDSTRANS_AXJ-114BUSCN5_4852-2148-5408_v1.pdf	24894 951a72260d0612e5020bfa0f0826d11042794677	no	2
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	IDS.pdf	80716 5c9a614aa4b26e09f5d6646a9657319d6706ae32	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
		Total Files Size (in bytes):	4646947		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

```
1/1 - (C) FILE REGISTRY
RN  - 219685-50-4  REGISTRY
ED  - Entered STN:  14 Feb 1999
CN  - Immunoglobulin, anti-(human complement C5 .alpha.-chain)
      (human-mouse monoclonal 5G1.1 heavy chain), disulfide with
      human-mouse monoclonal 5G1.1 light chain, dimer (9CI)  (CA INDEX
      NAME)
 OTHER NAMES:
CN  - Eculizumab
CN  - h5G1.1
CN  - h5G1.1VHC+h5G1.1VLC
CN  - Soliris
FS  - PROTEIN SEQUENCE
MF  - Unspecified
CI  - MAN
SR  - US Adopted Names Council (USAN)
LC  - STN Files:   ADISINSIGHT, BIOSIS, CA, CAPLUS, CBNB, CHEMCATS,
        CHEMLIST, EMBASE, IMSRESEARCH, IPA, PATDPASPC, RTECS*, TOXCENTER,
        USPAT2, USPATFULL
          (*File contains numerically searchable property data)
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1/1 - (C) FILE REGISTRY
RN  - 219685-50-4  REGISTRY
FS  - PROTEIN SEQUENCE
SQL - 1324,448,448,214,214
NTE - multichain
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type	location		description
bridge	Cys-22	- Cys-96	disulfide bridge
bridge	Cys-136	- Cys-214''	disulfide bridge
bridge	Cys-149	- Cys-205	disulfide bridge
bridge	Cys-228	- Cys-228'	disulfide bridge
bridge	Cys-231	- Cys-231'	disulfide bridge
bridge	Cys-262	- Cys-322	disulfide bridge
bridge	Cys-368	- Cys-426	disulfide bridge
bridge	Cys-22'	- Cys-96'	disulfide bridge
bridge	Cys-136'	- Cys-214'''	disulfide bridge
bridge	Cys-149'	- Cys-205'	disulfide bridge
bridge	Cys-262'	- Cys-322'	disulfide bridge
bridge	Cys-368'	- Cys-426'	disulfide bridge
bridge	Cys-23''	- Cys-88''	disulfide bridge
bridge	Cys-134''	- Cys-194''	disulfide bridge
bridge	Cys-23'''	- Cys-88'''	disulfide bridge
bridge	Cys-134'''	- Cys-194'''	disulfide bridge
uncommon	Glp-1	-	-
uncommon	Glp-1'	-	-

```
SEQ        1 XVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE
          51 ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF
         101 FGSSPNWYFD VWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL
         151 VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT
         201 QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD
         251 TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST
         301 YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY
         351 TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD
         401 SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK

SEQ        1 XVQLVQSGAE VKKPGASVKV SCKASGYIFS NYWIQWVRQA PGQGLEWMGE
          51 ILPGSGSTEY TENFKDRVTM TRDTSTSTVY MELSSLRSED TAVYYCARYF
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         301 YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY
         351 TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD
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SEQ        1 DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG
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         151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
         201 LSSPVTKSFN RGEC
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SEQ        1 DIQMTQSPSS LSASVGDRVT ITCGASENIY GALNWYQQKP GKAPKLLIYG
          51 ATNLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQN VLNTPLTFGQ
         101 GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
         151 DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
         201 LSSPVTKSFN RGEC
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BNSDOCID: <XP_____2767828A__I_>

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European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München
ALLEMAGNE

Formalities Officer
Name: Iltchev, Plamen
Tel: +49 89 2399 - 5861
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Collura, Alessandra
Tel: +49 89 2399 - 7870

Application No.	Ref.	Date
16 172 335.8 - 1466	P2913 EP/2	23.11.2017
Applicant: Alexion Pharmaceuticals, Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

In case you withdraw the application within the above-mentioned period, the examination fee will be refunded at a rate of 50% (Art. 11 (b) RFees).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered letter

The examination is being carried out on the **following application documents**

Description, Pages

1-55	as originally filed

Sequence listings, SEQ ID NO

1-10	as originally filed

Claims, Numbers

1-10	received on	31-05-2017	with letter of	31-05-2017

Drawings, Sheets

1/4-4/4	as originally filed

Reference is made to the documents already cited in the course of the procedure.

The following documents are cited by the Examiner. A copy of the documents is annexed to the communication and the numbering will be adhered to in the rest of the procedure.

D6 DATABASE REGISTRY [Online]
CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 14 February 1999 (1999-02-14), retrieved from STN Database accession no. 219685-50-4

D7 THOMAS T C ET AL: "Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv", MOLECULAR IMMUNOLOGY, PERGAMON, GB, vol. 33, no. 17-18, 1 January 1996 (1996-01-01), pages 1389-1401, XP002262113, ISSN: 0161-5890, DOI: 10.1016/S0161-5890(96)00078-8

1. Articles 76(1) and 123(2) EPC

With a letter dated 31.05.2017, the applicant filed an amended set of claims which is considered to extend the subject-matter of the claims beyond the original disclosure of the parent application and of the application as filed.

1.1 Claim 6 is directed to a pharmaceutical composition for use of claim 5 wherein the single unit dosage form is a 300 mg **antibody** single unit dosage form. The applicant indicated page 5, lines 3-5 as basis for the amended claim.

The attention of the applicant is drawn to the fact that paragraph 2 on page 5 does not allow to conclude that the 300 mg refer to the antibody and not to the weight of the whole single unit dosage form. No other passage in the original applicatio appears to provide pertinent basis for the subject-matter of claim 6. Therefore, the amendment carried out by the applicant on claim 6, and of the claims depending from claim 6, contravenes the requirements of Articles 76(1) and 1232(2) EPC.

1.2 Claim 9 is directed to a pharmaceutical composition for use of any of claims 1-8, wherein the patient **is dosed** according to the indicated dosage regimen.

As a preliminary comment, it has to be noted by the applicant that the wording "the patient is dosed" does not appear to be clear in its meaning.

Moreover, page 22, paragraph 2 indicated by the applicant as basis for the amendments carried out refer to the fact that the **antibody is administered** according to the indicated protocol and not to the fact that the patients is dosed witht e same protocol. The disclosure of paragraph 2 on page 22, therefore, does not appear to have the same scope as claim 9. Thus, claims 9 and 10 (which depends on claim 9) violate the requirements of Articles 76(1) and 123(2) EPC.

1.3 In his letter dated 31.05.2017, the applicant stated that page 44 had been amended in order to correct an obvious mistake in sequences 3 and 4.

It has however to be noted by the applicant that no amended sequence has been actually filed. The letter of the applicant dated 31.05.2017 also does not mention any amended sequence in the "Enclosures" (see last page of the letter).

Since the present application has been dealt with together with the related application EP16195355.9, belonging to the same family, it has been considered by the examining division that the amendments which the applicant intended to carry out were analogous the those filed for EP16195355.8.

Therefore, although no such amendment is present for the current application, for the sake of expediting the procedure, the examining division provides a preliminary opinion on them.

Should the applicant be minded to delete the leader peptide from the sequences 3 and 4 as he did for EP16195355.8, than the amendment would be considered as violating the requirements of Articles 76(1) and 123(2) EPC.

The applicant provided an explanation of the reason why the indicated amendments should be considered as the correction of an obvious mistake under Rule 139 EPC. He also enclosed a declaration by Bruce Andrien as technical expert.

The examining division has carefully considered the arguments of the applicant, but came to the conclusion that it cannot be excluded that the sequences 3 and 4 as originally filed were actually those for which protection was sought. No indication in the original application is present of the fact that sequences 3 and 4 did not have to include the leader peptide.

2. Article 54 EPC

As already objected in the European Search Opinion, the present application is considered not to meet the requirements of Article 54 EPC, because the subject-matter of the claims 1-4 and 8-10 is not new over the disclosure of D1-D4.

The applicant replied to this objection by saying that before the filing date of the parent/present application, i.e March 15, 2007, the sequence of eculizumab was not disclosed.

The arguments of the applicant are not considered to be correct for the following reasons.

All the cited prior art documents D1-D4 refer to eculizumab as a product available on the market. None of them contains an indication of the fact that the sequence of the antibody was secret or that any of the inventor of the patent D1 or of the members of the research group working on the studies published in D2 and D3 were bound to confidentiality with respect to the sequence of the antibody.

Therefore, the sequence of eculizumab was available to public since anybody skilled in the art could have performed a sequence listing of eculizumab with the knowledge available in the art.

D7 already discloses most of the sequence of the light and heavy chains of 5G1.1 (see Figure 1) and explains how the sequence was found. 5G1.1 is eculizumab (see D4).

Moreover, D6 teaches that eculizumanb was entered in the Registry Database on 14.02.1999.

For the reasons given above, the examining division concludes that the structure of eculizumab was available to the public well before the date of filing of the present application and that, as already pointed out in the ESOP the subject-matter of claims

is anticipated by the disclosures of D1-D4 teaching eculizumab for use in the treatment of paroxysmal nocturnal hemoglobinuria by intravenous administration and according to the dosage regimen indicated in the present claims.

3. Further objections

The objections raised in the ESOP concerning inventive step and double patenting (see points 4 and 5 of the communication) are presently maintained.

4. Article 83 EPC

In the description of the invention (see page 5 last paragraph), the applicant states that eculizumab is a specific embodiment of the described invention. The application also discloses examples in which eculizumab is tested. The complete structure of eculizumac has however not been disclosed in the application as filed. At most sequences 2 and 4 for the light and the heavy chain respectively have been said to be included in the sequence of eculizumab, but no indication is provided of the fact that the antibody contains also other sequences in the light and heavy chain.

On the contrary, present claim 2 which id dependent from claim 1 makes it clear that eculizumab is a more specific embodiment of antibodies in which the heavy chain consists of sequence 2 and the light chain consists of sequence 4.

In his letter dated 10.07.2017, the applicant argues that the structure of eculizumab had not been disclosed before the filing date of the present application.

The obvious consequence of this statement is that the skilled reader, at the filing date of the present application, did not know which antibody was actually tested and corresponded to the name "eculizumab".

Should the applicant therefore argue that the structure of the antibody was not known before the fining of the present application, than the application would be insufficiently disclosed.

If, on the contrary, the name "eculizumab" was known to indicate an antibody available to the public before the filing date of the present application, then the subject-matter of the claims would be not novel (see point 2 above).

5. Procedure

It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of Rule 43(1) EPC. The applicant should also indicate how the subject-matter of the new claim differs from the state of the art and the significance thereof.

Care should be taken not to violate the requirement s of Article 123(2) EPC.

Samsung Bioepis Exhibit No. 1002
Page 1067

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GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München
ALLEMAGNE

Formalities Officer
Name: Iltchev, Plamen
Tel: +49 89 2399 - 5861
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Collura, Alessandra
Tel: +49 89 2399 - 7870

Application No.	Ref.	Date
16 172 335.8 - 1466	P2913 EP/2	23.11.2017
Applicant Alexion Pharmaceuticals, Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

In case you withdraw the application within the above-mentioned period, the examination fee will be refunded at a rate of 50% (Art. 11 (b) RFees).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered letter
EPO Form 2001 11.16TRI

Collura, Alessandra
Primary Examiner
For the Examining Division

Enclosure(s): 5 page/s reasons (Form 2906)
File Registry 219685-50-4
XP002262113

Registered letter
EPO Form 2001 11.16TRI

Europäisches Patentamt
European Patent Office
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European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München
ALLEMAGNE

Formalities Officer
Name: Meacle, Anita
Tel: +49 89 2399 - 8780
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Collura, Alessandra
Tel: +49 89 2399 - 7870

Application No.	Ref.	Date
16 195 355.9 - 1466	P2913 EP/3	17.11.2017
Applicant Alexion Pharmaceuticals, Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

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Registered letter
EPO Form 2001 11.16TRI

Collura, Alessandra
Primary Examiner
For the Examining Division

Enclosure(s): 4 page/s reasons (Form 2906)
XP002262113

Registered letter
EPO Form 2001 11.16TRI

The examination is being carried out on the **following application documents**

Description, Pages

1-43, 45-55	as originally filed			
44	received on	10-07-2017	with letter of	10-07-2017

Sequence listings, SEQ ID NO

1-10	received on	10-07-2017	with letter of	10-07-2017

Claims, Numbers

1-3	as originally filed

Drawings, Sheets

1/4-4/4	as originally filed

Reference is made to the documents already cited in the course of the procedure.

Moreover, the following document is cited by the Examiner. A copy of the document is annexed to the communication and the numbering will be adhered to in the rest of the procedure.

D7 THOMAS T C ET AL: "Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv",
MOLECULAR IMMUNOLOGY, PERGAMON, GB,
vol. 33, no. 17-18, 1 January 1996 (1996-01-01), pages 1389-1401, XP002262113,
ISSN: 0161-5890, DOI: 10.1016/S0161-5890(96)00078-8

1. Articles 76(1) and 123(2) EPC

1.1 The objection raised in the European Preliminary Opinion (ESOP) under Article 76(1) EPC is presently maintained.

As already pointed out, the last paragraph on page 5, puts into relation sequence 2 with sequence 4 and not with sequences 8, 9 and 10.

The sequences 8, 9 **or** 10 of the heavy chain were put in relation with sequences 5, 6 **or** 7 of the light chain in a specific embodiment disclosed on page 5, lines 20-25.

No other passage of the application appears to disclose the subject-matter of present claim 1, in which the sequences 8, 9 and 10 have to be all part of the light chain.

It has to be noted by the applicant that the embodiments in which the heavy chain is characterised by sequences 5, 6 or 7 and the light chain by sequences 8, 9 **or** 10, actually include a plurality of embodiments which originate from the possibility of combining different alternative heavy chains (sequences 5, 6 or 7) with different light chains (sequences 8, 9 or 10).

Nowhere in the application as filed was the embodiment selected from these plurality of embodiments, i.e. the combination of sequences 8, 9 and 10, combined with the specific sequence 2.

1.2 With the letter dated 10.07.2017, the applicant filed amended sequences 3 and 4, in which the leader peptide has been deleted, and provided an explanation of the reason why the indicated amendments should be considered as the correction of an obvious mistake under Rule 139 EPC. He also enclosed a declaration by Bruce Andrien as technical expert.

The examining division has carefully considered the arguments of the applicant, but came to the conclusion that it cannot be excluded that the sequences 3 and 4 as originally filed were actually those for which protection was sought. No indication in the original application is present of the fact that sequences 3 and 4 did not have to include the leader peptide.

2. Article 54 EPC

As already objected in the European Search Opinion, the present application is considered not to meet the requirements of Article 54 EPC, because the subject-matter of the claims 1-3 is not new over the disclosure of D1-D4.

The applicant replied to this objection by saying that before the filing date of the parent/present application, i.e March 15, 2007, the sequence of eculizumab was not disclosed.

The arguments of the applicant are not considered to be correct for the following reasons.

All the cited prior art documents D1-D5 refer to eculizumab as a product available on the market. None of them contains an indication of the fact that the sequence of the antibody was secret or that any of the inventor of the patent D1 or of the members of the research group working on the studies published in D2 and D3 were bound to confidentiality with respect to the sequence of the antibody.

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D7 already discloses most of the sequence of the light and heavy chains of 5G1.1 (see Figure 1) and explains how the sequence was found. 5G1.1 is eculizumab (see D4).

Moreover, D6 teaches that eculizumanb was entered in the Registry Database on 14.02.1999.

For the reasons given above, the examining division concludes that the structure of eculizumab was available to the public well before the date of filing of the present application and that, as already pointed out in the ESOP the subject-matter of claims is anticipated by the disclosures of D1-D5 teaching eculizumab for use in the treatment of paroxysmal nocturnal hemoglobinuria by intravenous administration and according to the dosage regimen indicated in the present claims.

3. Article 56 EPC

The objection raised in the ESOP concerning inventive step (see point 3 of the communication) is presently maintained.

4. Article 83 EPC

In the description of the invention (see page 5 last paragraph), the applicant states that eculizumab is a specific embodiment of the described invention. The application also discloses examples in which eculizumab is tested. The complete structure of eculizumac has however not been disclosed in the application as filed. At most sequences 2 and 4 for the light and the heavy chain respectively have been said to be included in the sequence of eculizumab, but no indication is provided of the fact that the antibody contains also other sequences in the light and heavy chain.

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5. Procedure

It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, an independent claim should be filed taking account of Rule 43(1) EPC. The applicant should also indicate how the subject-matter of the new claim differs from the state of the art and the significance thereof.

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Page 1075

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European Patent Office
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European Patent Office
80298 MUNICH
GERMANY
Tel: +49 89 2399 0
Fax: +49 89 2399 4465

Vossius & Partner
Patentanwälte Rechtsanwälte mbB
Siebertstrasse 3
81675 München
ALLEMAGNE

Formalities Officer
Name: Meacle, Anita
Tel: +49 89 2399 - 8780
or call
+31 (0)70 340 45 00

Substantive Examiner
Name: Collura, Alessandra
Tel: +49 89 2399 - 7870

Application No.	Ref.	Date
16 195 355.9 - 1466	P2913 EP/3	17.11.2017
Applicant Alexion Pharmaceuticals, Inc.		

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from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

In case you withdraw the application within the above-mentioned period, the examination fee will be refunded at a rate of 50% (Art. 11 (b) RFees).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

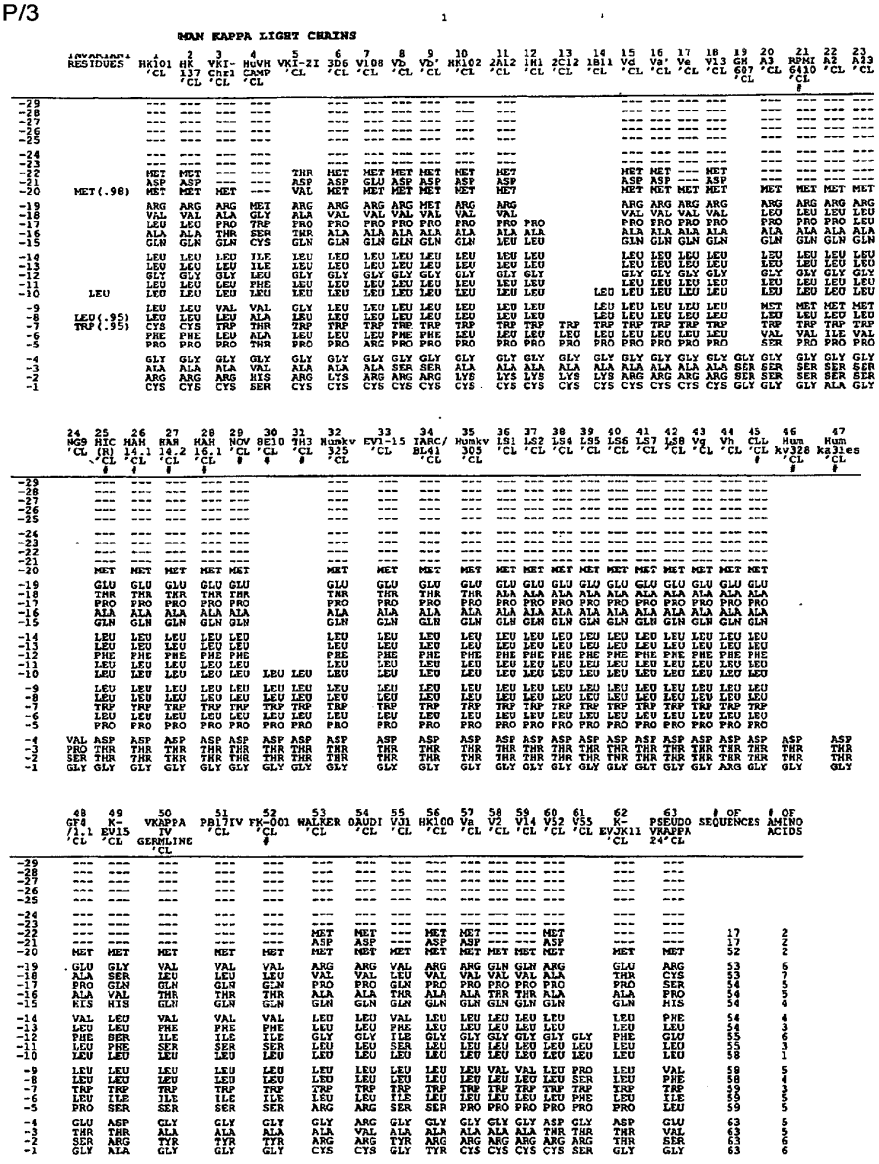
Registered letter
EPO Form 2001 11.16TRI

Collura, Alessandra
Primary Examiner
For the Examining Division

Enclosure(s): 4 page/s reasons (Form 2906)
XP002262113

Registered letter
EPO Form 2001 11.16TRI

Exhibit D



EP 16 19 5355.9
Alexion Pharmaceuticals, Inc.
Our Ref.: P2913 EP/3

Exhibit A

BRUCE A. ANDRIEN, Jr., Ph.D.

7 Finch Lane, Guilford, CT 06437, (203) 457-0067
E-Mail: bldandrien@comcast.net

CAREER EXPERIENCE:

Alexion Pharmaceuticals, Incorporated, Cheshire, Connecticut; Director Early Assay Development; July 2015 - Present.

Development responsibilities

- Developed processes to support Research's ever expanding needs including testing of proteins within the following areas: Biacore, HPLC, LOC, IEF, Mass Spectrometry, and biological assays.
- Lead the Process Development and Analytical Sciences Quality Improvement Team
- Lead the Process Development and Analytical Sciences Bi-Paratopic team
- Supported four diligences teams
- Supported three early research teams
- Provide response to regulatory agency questions

Alexion Pharmaceuticals, Incorporated, Cheshire, Connecticut; Director Analytical Sciences; July 2014 – July 2015.

GMP Compliance responsibilities

- Provide analytical support of CMC submissions, address comments from regulatory agencies regarding test methods and validation
- Direct and coordinate the transfer of release and stability test methods into Quality Control or to contract laboratories worldwide to support release testing of commercial drug product
- Provide support and troubleshooting to Quality Control groups for analytical test methods. Support includes assisting in assay invalids and/or OOS investigations, aberrant trends or special studies, etc.
- Manage, delegate, and prioritize GMP release and stability testing for all new pre-clinical and early stage (Phase 1 and Phase 2) clinical products.
- Direct formulation development activities, oversee design, execution, and analysis of formulation development studies.
- Manage qualification and validation of analytical methods for early stage clinical products in addition to existing commercial products.
- Manage in-process testing and coordinate outsource testing for new pre-clinical and early stage (Phase 1 and Phase 2) clinical products.
- Coordinate quarterly review meetings and provide updates, and generate reports for early stage (Phase 1 and Phase 2) clinical products.
- Generate or revise specifications for early stage (Phase 1 and Phase 2) clinical products
- Maintain appropriate compliance within area of responsibility with regards to current SOPs, validation / qualifications, and training. Represent the area functions as required during audits by external agencies and auditors, as well as by internal auditors
- Establish systems within area of responsibility to ensure compliance, good lab practices and efficiency

Development responsibilities

- Direct the development, improvement, qualification, and validation of analytical testing of proteins. Tests within area are: HPLC, SDS-PAGE, Western blots, IEF, ELISAs, biological assays and protein determinations.
- Generate and oversee product comparability protocols for early stage (Phase 1 and Phase 2) clinical products.
- Oversee the analytical support of cell culture and purification development groups in support of new clone or media optimizations and improvements to purification processes.
- Work with Purification Development to plan and coordinate formulation development studies, including generating and executing formulation stability protocols, compiling data, trending and presenting to all facets of the organization.

Other Responsibilities:

- Train, coach, and mentor Analytical Sciences laboratory personnel by working with employees to develop performance objectives and to monitor performance against the objectives.
- Interact with Alexion Pharmaceuticals personnel within Development, and other departments as required to meet objectives; interact with Alexion Pharmaceuticals business partners and technical representatives as required to meet objectives
- Represent Analytical services on Task Force or Planning Committees as assigned

BRUCE A. ANDRIEN, Jr., Ph.D.

7 Finch Lane, Guilford, CT 06437, (203) 457-0067

E-Mail: bldandrien@comcast.net

Alexion Pharmaceuticals, Incorporated, Cheshire, Connecticut; Director Protein Characterization; Sep. 2001 – Jul. 2014.

Manage the Protein Characterization group for characterizing proteins to support IND and BLA filings along with drug product understanding for FDA, EMEA, TGA, PMDA, and Health Canada. These assays include SDS-Page, vIEF, hIEF, 2D-Page, enzyme digestions, HPLC-UV (peptide maps, oligosaccharide, monosaccharide, sialic acid), CD, fluorometry, ligand/antigen kinetics by surface plasma resonance, N-terminal, flow field fractionation multi angel light scattering, ion mobility, mass spectrometry (small molecule contamination identification, intact molecular weight, peptide maps by µLC/nLC ion trap/TOF/Q-TOF, MALDI peptide mass fingerprints, disulfide mapping, identification of unknown proteins, glycan characterization, peptide confirmation by LC-MS/MS and MALDI-PSD, and in-house bioinformatics and proprietary Alexion database). Method robustness and method transfer. Review, write and oversee SOP's, GTR's, and protocols.

Managed more than $1,000,000 budget/year along with FTE's including Associate Directors, Ph.D., Masters, and Bachelors level as direct reports at Alexion.

Managed the staff meeting commutations between VP and Fermentation, Purification, Analytical Sciences, and Protein Characterization Groups.

Managed CMC documentation personal, review and write CMC sections for IND, NDA, BLA, updates and responses for drug product and drug substance for FDA, EMEA and other countries.

Support Alexion's Research, Fermentation, Purification, Quality Control/Quality Assurance and Clinical with techniques available in Protein Characterizations core facility.

Analytica of Branford, Inc., Branford, Connecticut; Senior Research Scientist; 1991 - 2001.

Conducted research and development on time-of-flight mass spectrometers, ion guides, ion optics, electrospray, nanoelectrospray and atmospheric pressure chemical ionization ion sources. Developed automation techniques using flow injection analysis and liquid chromatography for proteins, peptides, and small molecules. Generated data to support marketing, client needs, competitive demos, product development, research, and conference presentations. Author of patents, grants, manuals for various hardware, conference presentations, articles, and internal reports.

Principle Investigator on phase I and phase II NIH grants. Project manager of nanospray, dual electrospray, APCI, and parts of a TOF-MS project, taking these from the initial research and development phase though prototype design and finally to production and qualification testing. Responsible for installations, client training, and trouble shooting for electrospray, nanospray, dual electrospray, APCI, and TOF-MS products.

Conducted computer modeling scenarios on various parts of time-of-flight mass spectrometers, ion guides, and ion optics. Designed, developed, and coded software packages including: (1) "MoleculeMaker™" for generating theoretical isotope profiles and electrospray spectra from elemental formulas or amino acid sequences, (2) "Balancer" for calculating sample concentrations and dilution sequences, and (3) numerous other small programs and spread sheets. Project manager, which included supervising internal and external computer programmers, for a commercialized software package, "MacroMass™," used for deconvoluting multiply-charged electrospray mass spectra.

University of California, San Diego, California; Graduate Research Assistant; 1984 - 1991.

Ph.D. dissertation on metal cluster beams and magnetic thin films. Designed and constructed the following instruments: (1) Ultra High Vacuum (UHV) system, (2) 2200°C nozzle for metal beam film growth, and (3) UHV M-H Magnetometer. Analyzed thin films by Auger Electron Spectroscopy (AES), Low Energy Electron Diffraction (LEED), Temperature Program Mass Desorption (TPD), M-H Magnetometry, Electron Spectroscopy for Chemical Analysis (ESCA), and Transmission Electron Microscopy (TEM). Interfaced an Auger Electron Spectrometer, a M-H Magnetometer, and a Mass Spectrometer for temperature program mass desorption, to an IBM PC controller.

Lycoming College, Williamsport, Pennsylvania; Computer Assistant Manager; 1981 - 1984.

Responsibilities included tutoring, programming, systems operations, and supervision of assistants.

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BRUCE A. ANDRIEN, Jr., Ph.D.

7 Finch Lane, Guilford, CT 06437, (203) 457-0067
E-Mail: bldandrien@comcast.net

EDUCATION:

Ph.D., University of California, San Diego, 1991. Engineering Physics.
M.S., University of California, San Diego, 1986. Engineering Physics, (GPA) 3.54.
B.A., Lycoming College, Pennsylvania, 1984. Computer Science (GPA) 4.00, Physics (GPA) 3.88, Magna Cum Laude (GPA) 3.69.

FELLOWSHIPS AND HONORS:

Dissertation Research Fellowship, 1991.
University of California Regents Fellowship, 1984-1985.
Charles J. Kocian Computer Science Award, 1984.
Ferree Mathematical Sciences Award, 1984.
Phi Kappa Phi National Honor Society, 1984.
Lycoming Scholar, 1980-1984.
Dean's List, 1980-1981, 1983-1984.
Sigma Pi Sigma National Physics Honor Society, 1983.
Blue Key Superior Academic Freshman Award, 1981.

RELATED ACTIVITIES:

Society of Physics Students, Lycoming College, 1980-1984.
Student Advisory Committee for Mathematical Sciences, Lycoming College, 1983-1984.
Student Judiciary Appointment Board, Lycoming College, 1983-1984.
ACM Allegheny Region Programming Contest, 1982 and 1983.
SHARE program, observed engineering and computer departments at AVCO Lycoming, 1983.

PROFESSIONAL SOCIETIES:

American Society for Mass Spectrometry, American Chemical Society, American Vacuum Society, Materials Research Society, Phi Kappa Phi.

SPECIAL SKILLS:

Proteomics, Electrospray, Atmospheric Pressure Chemical Ionization (APCI), Time-of-Flight Mass Spectrometry (TOF-MS), Mass Spectrometry (MS), Molecular Beams, CAD, SPR BIACORE, Ion Mobility, AFFF/MALS, Visual Basic, computer programming.

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BRUCE A. ANDRIEN, Jr., Ph.D.

7 Finch Lane, Guilford, CT 06437, (203) 457-0067

E-Mail: bldandrien@comcast.net

SEMINARS:

Invited guest speaker at WATERS Japanese Executive Technology Forum 2009
Connecticut Separation Science Council (CSSC) Monthly Meetings (2001-present)
CT Mass Spectrometry Monthly Discussion Group (1991-2001)
Fenn 90 Symposium 2007
Discovery Proteomics, New Mass Spectrometry, Biomarker, Quantitation and PTM Analysis, Applied Biosystems, May 4, 2004
Invited Speaker for Amersham Biosciences European Proteomics Tour, (Summer 2001)

SHORT COURSES:

Practical Mass Spectrometric Characterization of Protein Therapeutics, (ASMS 2012)
Proteins Structural Analysis By Mass Spectrometry, (ASMS 2011)
MALDI Imaging Mass Spectrometry: Basic Tools and Techniques, (ASMS 2010)
Metabolomics (ASMS 2009)
Wyatt Light Scattering University (2007)
Quantitative MS, (ASMS 2007)
Proteins and Peptides by Mass Spectrometry, (ASMS 2005)
Biacore University SPR Basics Customer Training (April 2005)
Mass Spectrometry in Drug Discovery (ASMS 2004)
Applied BioSystems Voyager De-Pro Customer Training, (December 2002)
Bruker Esquire Ion Trap Customer Training, (April 2002)
Agilent 1100 HPLC ChemStation Customer Training, (Spring 2002)
Well Characterized Biologicals, (IBC's 5th International Conference 2001)
Characterization of Proteins and Peptides by Mass Spectrometry, (ASMS 2001)
Advanced SIMION 7.0 (ASMS 2000).
Fundamentals and Applications of MALDI-TOF-MS (ASMS 1999).
High Performance Liquid Chromatography, HPLC, and LC/MS (EAS 1998)
Quadrupole Ion Trap and Tandem Mass Spectrometry (ASMS 1998).
PHI Surface Analysis and Instrumentation Course on ESCA, (1987).

CONFERENCES ATTENDED:

American Society of Mass Spectrometry Conference, (1992-2012)
Well Characterized Biologicals, (IBC's Conference 2001 and 2009)
Next Generation Biologics, (IBC's Conference 2009)
Csaba Horvath Memorial Symposium (2005, 2007, 2009)
18th Annual International Light Scattering Colloquium(2007)
DiPIA 2007 Developments in Protein Interaction Analysis Biacore 2007
Pittsburgh Conference, (1993-2001)

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BRUCE A. ANDRIEN, Jr., Ph.D.

7 Finch Lane, Guilford, CT 06437, (203) 457-0067

E-Mail: bldandrien@comcast.net

ALEXION TRAINING:

GMP Training (2001-2015)
Presentation Skills (30Jul08)
Intercultural Training for Filing in Japan (29Jul08)
21 CFR Part 11 (General Awareness Training) (14Jun07)
Tips, Techniques & Shortcuts for Organizing & Maintaining Files & Records (Skillpath) (17Oct06)
Change Control Training (SOP-QA-0038), (11Jul06)
SAP Training, (07Jul06)
Performance Management Process Appraisal Writing & Delivery Training, (30Jun06)
SharePoint Portal Server 2003 Training, (16Jun06)
On-Site Regulatory Inspections (SOP-RA-1003.00), (April 3, 2006)
Change Control Program (SOP-QA-0038.03), (10Mar06)
cGMP Briefing Presentation for Pharmaceutical Stakeholders, (02Mar06)
CP-0001.00, CP-0002.00, CP-0003.00 (16Nov05)
WPD-TS-001-00, WPD-TS-002-00, WPD-TS-003.01 (16Nov05)
Coaching and Teambuilding Skills for Managers and Supervisors, SkillPath (June 15, 2005)
Goal Setting for Groups, SkillPath (May 18, 2005)
Excelling as a First-Time Manager, SkillPath (January 21, 2005)
VBA for MS Excel, (November 10 and 19, December 15, 2004)
Fundamentals of Successful Project Management, SkillPath, (November 3, 2004)
SOP-QA-0001.05, 0002.04, 0003.05, 0017.05 0022.05 Doc Control (04Jun04)
Excel Microsoft XP- Pivot Tables, (April 2004)
Excel Microsoft XP- Formulas, (March 2004)
RDM-0033.00, Determination of Eculizumab Purity by SEC-HPLC for In Process Testing (09Feb04)
SOP-CAL-0029.00 Standardization of the AND Electronic Balance, Model #FD-6000 (09Feb04)
RDM-0012.00 Quantification of Protein Concentration in Pexelizumab Samples by UV-Vis Spectrophotometry (03Feb04)

Sexual Harassment Prevention Training, (2003)
SOP-QA-0055.00 Labaratory Notebook Requisition, Issuance, and Tracking (22Dec03)
Laboratory Notebook Documentation, Jeff Gassman, (09Dec03)
PowerPoint Microsoft, Key-Logic, Dynamic Slide Enhancements, (28Oct03)
SOP-QCG-0025.03 Quality Control Sample Submission and Handling (20Oct03)
SOP-QA-0017.04 Document Control System, (04Aug03)
Intro to Good Scientific Practices (GSP), (23May03)
SOP-QA-0043.01, (21Jan03)

SOP-QA-0001.03, 0002.02, 0003.02, 0004.02, 0017.03, and 0022.03, (10Nov02)
Document Control System, Controlled Copy of SOP, and SOP Training (11Oct02)
21 CFR Compliance Training Session II; cGMP, GLP, GCP, and QA, (24Jun02)
Pipettes Training, Alpha-Omega, (29May02)
Basic Good Laboratory Practices (21 CFR Part 58), (28May02)

cGMP's and Compliance Document Control System, (17Sep01)
Annual OSHA Training/Safety Training, (Mar 2006, 2005, 2004, 2003, 2002, 2001)

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BRUCE A. ANDRIEN, Jr., Ph.D.

7 Finch Lane, Guilford, CT 06437, (203) 457-0067

E-Mail: bldandrien@comcast.net

PUBLICATIONS AND PRESENTATIONS:

"Kinetic analysis of a monoclonal therapeutic antibody and its single-chain homolog by surface plasmon resonance", Rekha Patel *, Bruce A. Andrien Jr., Anal. Biochem. 396 (2010) 59–68.

"Kinetic Analysis of Anti-C5 Subclasses to Gamma Receptors by Surface Plasmon Resonance", Rekha Patel, Bruce Andrien, Krista Johnson, Jeff Hunter, Pat Bento, Michelle Giannoni and Paul Tamburini, Developments in Protein Interaction Conference 2009

"The Role of LC/MS to Support Biotechnological/Biological Product Regulatory Submissions", Invited guest speaker at WATERS Japanese Executive Technology Forum 2009

"AFFF/MALS and Ion Mobility for Analysis of Antibodies and Non-Covalent Complexes", Bruce Andrien, Csaba Horvath Symposium 2009

"Integration of Waters BiopharmaLynx Application Manager into a Monoclonal Antibody Characterization Strategy", Adam Lucka, Rekha Patel, Christine Nowak, and Bruce Andrien, WATERS users meeting at the American Society of Mass Spectrometry Conference 2009

"Ion Mobility Spectrometry for Determining Binding, Bridging and the Formation of Non-Covalent Complexes", Bruce Andrien, Rekha Patel, Christine Nowak, and Adam Lucka, American Society of Mass Spectrometry Conference 2009

"Characterizing Five Deamidation Products from a Single Asparagine Residue in Recombinant mAb's Through LC-MS Peptide Mapping", Adam Lucka, Christine Nowak, Rekha Patel, and Bruce Andrien, American Society of Mass Spectrometry Conference 2009

"Analysis of Antibodies, Aggregates and Non-Covalent Complexes by IMS, SEC/MALS/IMS and AFFF/MALS/IMS", Bruce Andrien, Christine Nowak, and Adam Lucka, Invited Guest Speaker at TSI User Meeting at ASMS Conference, (2008).

"Coupling AFFF/MALS or SEC/MALS to Ion Mobility Spectrometry for Analysis of Antibodies, Fragments, Aggregates and Non-Covalent Complexes", Bruce Andrien, Christine Nowak, and Adam Lucka, 56th ASMS Conference, (2008).

"Characterizing Glycosylation Patterns in Recombinant IgG2/4 Monoclonal Antibodies by Combining Fluorescence HPLC, MALDI-ToF-MS, and LC-MS and MS/MS Data", Adam Lucka, Christine Nowak, Rekha Patel, and Bruce Andrien, 56th ASMS Conference, (2008).

"An Investigation of Protein Therapeutics Including Antibodies and Antibody Conjugates with Ion Mobility Spectrometry", Bruce A. Andrien, Rekha Patel, Lynellen Willard, and Rachael Alford, 55th ASMS Conference, (2007).

"Improving Monoclonal Antibody and SCFv Protein Characterization by Obtaining Complementary MALDI-TOF-MS Spectra from a Single Tryptic Digest", Adam Lucka, Rekha Patel, and Bruce Andrien, 55th ASMS Conference, (2007).

"Kinetic Analysis of a Monoclonal Antibody (eculizumab) and its Single Chain Homolog (pexelizumab) by Surface Plasmon Resonance", Rekha Patel and Bruce Andrien, DiPIA Conference 2007.

"Disulfide Bond Confirmation of a Humanized Anti-C5 Complement Monoclonal Antibody and Its Single Chain Homolog by Peptide Mapping", Bruce A. Andrien, Adam W. Lucka, and Rekha Patel, 54th ASMS Conference, (2006).

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BRUCE A. ANDRIEN, Jr., Ph.D.
7 Finch Lane, Guilford, CT 06437, (203) 457-0067
E-Mail: bldandrien@comcast.net

"Characterization of a Monoclonal Antibody and its Single Chain Therapeutic", Rekha Patel, Adam Lucka, and Bruce Andrien, Invited Guest Speaker at Agilent World Tour 2006, Cambridge, MA, (16May06).

"Workflow for the Characterization of Proteins Therapeutics", Bruce A. Andrien, Jr., Adam Lucka, Rekha Patel, Invited Guest Speaker at Agilent Lunch and Learn during 53th ASMS Conference, (2005).

"A Bioinformatics Strategy for the Characterization of Proteins versus Protein Identification", Bruce A. Andrien, Jr., Adam Lucka, Rekha Patel, 53th ASMS Conference, (2005).

"Improving Protein Coverage in nanoLC-MS Peptide Mapping by using a Sub-Ambient Enrichment Column to Bind Hydrophilic Peptides", Adam Lucka, Rekha Patel, Bruce A. Andrien, Jr., 53th ASMS Conference, (2005).

"Protein Identification after Two-Dimensional Gel Electrophoresis by MALDI ToF MS and LC ESI ToF MS", Staffan Renlund; Ylva Laurin; Maria Liminga; Henrik Wadensten; Bruce A. Andrien, Jr.; Marketa Berkova; Erol E. Gulcicek, 49th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, (2001).

"Confirmation Analysis of Protein Purification using Electrospray Time of Flight Mass Spectrometry", Henrik Wadensten; Ninni Salomonsson; Christel Ellström; Staffan Lindqvist; Staffan Renlund; Bruce A. Andrien, Jr.; Marketa Berkova; Erol E. Gulcicek, 49th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, (2001).

"Evaluation of Rugged Microelectrospray Iinterfaces for Identification of Peptides and Proteins Wiith APII-TOF-MS", Erol E. Gulcicek; Bruce A. Andrien, Jr; Marketa Berkova; Craig M. Whitehouse; Staffan Renlund, 49th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, (2001).

"Investigating the Trap-Pulse Mode of Operation to Improve the Sensitivity of Electrospray Time-Of-Flight Mass Spectrometer", Marketa Berkova; Craig Whitehouse; Erol Gulcicek; Bruce Andrien, 49th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, (2001).

"Identification of Post-Translational Modifications by Fast LC-MS and In-Source CID Using a New API TOF MS", Staffan Renlund, Henrik Wadensten, Lars Rönnstrand, Rannar Sillard, Bruce A . Andrien, Jr., Marketa Berkova, and Erol E. Gulcicek, Montreux (2000).

"Optimization of Rapid State Switching API TOF Operation for Fast LC-MS", Erol E. Gulcicek, Bruce A. Andrien, Marketa Berkova, James G. Boyle, Shida Shen, and Craig M. Whitehouse, and Staffan Renlund, Montreux (2000).

"Peptide and Protein Analysis and the Identification of Post-Translational Modifications Using Fast LC-MS with Rapid State Switching", Craig M. Whitehouse, Bruce A. Andrien, Jr., Staffan Renlund, Erol Gulcicek, Marketa Berkova, Lars Ronnstrand, and Rannar Sillard, 15th IMSC Barcelona (2000).

"Identification of Proteins and Post Translational Modifications Using New MALDI ToF and ESI ToF Mass Spectrometer Systems", Staffan Renlund, Jonas Åström, Henrik Wadensten, Rannar Sillard, Lars Rönnstrand, Bruce A. Andrien, Jr., Marketa Berkova, and Erol E. Gulcicek, 4th Int Seminar on Biomolecule Identification and Function (2000).

"Fast LC-MS for Peptide Mass Mapping, Protein Analysis and Identification of Post-Translational Modification Using API TOF", S. Renlund, H. Wadensten, J. Astrom, J. Ericsson, S. Ekman, U. Engstrom, L. Ronnstrand, B. A. Andrien, E. E. Gulcicek, 48th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Long Beach, CA, (2000).

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BRUCE A. ANDRIEN, Jr., Ph.D.
7 Finch Lane, Guilford, CT 06437, (203) 457-0067
E-Mail: bldandrien@comcast.net

"Analysis of Proteins from 2D-Gels by MALDI-TOF MS and LC-ESI-TOF MS", M. Raida, G. Reil, A. Gorg, J. Astrom, H. Wadensten, S. Renlund, and B. A. Andrien, 48th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Long Beach, CA, (2000).

"Combining Autoinjector and Nebulizer Hardware for Enhanced Automation in FIA-MS,", B. A. Andrien, J. G. Boyle, and M. Berkova, 48th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Long Beach, CA, (2000).

"Multipole Storage Assisted Dissociation for Enhancing Sequence and Structural Studies in LC-TOF-MS", C. M. Whitehouse, B. A. Andrien, and M. Berkova, 48th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Long Beach, CA, (2000).

"Evaluation of a New LC TOF-MS with Wide Dynamic Range for Full Chromatographic Compatibility", B. A. Andrien, E. E. Gulcicek, S. Shen, C. M. Whitehouse, and J. G. Boyle, Pittsburgh Conference Proceedings, (2000).

"High Performance at High Throughput Lessons from LC-API-TOF-MS", E. G. Gulcicek, B. A. Andrien S. Shen, C. M. Whitehouse, and J. G. Boyle, Pittsburgh Conference Proceedings, (2000).

"Increasing the Duty Cycle for Time-of-Flight by Trap-Pulse Mode", B. A. Andrien, C. M. Whitehouse, E. E. Gulcicek, 47th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Dallas, TX, (1999).

"Rapid API TOF State Switching with Fast LC-MS", C. M. Whitehouse, E. E. Gulcicek, B. A. Andrien, S. Shen, 47th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Dallas, TX, (1999).

"Obtaining High Mass Accuracy on LC-TOF-MS", E. E. Gulcicek, C. M. Whitehouse, B. A. Andrien, 47th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Dallas, TX, (1999).

"Dual Parallel Probes for Electrospray Sources", S. Shen, B. A. Andrien, M. Sansone, and C. M. Whitehouse, 47th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Dallas, TX, (1999).

"Multiple Inlet Probes for Electrospray and APCI Sources", B. A. Andrien, M.A. Sansone, and C. M. Whitehouse, 46th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Orlando, FL, (1998).

"Minimizing Chemical Noise through Rational Design of a "Universal" API Source", S. Shen, B. Andrien Jr., M. Sansone, and C. M. Whitehouse, 46th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Orlando, FL, (1998).

"A Two Dimensional Ion Trap API TOF Mass Spectrometer", C. M. Whitehouse, E. E. Gulcicek, J.F. Banks, B. Andrien, 46th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Orlando, FL, (1998).

"Performance of High Throughput API TOF MS Detector", E. E. Gulcicek, B. A. Andrien, J.F. Banks, J.G. Boyle, and C. M. Whitehouse, 10th Sanibel Conference on Mass Spectrometry, Sanibel, FL, (1998).

"Atmospheric Pressure Chemical Ionization and Electron Capture Negative Chemical Ionization Mass Spectrometry in Studying ß-Carotene Conversion to Retinol in Humans", Guangwen Tang, Bruce A. Andrien, Gregory G. Dolnikowski, and R. M. Russell, Methods in Enzymology, **282**, 140-154, (1998).

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BRUCE A. ANDRIEN, Jr., Ph.D.
7 Finch Lane, Guilford, CT 06437, (203) 457-0067
E-Mail: bldandrien@comcast.net

"A Disposable μ-Tip Probe for Low Flow Electrospray", B. A. Andrien, D. M. Sauro, M.A. Sansone, G.P Whitehouse, C. M. Whitehouse, and A.G. Burt, 45th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Palm Springs, CA (1997).

"Performance of a Hexapole Ion Guide on HP5988", B. A. Andrien, M.A. Sansone, B.L. Mancini, C. M. Whitehouse, A.G. Burt, Guangwen Tang, and Gregory G. Dolnikowski 45th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Palm Springs, CA (1997).

"Emerging Biomedical High Throughput Sample Inlet Systems Utilizing an API TOF MS Detector", E. E. Gulcicek, B. A. Andrien, J.F. Banks, J.G. Boyle, and C. M. Whitehouse, 45th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Palm Springs, CA (1997).

"Detecting the *in vivo* Conversion of b-Carotene-d_8 to Retinol-d_4 by APCI-MS and GC/ECNCI-MS", Guangwen Tang, Bruce A. Andrien, and Gregory G. Dolnikowski, 44th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Portland OR (1996).
"Atmospheric Pressure Ionization Flow Injection Analysis by Orthogonal Time-of-Flight Mass Spectrometry", B.A. Andrien, T. Dresch, P.J. Haren, and C. M. Whitehouse, 44th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Portland OR (1996).

"On-Line Detection of Fast Chromatographic Events by Electrospray Ionization Time-of-Flight Mass Spectrometry", Erol E. Gulcicek, B. Andrien, J.F. Banks, J.G.Boyle, T.Dresch, P.Haren,and C.Whitehouse, 44th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Portland OR (1996).

"Micro and Nano Flow Atmospheric Pressure Chemical Ionization", B. A. Andrien and C. M. Whitehouse, Pittsburgh Conference Proceedings, (1996).

"API Time of Flight Mass Spectrometry as a Chromatography Detector", B. Andrien, J. F. Banks, T.Dresch, E.Gulcicek, P.Haren, J.Quinn, and C.Whitehouse, Pittsburgh Conference Proceedings, (1996).

"Electrospray and APCI Interface for Mass Spectrometry", B. A. Andrien and J. G. Boyle, *Spectroscopy*, **10**, 2, 42-44, (1995).

"Improvements to Electrospray and APCI Ion Sources for CE/MS and LC/MS Applications with TOF, Quadrupoles, FTMS, Ion Traps and Magnetic Sector Spectrometers" C. M. Whitehouse, J. F. Banks, E.Gulcicek, T.Dresch, B. Andrien, and S. Shen, 37th Rocky Mountain Conference on Analytical Chemistry, Denver, CO, (1995).

"Atmospheric Pressure Chemical Ionization by Corona Discharge", B. A. Andrien, T. Dresch, P.J. Haren, C. M. Whitehouse, and S. Shen, 43th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Atlanta GA (1995).

"A Mass Analyzer for High Speed Liquid Chromatography", B. A. Andrien, J. F. Banks, J. G. Bolye, T. Dresch, P.J. Haren, and C. M. Whitehouse, 43th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Atlanta GA (1995).

"Performance of an Atmospheric Pressure Corona Discharge Ion Source with Time of Flight Mass Spectrometry", B. A. Andrien, T. Dresch, P.J. Haren, and C. M. Whitehouse, Pittsburgh Conference Proceedings, (1995).

"Atmospheric Pressure Chemical Ionization by Corona Discharge with Pneumatic and Ultrasonic Nebulization", B. A. Andrien, J. P. Quinn, and C. M. Whitehouse, 42th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Chicago (1994).

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BRUCE A. ANDRIEN, Jr., Ph.D.
7 Finch Lane, Guilford, CT 06437, (203) 457-0067
E-Mail: bldandrien@comcast.net

"Theoretical and Practical Considerations for Determining Resolution and Conducting Mass Calibration with Multiply Charged Ions", B. A. Andrien, P.J. Haren, and C. M. Whitehouse, 42th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Chicago (1994).

"Improved Performance of a New Electrospray and APCI source Interfaced to a ZAB or 7070 Series Magnetic Sector Mass Spectrometer", S. Shen, C. M. Whitehouse, B. A. Andrien, and Walter McMurrary, 42th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, Chicago (1994).

"Performance of an Atmospheric Pressure Corona Discharge Ion Source with Ultrasonic Nebulization", B. A. Andrien, J. P. Quinn, and C. M. Whitehouse, Pittsburgh Conference Proceedings, Chicago (1994).
"Performance of an Atmospheric Pressure Ion Source with Corona Discharge and Ultrasonic Nebulization", B. A. Andrien, C. M. Whitehouse, and J. P. Quinn, 41th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, San Francisco (1993).

"Deconvolution of Electrospray Generated Multiply Charged Ion Spectra Using a Three Dimensional Technique", B. A. Andrien, M. Labowski, and C. M. Whitehouse, The Pittsburgh Conference Proceedings (1993).

"A Comparison of Magnetic Properties of Thin Films of Fe/GaAs(100) and Ni/Mica", B. Andrien and D.R. Miller, Materials Research Society Symposia Proceedings (submitted Dec. 1992). Fall Meeting, Boston, MA, Dec. 1992.

"Deconvolution of Electrospray Generated Multiply Charged Spectra of Mixtures Using a Three Dimensional Technique", B. A. Andrien, M. Labowski, and C. M. Whitehouse, 40th ASMS Conference of Mass Spectrometry and Allied Topics Proceedings, (1992). Washington, DC (1992).

"Thin Film Growth and Magnetic Properties for Fe/GaAs(100)", B. Andrien and D.R. Miller, Materials Research Society Symposia Proceedings, **202**, 193 (1991). Fall Meeting, Boston, MA, Dec. 1990.

"Magnetization Loop Tracer for Superconductors", B. Andrien and J. Haugdahl, Review of Scientific Instruments **61(8)**, 2260 (1990).

"Chemisorption on Ferromagnetic Metal Films", B. Andrien and D.R. Miller, Materials Research Society, Spring Meeting, San Diego, CA, Apr. 1989.

"Thin Ferromagnetic Metal Cluster Films", B. Andrien and D.R. Miller, American Vacuum Society Vacuum Metallurgy Division, 15th International Conference on Metallurgical Coatings, San Diego, CA, Apr. 1988.

"Magnetic Properties of Thin Metal Cluster Films", B. Andrien, J. Haugdahl, and D.R. Miller, Journal of Vacuum Science and Technology A **6(3)**, 1865 (May 1988). American Vacuum Society, 34th National Symposium, Anaheim, CA, Nov. 1987.

"A Spectroscopic Investigation of Van Der Waals Complexes", B. Andrien, 38th Eastern Colleges Science Conference, Providence College, RI, Apr. 1984.

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BRUCE A. ANDRIEN, Jr., Ph.D.

7 Finch Lane, Guilford, CT 06437, (203) 457-0067
E-Mail: bldandrien@comcast.net

AWARDED PATENTS:

Title: "Nucleic Acid Encoding Anti-C5 Antibodies having Improved Pharmacokinetics"
Inventors: Bruce A. Andrien, Jr.; Douglas L. Sheridan; and Paul P. Tamburini
Patent No.: 9,206,251 B2
Date of Patent: Dec. 8, 2015

Title: "Methods of Treating C5 Mediated Complement-Associated Conditions with Anti-C5 Antibodies having Improved Pharmacokinetics"
Inventors: Bruce A. Andrien, Jr.; Douglas L. Sheridan; and Paul P. Tamburini
Patent No.: 9,107,861 B1
Date of Patent: Aug. 18, 2015

Title: "Anti-C5 Antibodies having Improved Pharmacokinetics"
Inventors: Bruce A. Andrien, Jr.; Douglas L. Sheridan; and Paul P. Tamburini
Patent No.: 9,079,949 B1; WO 2015/134894 A1; New Zealand 631007; European 15 710 396.1
Date of Patent: Jul. 14, 2015; 06Mar. 2015; 02Feb2016; 06.03.2015

Title: "Mass Spectrometry with Multipole Ion Guides"
Inventors: Craig M. Whitehouse, Bruce A. Andrien, Jr.; and Gulcicek; Erol E.
Patent No.: 6,753,523; 6,987,264; and 7,189,967
Date of Patent: June 22, 2004

Title: "Atmospheric Pressure Ion Source"
Inventors: Craig M. Whitehouse, Bruce A. Andrien Jr., Michael A. Sansone, Clement Catalano
Patent No.: 6,593,568 B1
Date of Patent: July 15, 2003

Title: "Direct Flow Injection Analysis Nebulization Electrospray and APCI Mass Spectrometry"
Inventors: Bruce A. Andrien Jr., Fred Banks, James Boyle
Patent No.: 6,458,597 B1; 6,858,437 B2; and 7,364,913
Date of Patent: October 1, 2002; and Feb 22, 2005

Title: "Curved Introduction for Mass Spectrometry"
Inventors: Bruce A. Andrien Jr., Michael A. Sansone, Allan G. Burt, Craig M. Whitehouse
Patent No.: 6,326,616 B1 and 6,573,494 B1
Date of Patent: December 4, 2001 and June 3, 2003

Title: "Multiple Sample Introduction Mass Spectrometry"
Inventors: Bruce A. Andrien Jr., Craig M. Whitehouse, Shida Shen, Michael A. Sansone,
Patent No.: 6,207,954 B1 and 6,541,768 B2
Date of Patent: Mar 27, 2001 and April 1, 2003

Title: "Disposable Microtip Probe for Low Flow Electrospray"
Inventors: Bruce A. Andrien Jr., Craig M. Whitehouse, Michael A. Sansone, Denise M. Sauro, Glenn P. Whitehouse
Patent No.: 6,127,680 and 6,337,480 B1
Date of Patent: October 3, 2000 and January 8, 2002

Title: "Time-Of-Flight Mass Spectrometry from Surfaces"
Inventors: Craig M. Whitehouse, Bruce A. Andrien Jr.
Patent No.: 6,040,575 and 6,204,500 B1 and 6,600,155 B1
Date of Patent: March 21, 2000 and Jul 29 ,2003

Title: "Multipole Ion Guide Trap Time-of-Flight Mass Spectrometry with MS/MS^n Analysis Capability"
Inventors: Craig M. Whitehouse, Thomas Dresch, and Bruce A. Andrien Jr.
Patent No.: 6,011,259
Date of Patent: January 4, 2000

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BRUCE A. ANDRIEN, Jr., Ph.D.

7 Finch Lane, Guilford, CT 06437, (203) 457-0067

E-Mail: bldandrien@comcast.net

PRINCIPLE INVESTIGATOR for the FOLLOWING GRANTS:

Title: "Microflow APCI Method for High Throughput LC-MS"
Funding: NIH Phase I (National Center for Research Resources)
ID Grant #: 1 R 43 GMS6604-01; Awarded: $90,000.00
Support Period: 9/1/97-3/1/98
Description: To Develop a microflow APCI interface for mass spectrometry to improve the limits of detection for trace non-polar species in complex mixtures, while at the same time making on-line coupling to microbore chromatographic methods easier, more reproducible and robust.

Title: "MSD Mass Detector with Atmospheric Pressure Inlet"
Funding: NIH Phase I (National Center for Research Resources)
ID Grant #: 1 R 43 RR12058-01; Awarded: $90,000.00
Support Period: 9/1/97-9/1/98
Description: Develop a platform which will provide a high productivity, low cost entry point for both LC and CE users, as well as for GC-MS labs needing the ability to handle non-volatile samples without requiring time consuming derivitization procedures.

Title: "Mass Spectrometer Detector for Liquid Chromatography"
Funding NIH Phase I and II (national Center for Research Resources)
ID Grant #: 1 R 43 RR08538-01, 2 R 44 RR092252-02; Awarded: $50,000, $500,000
Support Period: 3/1/94-8/31/94, 4/1/95-3/31/97
Description: Develop a pre-production prototype API-TOF-MS bench top system for non mass spectrometrist. It should connect to any LC or CE system and ionizes the sample by APCI and ESI to analyze polar and non-polar samples.

Title: "Deconvolution of Mass Spectra for Multiply Charged Ions"
Funding: NIH Phase I (National Center for Research Resources)
ID Grant #: 1 R 43 RR08538-01; Awarded: $50,000.00
Support Period: 9/30/92-3/29/93
Description: To Develop a 3D software package that will take full advantage of the coherent pattern for determining the mass of higher molecular weight compounds from a series of multiply charged peaks produced by any multiply charged ionization process.

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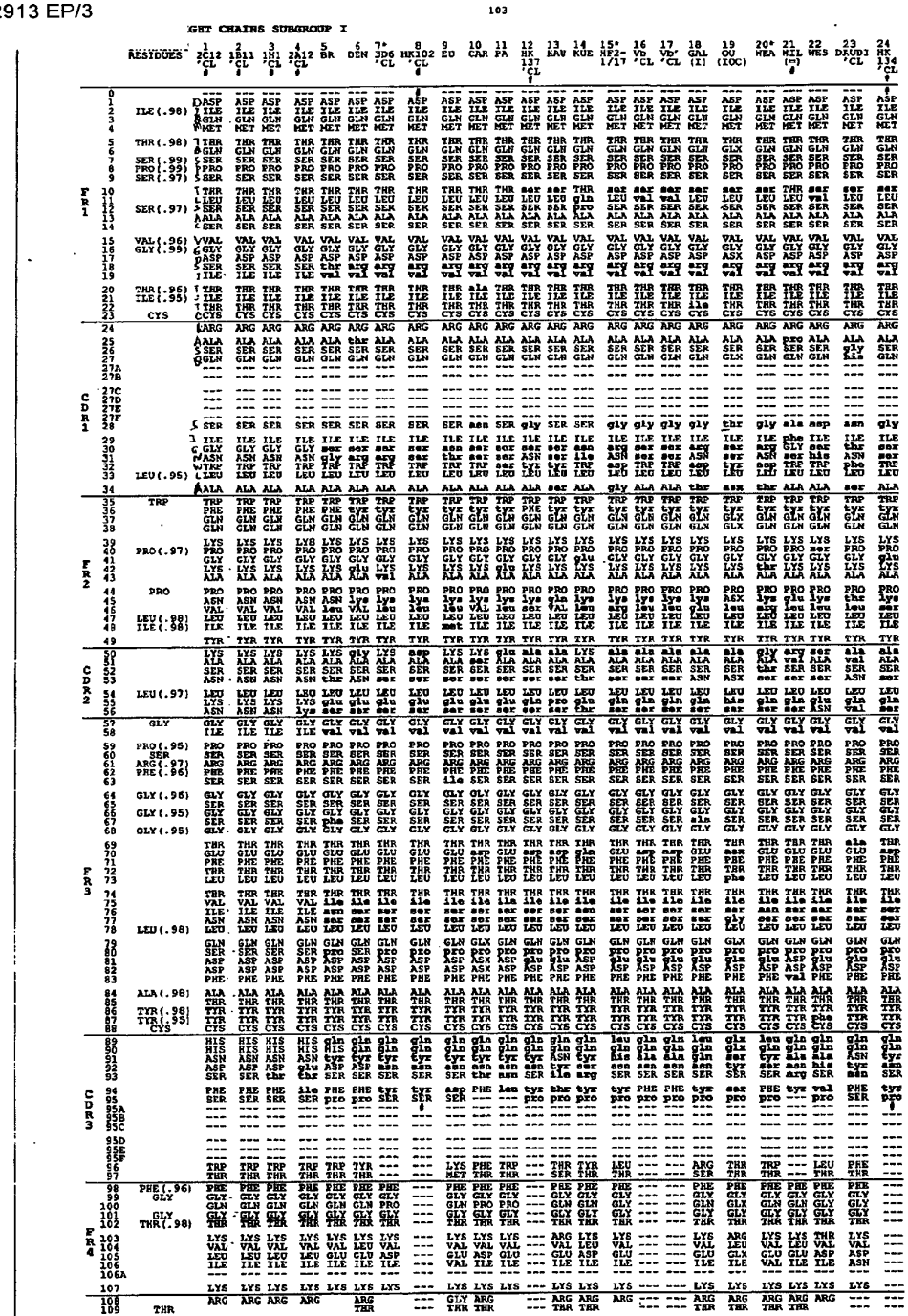
GET CHAINS SUBGROUP I
RESIDUES
1 2C12 'CL
2 1B11 'CL
3 1H1 'CL
4 2A12 'CL
5 BR
6 DEN
7* 3D6 'CL
8 HK102 'CL
9 EU
10 CAR
11 FA
12 HK 137 'CL
13 RAV
14 KUE
15* MF2-1/17
16 VD 'CL
17 VD' 'CL
18 GAL (I)
19 OU (IOC)
20* MEA
21 MIL (=7)
22 WE3
23 DAUD 'CL
24 HK 134 'CL
FR1
CDR1
FR2
CDR2
FR3
CDR3
FR4

HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)

		25 Va 'CL	26 WALKER 'CL	27 HIL01 'CL	28 Va 'CL	29 VRI-CHEJ 'CL	30 AMYLOID BAN	31 Va 'CL	32 VJ1 'CL	33 DEE	34 WIL (-)	35 AMO	36 V108 'CL	37 VRI-II 'CL	38 REI	39 AU	40 ROY	41 SI	42 HOVH CAMP 'CL	43 AG	44 SCW	45 REV	46 KA	47 LAY	48 SEL	49 NI
	0	---	---		---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	1	ASP	ASP	ASP	ala	ASP	ASP	ala	val	ASX	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
	2	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	val	ILE	ILE	ILE	ILE
	3	GLN	GLN	GLN	GLN	GLN	GLN	GLN	asn	GLX	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN
	4	leu	MET	MET	leu	MET	leu	MET	MET	MET	MET	MET	val	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	leu	MET
	5	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
	6	GLN	GLU	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN
	7	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
	8	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
	9	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
FR1	10	the	ser	ser	ser	ser	ser	ser	leu	ser	THR	ser	ser	ser	ser	ser	ser	pro	ser	ser	ser	ser	THR	ser	ser	ser
	11	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
	12	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
	13	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	val	ALA	ALA
	14	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	thr
	15	VAL	VAL	VAL	VAL	VAL	VAL	thr	thr	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
	16	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
	17	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	gly	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
	18	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	SER	asp	asp	asp	asp	asp	asp	asp	asp
	19	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val
	20	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	ile	THR	THR	THR	THR	THR
	21	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	phe	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	THR	ILE	ILE	ILE	ILE	leu
	22	THR	THR	THR	THR	THR	THR	THR	ser	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	leu
	23	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS
	24	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	gln	gln	gln	gln	lys	gln	gln	ARG	glu	gln	glu	glu
	25	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ser	ALA	val	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA
	26	SER	SER	asp	SER	SER	SER	SER	SER	gly	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
	27	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN
	27A	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	ser
	27B	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	val
CDR1	27C	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	leu
	27D	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	gln
	27E	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	ser
	27F	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	ser
	28	gly	SER	gly	gly	gly	SER	gly	gly	SER	SER	SER	gly	gly	asp	asp	asp	asp	asn	asp	asp	SER	thr	asn	asn	SER
	29	ILE	ILE	ILE	ILE	ILE	val	ILE	ILE	val	val	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ser	val	val	ILE	gly
	30	ser	ser	ser	ser	ser	ser	ser	ser	asn	ser	GLY	ser	ser	ile	ser	ser	asn	asp	val	leu	asn	ser	ser	asn
	31	ser	ASN	ser	ser	ASN	ASN	ser	ser	lys	tyr	gly	ASN	ASN	lys	asp	ile	ASN	lys	asp	ser	gln	ser	gln	lys	thr
	32	tyr	tyr	TRP	ala	asn	tyr	tyr	tyr	TRP	ser	gly	tyr	ser	tyr	tyr	tyr	tyr	tyr	TRP	leu	asp	tyr	thr		phe
	33	LEU	LEU	LEU	LEU	LEU	val	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU
	34	ALA	asn	ALA	ALA	asn	ALA	ALA	asn	ALA	asn	asn	asn	asn	asn	asn	asn	ile	asn	asn	asn	asn	asn	asn		ALA
	35	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP		TRP
	36	tyr	tyr	tyr	tyr	tyr	PHE	tyr	tyr	tyr	tyr	tyr	SER	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr		tyr
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	38	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN		GLN
	39	lys	LYS	LYS	LYS	LYS	ASN	LYS	LYS	LYS	LYS	LYS	LYS	LYS	the	LYS	LYS	LYS	LYS	$	LYS	LYS	LYS	LYS		LYS
	40	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	$	PRO	PRO	PRO	PRO		PRO
	41	GLY	GLY	glu	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	$	GLY	GLY	GLY	GLY	GLY	lys
	42	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	$	LYS	LYS	LYS	LYS	lys	LYS
	43	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	$	ALA	ALA	ALA	ALA	pro	ALA
	44	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
	45	lys	lys	ser	leu	lys	lys	glu	lys	ASN	ser	thr	lys	lys	lys	lys	lys	ser	lys	lys	lys	lys	lys	glu	lys	glu
	46	leu	leu	ser	leu	leu	ser	leu	leu	VAL	leu	leu	leu	leu	leu	leu	leu	leu	leu	leu	leu	leu	leu	leu	leu	leu
	47	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
	48	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE
	49	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR		TYR	phe	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	phe	TYR	TYR	TYR	TYR
	50	ala	ala	ala	asp	ala	asp	ala	ala	ala	glu	gly	ala	ala	glu	asp	asp	asp	asn	asp	asp	ala	gly	asp	asp	asp
	51	ASA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ala	ASP	ALA	ALA	ALA	ALA	ALA	ALA
CDR2	52	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	glu	SER	SER	SER	SER	SER	SER	SER
	53	thr	ser	ser	ser	ser	thr	thr	thr	ser	ile	ser	ser	ser	ser	ASN	lys	ASN	ASN	chr	ASN	ser	thr	thr	thr	ASN
	54	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	asp	LEU	LEU
	55	gln	gln	gln	gln	gln	gln	gln	gln	lys	asp	arg	gln	gln	gln	glu	glu	glu	glu	glu	glu	glu	glu	glu	lys	glu
	56	ser	ser	ser	ser	ser	ser	ser	ser	ser	ile	ser	ser	ser	ser	his	his	his	his	ile	ser	thr	thr	thr	thr	thr
	57	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLX	GLY	GLY	GLY	GLY	GLY
	58	PRO	thr	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	SER	PRO	PRO	PRO	PRO	PRO	PRO
	59	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
	60	ARG	ARG	ARG	ARG	ARG	asn	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG	ARG
	61	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE
	62	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	asp	SER	SER	SER	SER	SER	SER	SER
	63	GLY	GLY	GLY	GLY	asp	GLY	GLY	GLY	GLY	GLY	GLY	GLY	asp	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
	64	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	gly	thr	SER	SER	SER	gly	gln	SER	SER	SER	SER
	65	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLN	GLY	ile	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	asp	GLY	GLY	GLY	GLY	GLY
	66	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
	67	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLN	GLN
	68	THR	THR	THR	ala	THR	THR	THR	THR	THR	THR	THR	THR	ala	THR	ala	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
	69	GLU	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	asp	his	asp	asp	asp	asp	asp	asp	asp	his	asp	asp
	70	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	tyr	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE
	71	THR	THR	THR	THR	ile	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	ala	THR	THR	THR	THR	THR	THR	THR	THR
FR3	72	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	phe	phe	phe	LEU	phe	phe	LEU	LEU	phe	phe	LEU	phe
	73	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	ser	THR	THR	THR	THR	THR	THR	THR
	74	ile	ile	ile	ile	ile	ile	ile	ile	ile	ile	ile	ile	ile	ile	ile	ile	ile	ser	ile	ile	ile	ile	ile	ile	ile
	75	ser	ser	ser	arg	ser	ser	ser	ser	ser	ser	thr	ser	ser	ser	ser	ser	ser	ser	ser	ser	ser	ser	ser	ser	ser
	76	ser	ser	ser	ser	ser	ser	ser	ser	ser	cys	cys	gly	ser	ser	ser	ser	ser	gly	thr	ser	ser	ser	ser	ser	gly
	77	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
	78	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	leu	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN
	79	pro	PRO	PRO	PRO	PRO	PRO	SER	SER	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
	80	glu	glu	glu	glu	glu	glu	glu	glu	glu	ASP	glu	glu	glu	glu	glu	glu	glu	glu	glu	ASP	glu	glu	ala	glu	glu
	81	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	asn	ASP	ASP	ser	ile	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
	82	PHE	ser	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	PHE	ile	ile	ile	PHE	ile	ile	ile	PHE	PHE	ile	PHE	PHE
	83	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	gly	ALA	ALA	ALA	ALA	ALA	ALA
	84	THR	THR	THR	THR	THR	THR	THR	THR	THR	asp	ala	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	val
	85	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR
	86	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	phe	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR	TYR
	87	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS
	88	gln	gln	gln	gln	gln	gln	gln	gln	glx	gln	gln	leu	gln	gln	gln	gln	gln	leu	gln	gln	gln	gln	gln	gln	gln
	89	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln	gln
	90	leu	ser	tyr	phe	ser	tyr	tyr	tyr	ser	tyr	ser	asp	ser	tyr	tyr	phe	tyr	his	tyr	ser	tyr	tyr	tyr	tyr	tyr
	91	SER	tyr	SER	SER	ASP	SER	SER	SER	tyr	SER	SER	SER	tyr	ASP	ASP	ASP	tyr	ile	ASP	ASP	tyr	leu	asn	ASX	ASP
	92	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	thr	SER	SER	ser	SER	SER	ser	SER	SER	SER	asn	ile	asn	thr
CDR3	94	tyr	thr	tyr	tyr	thr	tyr	tyr	PHE	thr	tyr	ser	thr	thr	leu	len	len	len	arg	leu	val	asn	leu	trp	PHE	leu
	95	pro	leu	pro	pro	pro	pro	pro	pro	pro	---	pro	pro	pro	pro	pro	pro	pro	pro	pro	pro	pro	pro	pro	pro	pro
	95A	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	GLU	---	---	---	---	---
	95B	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	95C	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	95D	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	95E	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	95F	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	96	---	ILE	---	---	---	TYR	---	---	TYR	---	TRP	---	---	TYR	TRP	LEU	TYR	ARG	ARG	ILE	VAL	ARG	PRO	LEU	SER
	97	---	THR	---	---	---	THR	---	---	THR	---	THR	---	---	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
	98	---	PRO	---	---	---	PRO	---	---	PRO	PRO	PRO	---	---	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
	99	---	GLY	---	---	---	GLY	---	---	GLY	GLY	GLY	---	---	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
	100	---	GLN	---	---	---	GLN	---	---	PRO	GLN	GLN	---	---	GLN	GLN	GLY	GLN	GLN	GLN	GLN	GLY	GLN	GLN	GLY	VAL
	101	---	GLY	---	---	---	GLY	---	---	GLY	GLY	GLY	---	---	GLY	GLY	SER	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
	102	---	THR	---	---	---	THR	---	---	THR	THR	THR	---	---	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
FR4	103	---	ARG	---	---	---	LYS	---	---	LYS	LYS	LYS	---	---	LYS	LYS	LYS	LYS	LYS	LYS	ARG	THR	LYS	LYS	GLU	LYS
	104	---	LEU	---	---	---	$	---	---	VAL	LEU	VAL	---	---	LEU	VAL	VAL	LEU	VAL	ILE	LEU	VAL	VAL	VAL	VAL	VAL
	105	---	ILE	---	---	---	$	---	---	GLU	GLU	GLU	---	---	GLN	GLU	ASP	GLU	GLU	GLU	GLU	ASP	ASP	GLU	GLU	GLU
	106	---	ILE	---	---	---	ILE	---	---	MET	ILE	ILE	---	---	ILE	ILE	PHE	ILE	ILE	ILE	ASN	ILE	LEU	VAL	VAL	SER
	106A	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	107	---	LYS	---	---	---	LYS	---	---	THR	LYS	ARG	---	---	THR	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS	LYS
	108	---	---	---	---	---	ARG	---	---	ARG	ARG		---	---	ARG	ARG	ARG	ARG	ARG	ARG	GLY	ARG	ARG	ARG		ARG
	109	---	---	---	---	---	---	---	---	THR	THR		---	---	THR	THR	THR	THR		IRR	THR		THR			THR

HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)

		50 R2	51* Ku RSV19 VK #	52 RBJ 4	53 BJ 26 #	54 BJ 19 #	55 RF2	56 HA	57 PAU	58 PSM	59 JBL #	60 NE	61 FRA	62 BJ 40	63 MF3- 1C/6	64 MF2, 1/13B	65 MF2, 18/2	66 GR'	67 GI 'CL #	68 NOM	69 KER	70 ESM IGG	71 ESM IGM	72* DAV	73* FIN	74 PW #	75 SHE	76 ADA
	0	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---		---	---	---	---	---	---	---	---
	1	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP		ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
	2	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE		ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE
	3	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN		GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN
	4	MET	leu	MET	MET	leu	MET	MET	MET	MET	MET	leu	MET	MET	MET	MET	MET	MET		MET	MET	PRT	MET	MET	MET	leu	val
	5	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR		THR	THR	THR	THR	THR	THR	THR	THR
	6	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLX	GLN	GLN	GLN	GLN	GLN	GLN		GLX	GLN	GLN	GLN	GLN	GLN	GLN	GLN
	7	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER		SER	SER	SER	SER	SER	SER	SER	SER
	8	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
	9	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER		SER	SER	SER	SER	SER	SER	thr	SER
F	10	ser	ser	THR	ser	ser	ser	ser	THR	ser	ser	ser	THR	ser	ser	ser	ser	THR		ser	ser	ser	ser	ser	ser	ser	ser
R	11	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU
1	12	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER		SER	SER	SER	SER	SER	SER	SER	SER
	13	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA		ALA	ALA	ALA	ALA	thr	thr	ALA	val
	14	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	tyr	SER	SER	SER	SER	SER	SER		SER	SER	SER	SER	val	val	SER	phe
	15	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL		VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
	16	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY		GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
	17	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASX	ASP	ASP	ASP	ASP	ASP	ASP		ASP	ASP	ASP	ASP	ASP	ASP	ASX	ASP
	18	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg		arg	arg	arg	arg	arg	arg	arg	arg
	19	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val	val		val	ILE	val	val	val	val	val	val
	20	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR		THR	THR	THR	THR	THR	THR	THR	THR
	21	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE		ILE	ILE	ILE	ILE	ILE	val	phe	ILE
	22	THR	THR	THR	THR	THR	THR	THR	THR	THR	ala	THR	THR	THR	THR	THR	THR	THR		THR	THR	THR	THR	arg	arg	THR	THR
	23	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS		CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS
	24	gln	ARG	ARG	gln	gln	gln	gln	ARG	gln	ARG	glx	ARG		ARG	ARG	ARG	ARG		gln	gln	ARG	ARG	asp	asp	ARG	glx	glx
	25	ALA	ser	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA		ALA	ALA	ALA	ALA		ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA
	26	asn	SER	SER	SER	SER	asn	SER	SER	SER	SER	SER	SER		SER	SER	SER	SER		arg	SER	SER	SER	SER	SER	SER	SER	SER
	27	GLN	GLN	GLN	GLN	GLN	GLN	---	GLN	GLN	GLN	GLX	GLX		GLN	GLN	GLN	arg		his	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLX
	27A	---	thr	---	---	---	---	---	---	---	---	---	---		---	---	---	---		---	---	---	---	---	---	---	---	---
	27B	---	leu	---	---	---	---	---	---	---	---	---	---		---	---	---	---		---	---	---	---	---	---	---	---	---
C	27C	---	val	---	---	---	---	---	---	---	---	---	---		---	---	---	---		---	---	---	---	---	---	---	---	---
D	27D	---	ile	---	---	---	---	---	---	---	---	---	---		---	---	---	---		---	---	---	---	---	---	---	---	---
R	27E	---	thr	---	---	---	---	---	---	---	---	---	---		---	---	---	---		---	---	---	---	---	---	---	---	---
1	27F	---	---	---	---	---	---	---	---	---	---	---	---		---	---	---	---		---	---	---	---	---	---	---	---	---
	28	val	asp	SER	SER	asp	val	---	SER	asp	SER	asn	asn		gly	gly	gly	SER		asp	asp	SER	SER	asn	asn	SER	asn	asn
	29	ILE	gly	val	ILE	ILE	ILE	---	ILE	ILE	ILE	ILE	ILE		ILE	ILE	ILE	ILE		ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE
	30	ser	asn	asn	asn	asn	ser	arg	ser	arg	ser	ser	asn		asn	arg	arg	ser		ser	lys	ser	ser	ser	ser	GLY	ser	
	31	lys	thr	ASN	lys	thr	lys	ASN	ser	ser	thr	ASX	ASX		ASN	ASN	ASN	ser		ASN		ser	ser	ser	ser		ASX	ASX
	32	ser	tyr	TRP	tyr	phe	ser	tyr	ser	ser	tyr	tyr	tyr		asp	asp	asp	phe		tyr		tyr	tyr	TRP	TRP	tyr	tyr	tyr
	33	LEU	LEU	LEU	ala	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU	LEU	LEU	LEU		LEU		LEU	LEU	LEU	LEU	ser	LEU	LEU
	34	asn	glu	ALA	asn	asn	asn	asn	ALA	asn	ser	asn	ALA		gly	gly	gly	ALA		asn		asn	asn	ile	ile	asn	asn	asn
	35	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP	TRP		TRP	TRP	TRP	TRP		TRP		TRP	TRP	TRP	TRP	TRP	TRP	TRP
	36	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr	tyr		tyr	tyr	tyr	tyr		PHE		tyr	tyr	tyr	tyr	tyr	tyr	tyr
	37	GLN	GLN	GLN	GLN	glu	GLN	GLN	GLN	GLX	GLN	GLN	GLX		GLN	GLN	GLN	GLN		GLN		GLX	GLX	GLN	GLN	GLN	ala	GLY
	38	GLN	GLN	glu	GLN	GLN	GLN	GLN	GLX	GLN	GLN	GLX	GLX		GLN	GLN	GLN	gly		GLN				GLN	GLN	GLN	GLX	tyr
	39	arg	LYS	LYS	#	#	arg	LYS	LYS	LYS	LYS	LYS	LYS		LYS	LYS	LYS	arg		LYS				tyr	tyr	LYS	LYS	LYS
	40	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	gln	PRO	PRO	PRO		PRO	PRO	PRO	PRO		PRO				PRO	PRO		PRO	PRO
F	41	GLY	GLY	GLY	#	#	GLY	GLY	GLY	GLY	GLY	GLY								GLY								
R	42	gln	LYS	glx	LYS	LYS	gln	arg	glx	LYS	LYS	glx																
2	43	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA		ALA														
	44	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO		PRO														
	45	lys	lys	lys	lys	lys	lys	lys	lys	lys	lys	lys		lys														
	46	leu	leu	leu	leu	leu	leu	leu	leu	leu	leu	VAL																
	47	LEU	LEU	LEU		LEU	LEU	LEU	LEU	LEU	LEU	LEU		met														
	48	ILE	ILE	ILE		ILE	ILE	ILE	ILE	ILE	ILE			ILE														
	49	TYR	TYR	asx		TYR	TYR	TYR	TYR	TYR	TYR	TYR		gly														
	50	asp	arg	LYS		asp	asp	asp	glu	asp				asp														
C	51	ile	val	thr	asp	ALA	ALA	ALA		SER				ALA														
D	52	SER	SER	SER	SER	SER	SER	ala	phe					SER														
R	53	ASN	ASN	asx	arg	ser	ASX	ASN						asx														
2	54	LEU	arg	LEU	LEU	LEU	LEU	LEU		LEU				LEU														
	55	glu	phe	glu	glu	glu	glu	glu		glu				asx														
	56	ser	ser	arg	thr	thr		ala						ser														
	57	GLY	GLY	GLY	GLY	GLY	GLY	GLY						GLY														
	58	val	val	asx	val	val	val	val						val					ILE								
	59	PRO	PRO	PRO	PRO	gln	PRO	PRO						val					PRO								
	60	SER	SER	SER	SER	SER		SER						SER					SER								
	61	ARG	ARG	ARG	lys	ARG	ARG	ARG						ARG					ARG								
	62	PHE	PHE	PHE	val	PHE	PHE							gln					PHE								
	63	thr	SER	ala	SER	leu	thr							SER					SER								
	64	GLY	GLY	GLY	GLY	GLY	GLY							GLY					GLY								
	65	SER	SER	SER	SER	SER								SER					SER								
	66	GLY	GLY	GLY	asx	GLY								GLY					GLY								
	67	SER	SER		phe									SER					SER								
	68	GLY	GLY		glu	asx								GLY					GLY								
	69	THR	THR		THR	THR								THR					THR								
	70	asp	asp		asp	lys								asp					GLU								
	71	PHE	PHE		val									pro					PHE								
F	72	phe	THR		THR									ser					THR								
R	73	LEU	phe		val									LEU					LEU								
3	74	THR	THR		asn									gln					THR								
	75	ile	ile		gln									VAL					VAL								
	76	ser	ser		ser									ser					ILE								
	77	ser	ser		ser									arg					ASN								
	78	LEU	LEU		LEU														LEU								
	79	arg	GLN		GLN														GLN								
	80	pro	pro		pro														SER								
	81	gln	glu		glu														ASP								
	82	ASP	ASP		ASP														ASP								
	83	val	ile		ile														PHE								
	84	ALA	ALA		ALA														ALA								
	85	THR	THR		pro														THR								
	86	TYR	TYR		lys														TYR		TYR						
	87	phe	TYR																TYR		TYR						
	88	CYS	CYS																CYS		CYS						
	89	gln	phe		gln														HIS		gln						
	90	glu	gln		gln														HIS		gln						
	91	tyr	gly		arg	phe								gly					ASN		tyr						
	92	ile	ser		ASP	ASP								glu					ASP		ASP						
	93	asn	ile		asp	asp								SER					thr		asp						
C	94	leu	leu		leu	leu								asp					PHE		leu						
D	95	pro	pro		pro	pro								SER					SER		pro						
R	95A	---	---		---	---								---					---		---						
3	95B	---	---		---	---								---					---		---						
	95C	---	---		---	---								---					---		---						
	95D	---	---		---	---								---					---		---						
	95E	---	---		---	---								---					---		---						
	95F	---	---		---	---								---					---		---						
	96	LEU	ARG		TYR	TYR								ARG					TRP		PRO						
	97	THR	THR		THR	THR								THR					THR		THR						
	98	PRO	PRO		LEU	PRO								PRO					PRO		PRO						
	99	GLY	GLY		GLY	GLY								GLY					GLY		GLY						
	100	GLY	GLY		GLY	PRO								GLN					GLN		PRO						
	101	GLY	GLY		GLY	GLY								GLY					GLY		GLY						
	102	THR	THR		THR	THR								THR					THR		THR						
F	103	LYS	LYS		LYS	LYS								LYS					LYS		LYS						
R	104	VAL	VAL		VAL	VAL								VAL					VAL		VAL						
4	105	GLU	GLU		GLU	GLU								GLU					LEU		ASP						
	106	ILE	ILE		MET	LEU								VAL					ILE		LEU						
	106A	---			---	---								---					---		---						
	107	LYS			LYS	LYS								LYS					LYS		LYS						
	108																		ARG								
	109																										

HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)

		77 AMYLOID VIII-B	78 PAUL	79 RI #	80 WAT	81* LOW	82 AMYLOID ES305 #	83 OCO	84 BOL	85 AMYLOID X	86 SAC	87 BJ	88 GO	89 F- GUI #	90 S- GUI #	91 HF6- 21/28	92 DIE	93 CAR A	94 TEI	95 MON	96 ALE	97 JOH	98 POT	99 CON	100 TRA	101* R-G2b
	0	---	---	pca	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	1	ASP	ASP	ASP	ASP	ASP	ASP	ASX	ASP	ASP	ASP	ASX	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASX	ASP	ASP	ASP	ASP	ASP
	2	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE		val	ILE	ILE	val	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE
	3	GLN	GLN	GLN	GLN	GLN	GLN	GLX	GLN	GLN	GLN		GLN	GLN	GLN	val	GLN	GLN	GLN	GLN	GLX	GLN	GLN	GLN	GLN	GLN
	4	MET	MET	MET	MET	MET	leu	MET	ile	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET
	5	THR	THR	THR	THR	THR	THR	THR	met	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
	6	GLN	GLN	GLN	GLN	GLN	GLN	GLX	GLX	GLN	GLN	GLN	GLX	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLX	GLN	GLN	GLN	GLN	GLN
	7	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER		SER	SER	ala	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
	8	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	ala	PRO		PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO
	9	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER		SER	SER	SER	leu	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
F	10	ser	THR	THR	ser	ser	ser	ser	ser	ser	ser		phe	ser	ser	ser	ser	ser	ser	THR		ser	ser	ser	ser	ser
R	11	LEU	LEU	LEU	LEU	LEU	LEU	LEU	val	LEU	LEU		val	LEU	LEU	LEU	LEU	LEU	LEU	LEU		LEU	LEU	LEU	LEU	LEU
1	12	SER	SER	SER	SER	SER	SER	val	SER	SER	SER		SER	SER	SER	pro	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
	13	ALA	ALA	ALA	ALA	ALA	ALA	met	ala	ALA	ALA		ALA	ALA	ALA	val	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA
	14	SER	SER	SER	SER	SER	SER	pro	SER	SER	SER		SER	SER	SER	thr	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER
	15	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL		VAL	VAL	VAL	leu	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL	VAL
	16	GLY	GLY	GLY	GLY	GLY	CLY	GLY	GLY	GLY	GLY		GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY	GLY
	17	ASP	ASP	ASP	ASP	ASP	ASP	ASX	ASX	ASP	ASP		ASX	ASX	ASX	gly	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP
	18	arg	arg	gly	arg	arg	leu	arg	arg	arg	---	arg	arg	arg	arg	pro	arg	arg	arg	arg	arg	arg	arg	arg	arg	arg
	19	val	val	val	val	val	val	val	val	val	---	val	val	val	val	ala	val	val	val	val	val	val	val	val	val	val
	20	THR	THR	THR	THR	THR	THR	THR	THR	ile	---	THR	THR	THR	THR	ser	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR
	21	ILE	ILE	ILE	ILE	ILE	#	ILE	ILE	ILE	---	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	leu	ILE	ILE	ILE	ILE	ILE
	22	THR	THR	ser	THR	THR	THR	THR	THR		---	THR	THR	THR	THR	ser	THR	THR	THR	THR	THR	THR	THR	THR	ILE	THR
	23	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS	---	CYS	CYS	CYS	CYS	CYS	CYS	CYS	CYS		CYS	CYS	CYS			
	24	gln	ARG	ARG	glx	ala	gln	glx	ARG	gln	---	gln	ARG		ARG	ARG					ARG					
	25	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	ALA	---	ALA	ALA	ALA	ALA	ser										
	26	SER	SER	SER	SER	SER	SER	SER	SER		---	SER	SER			SER										
	27	GLN	GLN	GLX	GLN	GLN	glu	GLX	GLX	GLX	---	GLN				GLN										
	27A	----	----	----	----	----	----	----	----	----	---	----				ser										
	27B	----	----	----	----	----	----	----	----	----	---	----				leu										
	27C	----	----	----	----	----	----	----	----	----	---	----				val										
C	27D	----	----	----	----	----	----	----	----	----	---	----				lys										
D	27E	----	----	----	----	----	----	----	----	----	---	----				ser										
R	27F	----	----	----	----	----	----	----	----	----	---	----				---										
1	28	asx	SER	SER	asp	asx	ala	asx	gly	asn	---	asp				asp										
	29	ILE	ILE	ILE	ILE	ILE	#	ILE	ILE	ILE	---	ILE				gly										
	30	GLY	ser	ser	ser	ser		ser			---	ser				asp										
	31		asp		tyr		ASN	ASX		pro	---	lys				ser										
	32	tyr	tyr		val		tyr	tyr		tyr	---					tyr										
	33	LEU	val				LEU			LEU	---					LEU										
	34		asn								---					glu										
	35	TRP	TRP		TRP		TRP				---					TRP										
	36						tyr			tyr	---					tyr										
	37										---					GLN										
	38										---					GLN										
	39										---					LYS										
	40										---					PRO										
F	41										---															
R	42										---															
2	43										---															
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	48										---															
	49										---															
	50										LYS															
	51										ser															
C	52										---															
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	85										---															
	86										---	TYR														
	87										---	TYR														
	88										CYS	CYS														
	89										glx	gln														
	90										gln	gln														
	91										glx	tyr														
	92										ASX	gln														
	93										ala	asn														
C	94										ala	leu														
D	95										thr	pro														
R	95A										---	---														
3	95B										---	---														
	95C										---	---														
	95D										---	---														
	95E										---	---														
	95F										---	---														
	96										ILE	TYR														
	97										PRO															
	98										ILE															
	99										GLY															
	100										GLY															
	101										GLY															
	102										THR															
F	103										LYS															
R	104										VAL															
4	105										ASX															
	106										VAL															
	106A										---															
	107										LYS															
	108										ARG															
	109										THR															

HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)

	102* K-G2	103 BRA	104 LUX	105* HEI	106 PAP	107* R-G2s	108 CRA	109 AMYLOID LEP	110* WAG	111 KOE	112 HBJ 1	113 AMYLOID 547	114 WEB	115 HBJ 10	116 LOO	117 BEN	118 MAA	119 GR	120 MUR	121 GM131 'CL'	122 AMYLOID 394	123* MAR	124 CL*
0	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
1	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP	ASP		ASP	ASP	---
2	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE	ILE		ILE	ILE	---
3	GLN	GLN	GLN	GLN	GLN		GLN	GLN	GLN	GLN	leu	GLX	GLN	GLN	GLN	GLN	GLN	GLN	GLN		GLN	GLN	---
4	MET	MET	leu	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET	MET		MET	leu	MET	MET		MET	leu	---
5	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR	THR		THR	THR	---
6	GLN	GLX	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLN	GLX	GLN	GLN	GLN	GLN	GLN	GLN	GLN		GLN	GLN	---
7	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER		SER	SER	---
8	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO	PRO		PRO	PRO	---
9	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	thr	SER	SER	SER	SER	SER	SER	SER	SER		SER	SER	---
10	SER	SER	Phe	THR	SER	SER	SER	SER	SER	THR	SER	SER	ser	SER	THR	ser	THR	ser	ser		SER	SER	---
FR 1 11	LEU	LEU	LEU	LEU	LEU	LEU	LEU	LEU	SER	LEU	LEU	LEU	VAL	LEU		LEU	LEU	LEU	LEU		LEU	LEU	---
12	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER				---
13	ALA	val	ALA	ALA	val	ALA	ALA	ALA	ALA	ALA	SER	ALA	ALA	ALA	ALA	ALA	ALA	val					---
14	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER	SER									---
15	VAL	VAL	VAL	VAL	VAL	VAL	leu	VAL	VAL	VAL	VAL	VAL	VAL		VAL								---
16	GLY	GLY	GLY	GLY	GLY	GLY	arg	GLY	GLY		GLY												---
17	ASP	gln	ASP	ASP	ASP	ASP	ASP	ASP	ASP		ASP												---
18	arg	arg	arg	arg	arg	arg	arg	arg															---
19	val	val	val	val	val	val	val	val															---
20	THR	THR	THR	THR	THR		THR	THR															---
21	ILE	ILE	ILE		ILE	ILE	ILE																---
22	THR	THR	THR		ala	THR	THR																---
23		CYS																					---
24																							---
25																							---
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27																							---
27A																							---
27B																							---
CDR 1 27C																							---
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FR 2 41																							---
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FR 3 72																							---
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78																				LEU			---
79																				GLN			---
80																				PRO			---
81																				glu			---
82																				ASP			---
83																				PHE			---
84																				ALA			---
85																				THR			---
86																				TYR			---
87																				TYR			---
88																				CYS			---
89																				gln			---
90																				phe			---
91																				his			---
92																				ASP		ASP	---
93																				his		ile	---
94																				leu		PHE	---
CDR 3 95																				pro		pro	---
95A																				---		---	---
95B																				---		---	---
95C																				---		---	---
95D																				---		---	---
95E																				---		---	---
95F																				---		---	---
96																				LEU		GLY	---
97																				THR		THR	---
98																				PHE		PHE	---
99																				GLY		GLY	---
100																				GLY		GLN	---
101																				GLY		GLY	---
102																				THR		THR	---
FR 4 103																				THR		LYS	---
104																				VAL		VAL	---
105																				GLU		GLU	---
106																				MET		ILE	---
106A																				---		---	---
107																				LYS		LYS	---
108																				ARG		ARG	---
109																				THR		THR	---

HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)

		125 AMYLOID	126 ABJ .6	127 AMYLOID MS #	128 BEN	# OF SEQUENCES	# OF AMINO ACIDS	OCCURRENCES OF MOST COMMON AMINO ACID	VARIABILITY
	0	---	---	---	---	1	1	1(PCA)	
	1	ASP	ASP	ASP	ASP	125	3,4	122(ASP),118(ASP)	3.1,4.2
	2	ILE	ILE	#	ILE	123	2	120(ILE)	2.
	3	glu	GLN	GLN	GLN	123	7	116(GLN),112(GLN)	7.4,7.7
	4	MET	MET	MET	MET	124	4	109(MET)	4.6
	5	pro	THR	THR		124	3	122(THR)	3.
	6	GLN	GLN			123	1,2	123(GLN),116(GLN)	1.,2.1
	7	SER				121	2	120(SER)	2.
	8	PRO				121	2	120(PRO)	2.
	9	SER				121	4	117(SER)	4.1
FR1	10	ser				120	5	89(SER)	6.7
	11	LEU				119	4	111(LEU)	4.5
	12					118	3	113(SER)	3.1
	13					117	4	107(ALA)	4.4
	14					113	6	106(SER)	6.4
	15					113	3	109(VAL)	3.1
	16					109	3	108(GLY)	3.
	17					109	3,4	106(ASP),98(ASP)	3.1,4.8
	18					106	6	97(ARG)	6.6
	19					107	3	101(VAL)	3.2
	20					106	4	102(THR)	4.2
	21					104	4	99(ILE)	4.2
	22					104	6	95(THR)	6.6
	23					96	1	96(CYS)	1.
	24					88	6	57(ARG)	9.3
	25					88	6	82(ALA)	6.4
	26					85	4	79(SER)	4.3
	27					84	4	79(GLN),66(GLN)	4.3,5.1
	27A					3	2	2(SER)	
	27B					3	2	2(LEU)	
	27C					3	2	2(VAL)	
CDR1	27D					3	3	1(+)	
	27E					2	2	1(+)	
	27F								
	28					84	7	29(SER)	20.
	29					83	5	72(ILE)	5.8
	30					81	11	41(SER)	22.
	31					79	12	27(ASN),24(SER)	35.,39.
	32					79	9	34(TYR)	21.
	33					77	4	73(LEU)	4.2
	34					73	7,8	30(ALA)	17.,19.
	35					76	1	76(TRP)	1.
	36					74	2	66(TYR)	2.2
	37					73	4	68(GLN),61(GLN)	4.3,4.8
	38					71	4	68(GLN),63(GLN)	4.2,4.5
	39					68	4	62(LYS)	4.8
	40					70	3	68(PRO)	3.1
	41					68	3	54(GLY)	3.2
	42					60	6	49(LYS)	7.3
FR2	43					61	4	57(ALA)	4.5
	44					61	1	61(PRO)	1.
	45					61	7,8	46(LYS)	9.3,11.
	46					60	7	42(LEU)	10.
	47					59	2	58(LEU)	2.
	48					57	2	56(ILE)	2.
	49					59	4	55(TYR)	4.3
	50					59	9	12(ALA)	20.
	51					59	3	50(ALA)	5.9
	52					58	6	53(SER)	6.6
CDR2	53					57	6,7	26(SER)	13.,15.
	54					58	2	56(LEU)	2.1
	55					58	8,9	23(GLU)	19.,21.
	56					56	8	34(SER)	13.
	57					57	1	57(GLY)	1.
	58					57	3	50(VAL)	3.5
	59					57	4	54(PRO)	4.2
	60					57	1	57(SER)	1.
	61					58	3	56(ARG)	3.1
	62					57	3	55(PHE)	3.1
	63					57	6	50(SER)	6.8
	64					57	2	55(GLY)	2.1
	65					56	5	51(SER)	5.5
	66					57	4	54(GLY)	4.2
	67					55	3	51(SER)	3.2
	68					55	3	52(GLY)	3.2
	69					55	2	51(THR)	2.2
	70					55	5,6	33(ASP),31(ASP)	8.5,11.
	71					54	4	49(PHE)	4.4
FR3	72					54	5	50(THR)	5.4
	73					54	3	43(LEU)	3.8
	74					54	4	51(THR)	4.2
	75					54	3	47(ILE)	3.4
	76					53	5	43(SER)	6.2
	77					54	6	40(SER)	8.1
	78					54	2	53(LEU)	2.
	79					54	3,4	52(GLN),48(GLN)	3.1,4.5
	80					54	2	46(PRO)	2.3
	81					54	3,5	37(GLU),34(GLU)	4.4,7.9
	82					54	2	53(ASP),50(ASP)	2.,2.2
	83					54	4	40(PRE)	5.4
	84					54	2	53(ALA)	2.
	85					54	6	48(THR)	6.7
	86					56	2	55(TYR)	2.
	87					55	2	52(TYR)	2.1
	88					56	1	56(CYS)	1.
	89					57	4,5	46(GLN),43(GLN)	5.,6.6
	90					57	2,3	51(GLN),46(GLN)	2.2,3.7
	91					58	11,12	20(TYR)	23.,28.
	92					60	9	20(ASN),19(+)	27.,28.
	93					60	9	29(SER)	19.
	94					60	12	15(LEU)	48.
CDR3	95					56	4	44(PRO)	5.1
	95A					1	1	1(GLU)	
	95B								
	95C								
	95D								
	95E								
	95F								
	96					44	12	10(TRP)	53.
	97					43	4	39(THR)	4.4
	98					46	3	44(PHE)	3.1
	99					46	1	46(GLY)	1.
	100					46	4,5	28(GLN),27(GLN)	6.6,8.5
	101					46	1	46(GLY)	1.
	102					46	2	45(THR)	2.
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	104					45	2	36(VAL)	2.5
	105					45	4,5	29(GLY),28(GLU)	6.2,8.
	106					46	7	30(ILE)	11.
	106A								
	107					45	3	42(LYS)	3.2
	108					33	2	31(ARG)	2.1
	109					22	1	22(THR)	1.

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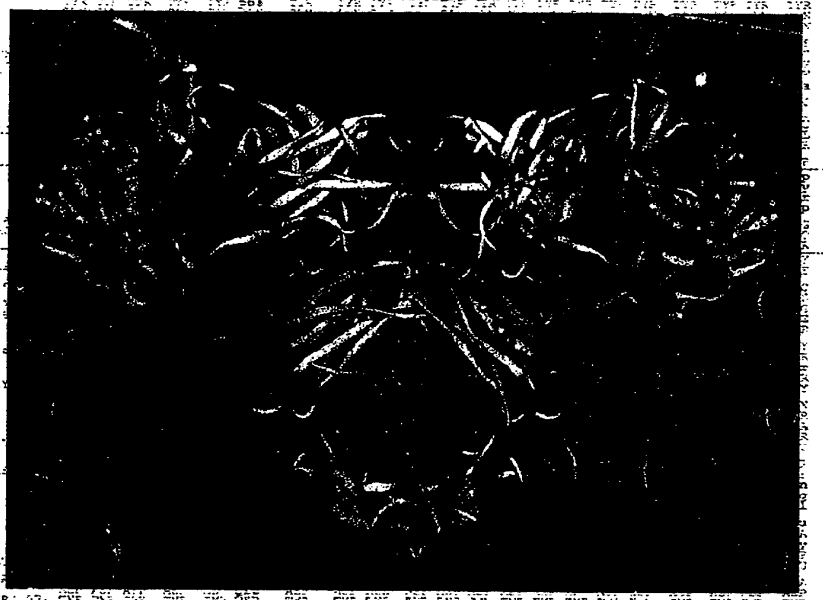
Exhibit B

SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST

VOL. I

FIFTH EDITION



1991

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST

FIFTH EDITION

Tabulation and Analysis of
Amino Acid and Nucleic Acid Sequences of Precursors,
V-Regions, C-Regions, J-Chain, T-Cell Receptors for Antigen,
T-Cell Surface Antigens, β_2-Microglobulins,
Major Histocompatibility Antigens, Thy-1, Complement,
C-Reactive Protein, Thymopoietin, Integrins, Post-gamma Globulin,
α_2-Macroglobulins, and Other Related Proteins

1991

Elvin A. Kabat, Tai Te Wu*, Harold M. Perry†,*
Kay S. Gottesman‡, and Carl Foeller†

*Depts. of Microbiology, Genetics and Development, and Neurology, Cancer Center/Institute of Cancer Research, College of Physicians and Surgeons, Columbia University, New York, NY 10032 and the National Institute of Allergy and Infectious Diseases, and the Office of the Director National Institutes of Health, Bethesda, MD 20892.

*Depts. of Biochemistry, Molecular Biology, and Cell Biology, and Engineering Sciences and Applied Mathematics and Biomedical Engineering, Northwestern University, Evanston, IL 60208 and the Cancer Center, Northwestern University Medical School, Chicago, IL 60611

†BBN Systems and Technologies, 10 Moulton Street, Cambridge, MA 02138

‡Formerly with BBN. Present address Laboratory for Applied Research in Academic Information, William H. Welch Medical Library, The Johns Hopkins University, Baltimore, Md 21205

The collection and maintenance of this data base is sponsored under grant 5R01 AI-125616 to E.A. Kabat of Columbia University by the following components of the National Institutes of Health, Bethesda, MD 20892:

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U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES

Public Health Service
National Institutes of Health

NIH Publication No. 91-3242

Samsung Bioepis Exhibit No. 1002
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dfmp
Dörries Frank-Molnia & Pohlman
Patentanwälte Rechtsanwälte PartG mbB

Patents – Trademarks – Designs

Theatinerstraße 16
80333 Munich
Germany

Phone +49 89 210296-0
Fax +49 89 210296-33

info@df-mp.com
www.df-mp.com

European Patent Office
Bob-van-Benthem-Platz 1
80469 München

December 12, 2017

Third Party Observations

Application Number	16 195 355.9 - 1466
Publication Number	EP 3 167 888
Title	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
Applicant	Alexion Pharmaceuticals, Inc.
Our file reference	AMG17203ADV-EP888

Third Party Observations

Amgen Inc. would like to bring the following to the Examining Division's attention:

I. According to Alexion's own submissions, eculizumab and its structure were known in the prior art.

Alexion has submitted in the brief dated July 10, 2017 with regard to the present patent application that D1 to D5 are not novelty-destroying, because only the name, not the structure of eculizumab was known in the prior art before the priority date.

This is in stark contrast to actions and statements made by Alexion in the past:

I.1 Previous patents and patent applications filed by Alexion

Alexion has filed and obtained a significant number of other European patents with one or more claims directed to the use of "eculizumab," e.g., EP2380907B1, EP1988882B1, EP1755674B1, EP2061810B1, EP1720571B9, and also filed various patent applications, all predating the

H. Ulrich Dörries [1234]
Dr. sc. nat., Dipl.-Biol.
David Molnia [12347]
M.S. Elec. Eng., B.S. Physics
Sandra Pohlman [568]
B.S. Biology
Michael Eder [1234]
Dr. sc. nat., Dipl.-Chem.
Oliver Schulz [1234]
Dipl.-Phys.
Rainer Friedrich [1234]
Dr. rer. nat., Dipl.-Biochem.
Elisabeth Greiner [1234]
Dr. rer. nat., Mag. pharm.
Philipp Nordmeyer [1234]
LL.M., Dipl.-Phys.
Dominik Ho [1234]
Dr. rer. nat., MEng (Cornell)
Holger Schimmel [1234]
Dr. rer. nat., Dipl.-Ing.
Annette Hilgendorf [1234]
Dr. rer. nat., Dipl.-Biochem.
Solveig Moré [1234]
Dr. rer. nat., Dipl.-Biochem.
Florian Brandt [1234]
Dr. rer. nat., Dipl.-Biochem.
Andreas Brzank [1234]
Dr. rer. nat., Dipl.-Phys.
René Okoampah [1234]
Dipl.-Ing.
Julia Mössinger [1234]
Dr. rer. nat., Dipl.-Biol.
Judith Hesse [8]
LL.M.
Helena Bertelsmeier [8]
LL.M.
Barbara Englert [1234]
Dr. rer. nat., Dipl.-Phys.

1 European Patent Attorney
2 European Trademark Attorney
3 European Design Attorney
4 Patentanwalt
5 Solicitor (England & Wales)
6 U.S. Patent Attorney
7 U.S. Patent Agent
8 Rechtsanwalt

Partnerschaftsregister des AG München
PR-Nr. 1278

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

MAR 16 2007

Our STN: BL 125166/0

Alexion Pharmaceuticals
Attention: Nancy Motola, Ph.D., RAC
Senior Vice President, Regulatory and Quality
352 Knotter Drive
Cheshire, CT 06410

Dear Dr. Motola:

We are issuing Department of Health and Human Services U.S. License No. 1743 to Alexion Pharmaceuticals, Inc., Cheshire, Connecticut, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are approved to manufacture the product eculizumab, which is indicated for the treatment of paroxysmal nocturnal hemoglobinuria to reduce hemolysis.

You are approved to manufacture eculizumab drug substance at Lonza Biologics, PLC in Portsmouth, NH. The final formulated product will be manufactured, filled, labeled, and packaged at [redacted]. You may label your product with the proprietary name Soliris™ and will market it in 300 mg vials.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

The dating period for eculizumab drug product shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 18 months when stored at 2-8°C.

You currently are not required to submit samples of future lots of eculizumab to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601 12 for any changes in the manufacturing, testing, packaging or labeling of eculizumab, or in the manufacturing facilities.

We acknowledge your written commitments as described in your letter of February 22, 2007, March 12, 2007 and March 12, 2007 as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To evaluate long-term safety of eculizumab by analyzing outcomes in the Soliris Safety Registry for a time period of no less than five years. At the end of the five year period, a study report will be submitted to the Biological License Application (BLA) that describes the major safety findings from the registry program, including the specific items listed below and proposing labeling changes as appropriate. Additionally, annual interim reports will be submitted to the BLA, along with expedited reports as specified below. The protocol for addressing this PMC will be submitted to the IND by May 31, 2007, and the five year study report will be submitted by June 30, 2012. All patients within the registry will be followed for the occurrence of:

    a. Serious infections, defined as infections necessitating or prolonging hospitalization or resulting in death. Alexion commits to collecting follow-up information from these patients to assess the nature of the serious infection, the duration of hospitalization, the major features of the clinical course and the survival status. Expedited reporting (15 day telephone or facsimile Medwatch communication) will be provided for the occurrence of these serious infections.

    b. Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy;

    c. Use of eculizumab among pediatric patients under 16 years of age, to include collection of eculizumab dosage information, as well as the same information being required for adult patients in the registry;

    d. Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to the women exposed to eculizumab during the pregnancy.

    e. Thrombotic events, including the nature of the event, the clinical outcome as well as the anticoagulant management prior to and after the event.

2. To submit a comprehensive description of the Soliris Guardian Program Risk Minimization Action Plan (RiskMAP), including all items listed below. Fulfillment of this post-marketing commitment will be contingent upon FDA concurrence upon the expectations of the Soliris Guardian Program. Submission of all items listed below will occur no later than May 18, 2007. The submitted information will include:

   a. A final version of the Soliris Guardian Program document that, in addition to any other items, provides information fully consistent with the approved prescribing information.

   b. A copy of all educational materials to be provided as part of the program, including but not limited to all components of the Soliris Starter Kit, the Drug Fact Sheet and patient-health care provider documents relating to the Soliris Safety Registry.

   c. A commitment to develop and submit a protocol (with the understanding that this protocol may need modification based upon FDA review findings) that uses surveys of health care providers and patients to assess compliance with the vaccination requirements as well as their knowledge of the risks of eculizumab and the need for vaccination.

   d. A copy of the Soliris Safety Registry protocol and any supportive documents to be provided to health care providers and patients. These documents may need modification based upon FDA review findings. The submitted protocol will indicate that the Registry will continue until Alexion receives written concurrence from FDA to terminate the registry. The protocol will include collection of the occurrence of the following events:

      i. Death;

      ii. Meningococcal vaccination (type and dates of all vaccinations);

      iii. eculizumab administration dates, at designated time points to establish initiation and termination of therapy as well as to correlate eculizumab administration with the fatalities and the events listed below:

         - All meningococcal infections causing sepsis or meningitis
         - Other serious infections
         - Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy;
         - Use of eculizumab among pediatric patients under 16 years of age, to include collection of eculizumab dosage information, as well as the required information for adult patients in the registry;
         - Use of eculizumab by indication;

- Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among off-spring of the women exposed to eculizumab during a pregnancy and;
- Serious hemolysis, as defined by specific criteria.

e. A commitment to submit quarterly RiskMAP reports for the first year and annual reports thereafter (unless FDA provides written request for more frequent submissions) summarizing all information relating to the Soliris Guardian Program. The reports should include the following:

i. An analysis of all cases of the following, including a root cause analysis and factors that might have contributed to serious outcomes:
- Meningococcal sepsis or meningitis, including the timing of all vaccinations relative to administration of Soliris
- Other infections (with serious outcomes)
- All deaths
- Cases of serious hemolysis and all cases of hemolysis with serious outcomes

ii. Soliris use patterns including indication for use;

iii. Extent of compliance with RiskMAP requirements such as the percentage of patients that were vaccinated prior to receiving eculizumab and the percentage of patients that were re-vaccinated at 3-year or 10-year intervals (as applicable);

iv. Analysis of all cumulative data collected in the Soliris Safety Registry;

v. Results from all health care provider and patient surveys, including:

- Any known data about patients or physicians who refused to participate in the surveys
- Any known data about survey participants who are considered "lost" (drop-outs).

3. To conduct a randomized, controlled clinical study to assess the effects of anticoagulant withdrawal among PNH patients receiving eculizumab. This study will randomize at least 100 anticoagulated patients to either continue or discontinue anticoagulation therapy. The major outcomes will assess the safety of discontinuation of anticoagulant therapy while continuing eculizumab, especially with respect to providing important evidence regarding major bleeding and that this discontinuation does not increase the risk for occurrence of thrombotic events in these patients. A full study report and data from this study will be submitted to the BLA and may include a label revision, contingent upon the importance of the study results. The study protocol will be submitted to the investigational new drug application (IND) by June 30, 2007 and patient accrual completed no later than June 1, 2009. A final study report will be submitted no later than March 31, 2014.

4. To develop a validated and quantitative assay for the measurement of human anti-human antibodies (HAHA) for the detection of antibody formation to eculizumab. This assay will assess potential immune responses to the whole eculizumab molecule. Description of the validated assay will be submitted to the BLA as a CBE 30 by July 9, 2008.

5. To develop a validated and sensitive assay for the measurement of neutralizing HAHA to eculizumab. Alternatively, Alexion commits to submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed and that the assessment of serum lactate dehydrogenase (LDH) is a sufficiently sensitive indicator of the presence of neutralizing antibodies. This information will be submitted to the BLA by July 9, 2008.

6. To utilize samples from the ongoing E05-001 Phase III extension study (approximately 170 patients for at least 2 years) as test samples for the new validated HAHA assays. Alexion will continue to obtain serum samples from those patients who transition from E05-001 to the Soliris Safety Registry, at intervals of no less than one year, and continue this collection process for an additional three years. Sample collection will cease during this additional three year period for patients who terminate eculizumab administration. Additionally, serum samples will be obtained based upon physician reports of suspected loss of eculizumab bioactivity, based upon unanticipated alterations in serum LDH concentrations. All serum samples will be assayed at least annually and the results provided within an annual report to the BLA. Clinical data, to include the results of serum LDH concentrations, will also be obtained from any patients who show evidence of antibody formation. The protocol describing Alexion's plan for responding to this commitment will be submitted by May 1, 2007 and the final study report submitted by January 31, 2011.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

7. To revalidate the linearity and accuracy of the Osmolality method across the full specification range using a combination of product samples diluted to lower osmolality and product samples spiked with osmolality standards. The revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

8. To revalidate the linearity of the IEF method across a load range of [—] The revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 supplement by August 31, 2007.

9. To revise the IEF method SOP to specify that the method is validated only for a [—] This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

10. To improve and revalidate the existing hemolytic assay. Improvements include increasing the number of sample replicates and qualifying the chicken erythrocytes reagent. The revised method SOP and revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

11. To develop a new quantitative biological activity assay to replace the existing hemolytic assay, or submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed. This information will be submitted to the BLA by February 29, 2008. Validation of the quantitative biological activity assay will be submitted by July 9, 2008.

12. To provide FDA with a completed drug substance and drug product container closure system leachables evaluation using end-of-shelf-life, long-term 2-8°C stability samples. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

13. To develop a suitable [redacted] assay and subsequently confirm [redacted] on three drug substance batches. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125166. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125166. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment Protocol**
- **Postmarketing Study Commitment Final Study Report**
- **Postmarketing Study Commitment Correspondence**
- **Annual Status Report of Postmarketing Commitment Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm) for further information.

Under 21 CFR Part 208, we have determined that this product poses a serious and significant public health concern requiring the distribution of a Medication Guide. Eculizumab is a product for which patient labeling could help prevent serious adverse effects and inform the patient of serious risks relative to benefit that could affect their decisions to use, or continue to use, the product. Therefore, a Medication Guide is necessary for safe and effective use of this product and FDA hereby approves the draft Medication Guide you submitted March 15, 2007. Please note that:

- this Medication Guide must be reprinted at the end of the package insert or accompany it [21 CFR 201.57(c)(18)];
- you are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208];
- the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.24, including a minimum of 10 point text; and
- you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided.

Please submit within 30 days content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text dated March 16, 2007. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

Sincerely,

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

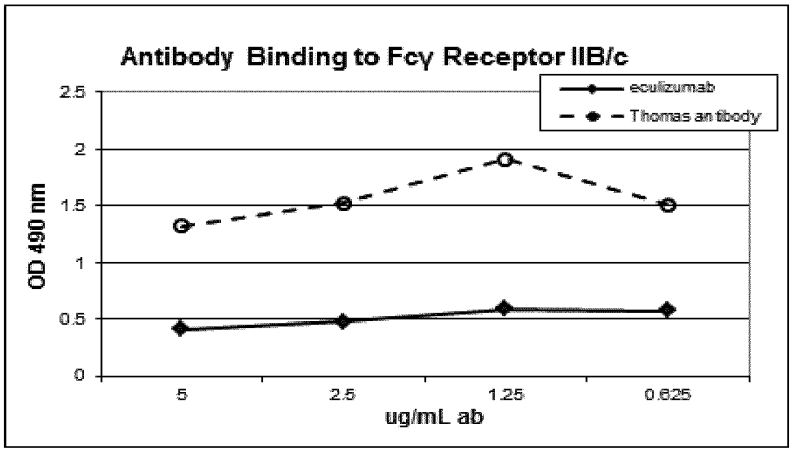
Enclosure: Package Insert
Carton and Vial Labeling
Medication Guide
Patient Safety Card

Experimental Report

Methods

Ni-NTA pre-coated plates (Qiagen, Ca#35061) were incubated with 50 µL/well of His-tagged human FcγR IIb/c (R and D systems Cat# 1875-CD) at a receptor concentration of 5 µg/mL in PBS, overnight at 4°C. Following overnight incubation with receptor, the plates were washed 3 times with PBS buffer containing 0.02% Tween-20 using a multiwash advantage plate washer. After washing, 50 µL of complexed antibodies were diluted in PBS buffer containing 0.05% Tween-20 and incubated in the plate for 60 minutes at room temperature. Complexed antibody was prepared by prior incubation of antibodies (eculizumab and the anti-C5 IgG4 antibody described in Thomas et al. (1997) Mol. Immunol. 33: 1389-1401) overnight with a biotinylated $F(ab')_2$ fraction of goat-anti-human $F(ab')_2$ (Jackson Immunolabs Cat#109-066-006), at a 2:1 antibody: $F(ab')_2$ molar ratio in PBS. Following incubation of the plate wells with complexed antibody, the plates were washed as described above and followed by the addition of 50 µL/well of the secondary antibody streptavidin-HRP to detect biotinylated complexed antibodies (Zymed Cat#43-4323, diluted 1/2000 in PBS buffer containing 0.05% Tween-20). Incubation with secondary antibody was for 60 minutes at room temperature. Following this incubation, wells were washed and color development initiated with 100 µL/ well of *o*-phenylenediamine dihydrochloride (OPD, Sigma Cat#P 9187). Reactions were stopped with 25 µL/well 12.5% H_2SO_4 and the absorbance read at 490 nm.

Results



The Figure above shows the binding of the cross linked antibodies to Fcγ Receptors as immune complexes with $F(ab')_2$-anti-$F(ab')_2$, measured using an ELISA format. Concentration of antibody (µg/mL) is described on the X axis, and the Y axis reflects signal

as measured via optical density at 490 nm. The binding profile of the IgG4 subtype antibody (Thomas antibody) to FcγRIIB, the inhibitory FcγR, is markedly different from the binding profile exhibited by eculizumab. Binding of eculizumab to FcγRIIB is weaker than the binding of the IgG4 antibody to FcγRIIB.

FDA Approves Alexion's Soliris(TM) for All Patients With PNH

- First Therapy Approved for This Rare and Life-Threatening Blood Disease -

CHESHIRE, Conn., March 16, 2007 /PRNewswire-FirstCall via COMTEX News Network/ -- Alexion Pharmaceuticals, Inc., (Nasdaq: ALXN) announced today that it has received marketing approval from the U.S. Food and Drug Administration (FDA) for Soliris(TM) (eculizumab). Soliris is the first therapy approved for paroxysmal nocturnal hemoglobinuria (PNH), a rare, disabling and life-threatening blood disorder defined by chronic red blood cell destruction, or hemolysis. Soliris is indicated for the treatment of patients with PNH to reduce hemolysis.

Hemolysis can cause one or more of the following symptoms in patients with PNH: severe anemia, disabling fatigue, recurrent pain, shortness of breath, pulmonary hypertension, intermittent episodes of dark colored urine (hemoglobinuria), kidney disease, impaired quality of life and blood clots (thromboses).(1,2) PNH often strikes people in the prime of their lives, with an average age of onset in the early 30's.(3) The estimated median survival for PNH patients is between 10 and 15 years from the time of diagnosis.(3,4)

Patients with PNH are missing a specific protein that normally protects red blood cells from destruction by a component of the immune system called terminal complement. Soliris, the first complement inhibitor approved in the United States for the treatment of any disease, prevents hemolysis by selectively blocking terminal complement.

"Soliris brings real hope to people who live daily with the devastating effects of PNH. With the approval of Soliris, we now have a therapy that dramatically improves the lives of patients suffering from this disease. Importantly, all patients with this life-threatening disease will be eligible for treatment," said Leonard Bell, MD, chief executive officer of Alexion Pharmaceuticals.

"Soliris directly targets the underlying disease process responsible for debilitating symptoms that may contribute to shortened life spans of PNH patients," said Wendell F. Rosse, MD, Florence McAlister Professor of Medicine Emeritus, Duke University. "Having cared for more than 300 patients with PNH over my career, I believe this is the most important advance that has been made in the treatment of this disease. Treatment with Soliris markedly decreases the hemolysis responsible for anemia, fatigue, poor patient functioning and blood clots in PNH patients."

Clinical Data

Soliris has proven to be a safe and effective therapy for PNH in three multi-national clinical studies: TRIUMPH, a placebo-controlled 26 week Phase 3 study involving 87 PNH patients,(5) SHEPHERD, an open-label 52 week Phase 3 trial involving 97 PNH patients,(6) and E05-001, a long term extension study.(7)

These studies showed that Soliris reduced hemolysis in every treated patient. Hemolysis was dramatically reduced from a baseline LDH of 2,032 U/L to 239 U/L at week 26 ($p<0.001$). The reductions in hemolysis occurred within one week of initiating treatment and were sustained for periods of up to 54 months with continued dosing of Soliris. The reduction in hemolysis expands the number of circulating PNH cells and, thereby, increases the hemoglobin level. Hemoglobin stabilization and the number of transfused packed red blood cell units, the pivotal study's co-primary endpoints, were both achieved; half of the Soliris-treated patients achieved hemoglobin stabilization compared with none of the patients in the placebo group, the median number of transfusions was reduced from 10 units/patient to 0 units/patient, respectively ($p < 0.001$ in both cases). Soliris patients reported less fatigue and improved health-related quality of life. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment.

"The Aplastic Anemia & MDS International Foundation (AA&MDSIF) is extremely pleased that PNH patients now have a treatment specifically for their disease. This is a tremendous step forward for all who suffer from PNH -- and for anyone with bone marrow failure," said Sherrie VanVliet, vice-chairperson, AA&MDSIF, and the mother of a child with aplastic anemia. "We also appreciate that Alexion, in cooperation with the National Organization of Rare Diseases, has established a program to ensure that all patients who need eculizumab have access to it."

"Patients with rare diseases face huge challenges -- first getting a proper diagnosis, then finding effective treatments and access to them," said Abbey Meyers, president, National Organization for Rare Disorders (NORD). "Now that Soliris has been approved, people with PNH will have an effective treatment, and through NORD's PNH Foundation, the uninsured and underinsured will receive help to assure they will have access. This is a sign of hope for others with orphan illnesses, that their needs will one day be met," she added.

Introducing Soliris OneSource(TM)

Alexion also today introduced Soliris OneSource(TM), a treatment support service for all PNH patients and their healthcare providers. Each patient enrolled in the program receives support from an Alexion Case Manager at OneSource. Alexion Case Managers are Registered Nurses and provide education about PNH and Soliris and facilitate solutions to help patients obtain Soliris. Alexion's goal is that all PNH patients who can benefit from Soliris will have access to it. Patients and their health care providers can learn more about OneSource by calling 1-888-SOLIRIS (1-888-765-4747) or visiting www.soliris.net.

Important Safety Information

Soliris is generally well tolerated. The most frequent adverse events observed in clinical studies were headache, nasopharyngitis (a runny nose), back pain and nausea.(8) Treatment with Soliris should not alter anticoagulant management because the effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established.

The product label for Soliris also includes a boxed warning: "Soliris increases the risk of meningococcal infections. Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of Soliris; revaccinate according to current medical guidelines for vaccine use. Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary. "Two out of 196 vaccinated PNH patients treated with Soliris experienced a serious meningococcal infection.

Prior to beginning Soliris therapy, all patients and their prescribing physicians will be enrolled in the Soliris Safety Registry which is part of a special risk management program that involves initial and continuing education and long-term monitoring for detection of new safety findings.

Please see full prescribing information at www.soliris.net.

Conference Call Information

Alexion will host a conference call/webcast to discuss FDA approval of Soliris. The call is scheduled for Monday, March 19th at 9:00 a.m., Eastern Time. To participate in this call, dial 913-981-4900, confirmation code 4700435, shortly before 9:00 a.m., Eastern Time. A replay of the call will be available for a limited period following the call, beginning at 12:00 p.m., Eastern Time. The replay number is 719-457-0820, confirmation code 4700435. The audio webcast can be accessed at: www.alexionpharm.com.

About PNH

PNH is an acquired genetic blood disorder defined by hemolysis, in which patients' red blood cells are destroyed by complement, a component of the body's immune system. PNH is a rare disease that affects an estimated 8,000 to 10,000 people in North America and Europe. Ten percent of all patients first develop symptoms at 21 years of age or younger.(2) PNH develops without warning and can occur in men and women of all races, backgrounds and ages. PNH often goes unrecognized, with delays in diagnosis often ranging from one to more than 10 years. PNH has been identified more commonly among patients with diseases of the bone marrow, including aplastic anemia (AA) and myelodysplastic syndrome (MDS). In patients with thrombosis of unknown origin, PNH may be an underlying cause.

Prior to approval of Soliris, there were no therapies specifically available for the treatment of PNH. PNH treatment was limited to symptom management through periodic blood transfusions, non-specific immunosuppressive therapy and, infrequently, bone marrow transplantations -- a high-risk and painful procedure used as a last resort.(2)

About Alexion

Alexion Pharmaceuticals is a biotechnology company working to develop and deliver life-changing drug therapies for patients with serious and life- threatening medical conditions. Alexion's lead product, Soliris(TM) (eculizumab), is indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Alexion is engaged in the discovery and development of therapeutic products aimed at treating patients with severe disease states, including hematologic diseases, cancer and autoimmune disorders. In September 2006, Alexion applied for marketing authorization with the European Medicines Evaluation Agency for the use of Soliris(TM) (eculizumab) in PNH patients. This press release and further information about Alexion Pharmaceuticals, Inc. can be found at: http://www.alexionpharm.com.

This news release contains forward-looking statements, including statements related to medical benefits and commercial potential of Soliris(TM)(eculizumab), initiation and conduct of the PNH OneSource(TM) treatment support service, and estimates of the number of people living with PNH. Forward-looking statements are subject to factors that may cause Alexion's results and plans to differ from those expected, including requests by regulatory authorities for additional information following marketing approval, delays in arranging satisfactory manufacturing capability, inability to acquire funding on timely and

satisfactory terms, delays in or failure to establish internal sales and marketing capabilities, delays in developing or adverse changes in commercial relationships, the possibility that results of clinical trials are not predictive of the safety and efficacy of Soliris(TM)(eculizumab) when made available to larger number of people, the risk that third parties won't agree to license any necessary intellectual property to us on reasonable terms, the risk that third party payors will not reimburse for the use of Soliris(TM) at acceptable rates or at all, the risk that estimates regarding the number of people living with PNH are inaccurate, and a variety of other risks set forth from time to time in Alexion's filings with the Securities and Exchange Commission, including but not limited to Alexion's Annual Report on Form 10-K. Alexion does not intend to update any of these forward-looking statements to reflect events or circumstances after the date hereof, except when a duty arises under law.

(1) Rother R, Bell L, Hillmen P, Gladwin M. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin. JAMA 2005; 293:1653-1662.

(2) Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood 2005; 106:3699-3709.

(3) Socie G, Mary J Yves, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. Lancet 1996; 348:573-577.

(4) Hillmen P. Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1995; 333:1253-1258.

(5) Hillmen P, Young N, et al. The Complement Inhibitor Eculizumab in Paroxsysmal Nocturnal Hemoglobinuria. N Engl J Med 2006; 355:1233-1243.

(6) Young N, Antonioli E, Rotoli B, et al. Safety and efficacy of the terminal complement inhibitor eculizumab in patients with paroxysmal nocturnal hemoglobinuria: SHEPHERD phase III clinical study results. Blood 2006; 108:971.

(7) Hillmen P, Muus P, Duhrsen U, et al. The terminal complement inhibitor eculizumab reduces thrombosis in patients with paroxysmal nocturnal hemoglobinuria. Blood 2006; 108:123.

(8) Soliris(TM) (eculizumab) prescribing information. Alexion Pharmaceuticals, Inc., 2006.

SOURCE Alexion Pharmaceuticals, Inc.

Leonard Bell, M.D., Chief Executive Officer, of Alexion Pharmaceuticals, Inc., +1-203-272-2596; or Media, David Patti, of Makovsky + Company, +1-212-508-9623, dpatti@makovsky.com; or Investors, Rhonda Chiger, of Rx Communications Group, LLC, +1-917-322-2569, rchiger@rxir.com, both for Alexion Pharmaceuticals, Inc.

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News Provided by COMTEX

DECLARATION BY STEPHEN A. SAXE, PH.D., J.D.

Dear Sir:

I, Stephen A. Saxe, Ph.D., J.D., was Associate General Counsel, Intellectual Property at Alexion Pharmaceuticals, Inc. ("Alexion") from October 2001 through May 2014. In that role, I was the primary intellectual property counsel at Alexion responsible for handling matters related to Soliris®(eculizumab) from at least 2001 through 2009. I declare that:

1. In late March 2009, in the course of reviewing papers related to a matter in Australia, I noticed that eculizumab had a registry number assigned to it from the Chemical Abstracts Service ("CAS"). I inquired internally at Alexion and learned that in early 1999 CAS had assigned the molecule that would later be called "eculizumab" the CAS Registry Number 219685-50-4. However, I also learned at that time that incorrect information had been submitted to CAS in 1999 to support the CAS registry entry. In particular, there were numerous errors in the sequence of the molecule described in CAS Registry Number 219685-50-4.

2. On April 20, 2009, I emailed CAS and explained that it had recently come to our attention that the entry information submitted in 1999 was incorrect, and I proposed that the registry entry should be corrected. (See attached Exhibit A.)

3. Following up to that email, on April 28, 2009, I sent another email with an attached letter to CAS, detailing the errors and requesting correction of CAS Registry Number 219685-50-4. (See attached Exhibit B.) For example, I explained that the heavy chain is in fact 448 amino acids long, not 650 amino acids in length as had initially been submitted in 1999. (See Exhibit B letter, 3rd paragraph.) I also explained that there was an error in the sequence of the light chain that was submitted in 1999. (See Exhibit B letter, 3rd paragraph.) I provided complete and accurate amino acid sequences for both the heavy chain and the light chain of eculizumab.

4. On May 1, 2009, Ms. Lois Bishop at CAS responded to my April 28, 2009 communication and indicated that the changes I requested to CAS Registry Number 219685-50-4 had been made and that it would take a couple of days for these to appear on STN. (See attached Exhibit C.)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Stephen A. Saxe — January 12, 2018

Stephen A. Saxe, Ph.D., J.D. — Date

Samsung Bioepis Exhibit No. 1002
Page 1115

answers @ cas.org
send new seqs, reference old order #
sf disulfide bond change - let them know,
Lois Bishop 614-447-3600,
x 2863

Saxe, Stephen

From: Saxe, Stephen
Sent: Monday, April 20, 2009 4:35 PM
To: 'help@cas.org'
Subject: Registry Number 219685-50-4

Dear Sir or Madam,

About 10 years ago my company (Alexion Pharmaceuticals) obtained a registry number (219685-50-4) for our antibody called eculizumab. We submitted amino acid sequences which we stated were for the two chains of eculizumab. It has recently come to our attention that the sequences we submitted to you 10 years ago were incorrect. How can we have this corrected? At present, I am uncertain whether the sequences we submitted are publicly available in a database. Whether publicly available or not, we feel that we should correct the sequences that were erroneously sent to you in 1999 and which we only recently realized were sent in error. Can we simply submit the correct sequences and keep the same registry number or is it necessary to obtain a new registry number? If the latter, we would like the original registry number deleted since the sequence associated with it is incorrect. Please let me know how we should proceed to get this matter corrected. Thank you.

Stephen A. Saxe, Ph.D.
Associate General Counsel, Intellectual Property
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
U.S.A.
Tel. 203-271-8289
Fax 203-271-8195

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****

Saxe, Stephen

From: Saxe, Stephen
Sent: Tuesday, April 28, 2009 3:03 PM
To: 'answers@cas.org'
Subject: CAS Registry Number 219685-50-4
Attachments: Letter to CAS 04-28-09.pdf

Dear Sir or Madam:

Please see the attached letter regarding correcting information for CAS Registry Number 219685-50-4. Please contact me if you need additional information. Thank you.

Stephen A. Saxe, Ph.D.
Associate General Counsel, Intellectual Property
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
U.S.A.
Tel. 203-271-8289
Fax 203-271-8195

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ALEXION pharmaceuticals

Stephen A. Saxe, Ph.D.
Associate General Counsel, Intellectual Property

saxes@alxn.com
Direct Tel. 203-271-8289

April 28, 2009

Dear Sir or Madam:

On February 8, 1999 Alexion Pharmaceuticals, Inc. submitted an application form for a new CAS registry number for Alexion's whole monoclonal antibody named 5G1.1. This was processed under your Order Number 41875. The antibody was assigned CAS Registry Number 219685-50-4. It recently came to Alexion's attention that incorrect information was submitted in 1999. At this time Alexion would like to correct the error that was made in 1999. Attached is information showing the correct sequence information. In the 1999 filing, the antibody was described as follows:

> 5G1.1 is a fully humanized monoclonal antibody (originally of murine origin) specifically reactive with the fifth component of human complement (C5). 5G1.1 specifically binds to the alpha chain of C5. It blocks the activation of C5 and thereby blocks downstream complement system function. It thus 1) blocks complement hemolytic activity, 2) blocks the assembly of the C5b-9 membrane attack complex of complement, and 3) blocks the generation of the anaphylatoxic complement C5 cleavage product, C5a. 5G1.1 consists of a heavy chain that is 650 amino acids long and a light chain that is 214 amino acids long. The amino acid sequence of the light chain is:

There is one error in the information provided in the above paragraph. The heavy chain is in fact 448 (not 650) amino acids long. The correct sequence is shown on the attached sheet. The light chain is 214 amino acids long and that information in the above paragraph is correct. However, there was a single error in the sequence of the light chain that was submitted in 1999 and the correct sequence is shown on the attached sheet. Both sequences on the attached sheet (labeled as Figure 3.2.S.1.2.2) are presented using the standard one-letter amino acid code. If you need more information than that, please let me know. We would like the heavy- and light-chain sequences shown on the attached sheet to be inserted into the CAS database in place of the two sequences that were erroneously sent to you in 1999.

Additionally, the disulfide bonds of the whole antibody are known. These bonds are as follow:

Samsung Bioepis Exhibit No. 1002
Page 1118

Disulfide Bonds Solely within a Light Chain
Cys23Light - Cys88Light
Cys134 Light - Cys194Light

Disulfide Bonds Solely within a Heavy Chain
Cys22Heavy - Cys96Heavy
Cys149Heavy - Cys205Heavy
Cys262Heavy - Cys322Heavy
Cys368Heavy - Cys426Heavy

Disulfide Bonds Connecting the Light and Heavy Chains
Cys136Heavy - Cys214Light

Disulfide Bonds Connecting Two Heavy Chains
Cys228Heavy - Cys228Heavy
Cys231Heavy - Cys231Heavy

From the above you see that each light chain has two intrachain disulfide bonds, each heavy chain has four intrachain disulfide bonds, there is a single disulfide bond connecting a light chain to a heavy chain, and there are two disulfide bonds connecting the two heavy chains to each other.

Additionally, there is one N-linked glycosylation site at Asn298 of the heavy chain.

We would like the same CAS Registry Number to be maintained for this molecule and to simply have the correct amino acid sequences for the light and heavy chains replace the incorrect sequences that were inadvertently submitted in 1999. Please let me know when the correction has been made. Please contact me if you need additional information.

Very truly yours,

Stephen A. Saxe

Stephen A. Saxe

Figure 3.2.S.1.2.2: Expected Amino Acid Sequence for h5G1.1-mAb

Heavy Chain

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLR
SEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY
TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHY
TQKSLSLSLGK

N-Terminal = Pyroglutamate
C-Terminal = OH
Average Mass = 49,502 Da

Light Chain

DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ
NVLNTPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST
LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

N-Terminal = H
C-Terminal = OH
Average Mass = 23,135 Da

Samsung Bioepis Exhibit No. 1002
Page 1120

Saxe, Stephen

From: Bishop, Lois [lbishop@cas.org]
Sent: Friday, May 01, 2009 8:18 AM
To: Saxe, Stephen
Subject: RE: CAS Registry Number 219685-50-4

Dear Dr. Saxe,

The changes to your sequence for CAS Registry Number 219685-50-4 have been made. It may take a couple of days before they appear on STN. Let us know if we can be of further assistance.

Best regards,
Lois Bishop
CAS Client Services
614-447-3600 x2863

From: Saxe, Stephen [mailto:SaxeS@alxn.com]
Sent: Tuesday, April 28, 2009 3:03 PM
To: answers
Subject: CAS Registry Number 219685-50-4

Dear Sir or Madam:

Please see the attached letter regarding correcting information for CAS Registry Number 219685-50-4. Please contact me if you need additional information. Thank you.

Stephen A. Saxe, Ph.D.
Associate General Counsel, Intellectual Property
Alexion Pharmaceuticals, Inc.
352 Knotter Drive
Cheshire, CT 06410
U.S.A.
Tel. 203-271-8289
Fax 203-271-8195

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D9

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Patentanwälte Rechtsanwälte

VOSSIUS & PARTNER * POB 86 07 67 * 81634 München * Germany

EPO - Munich
75

30. Dez. 2013

European Patent Office

80298 M U N I C H

Opposition against EP 1720571
(Application No.: 05 71 2607.0)
Patentee: Alexion Pharmaceuticals, Inc.
Opposition by: Pfizer Inc.
Our Ref.: M2367 OPP(EP)

München, December 30, 2013
WA/ARO/FLG

This is in response to the Official Communication of April 19, 2013 issued by the European Patent Office in the above-referenced opposition proceedings.

It is requested that the patent EP-B1 1720571 is maintained on the basis of the claims as granted. As will be evident from our written submissions herein below, our request that the patent be maintained on the basis of the granted claims is fully justified. Since furthermore the Opponent, Pfizer Inc., formally and irrevocably has withdrawn its opposition on October 7, 2013, it is requested that the opposition proceedings are promptly terminated.

In case the Opposition Division would be inclined to proceed differently, we request oral proceedings in accordance with Article 116 EPC. In that case we request that we be allowed to submit one or more additional claim request(s).

PATENTANWÄLTE - DEUTSCHLAND
EUROPEAN PATENT ATTORNEYS
EUROPEAN TRADEMARK ATTORNEYS
DR. DIETER HEUNEMANN, Dipl.-Phys.
DR. GERHARD HERMANN, Dipl.-Phys.
JOSEF SCHMIDT, Dipl.-Ing.
DR. HANS-RAINER JAENICHEN, Dipl.-Biol.
DR. ALEXA V. UEXKÜLL, M.Sc.
DR. RUDOLF WEINBERGER, Dipl.-Chem.
DR. JOACHIM WACHENFELD, Biol.
DR. FRIEDERIKE STOLZENBURG, Dipl.-Biol.
RAINER VIKTOR, Dipl.-Ing.
DR. NATALIA BERRYMAN, Dipl.-Chem.
DR. JÜRGEN MEIER, Dipl.-Biol.
DR. STEFAN FICKERT, Dipl.-Chem., LL.M.
ARNOLD ASMUSSEN, Dipl.-Ing.(FH)
ELARD SCHENCK ZU SCHWEINSBERG, Dipl.-Ing., LL.M.
DR. DIRK HARMSEN, Dipl.-Chem.
DR. KATHARINA HAAS, Dipl.-Chem.
BARBARA BROSZAT, Dipl.-Phys.
DR. SUSANNE FISCHER-KRUMMER, Apothekerin
DR. JÖRG HAHN, Dipl.-Chem.
DR. CHRISTOPH EISENMANN, Dipl.-Phys.
DR. MICHAELA WESSE, Apothekerin
DR. OLIVER SAHR, Dipl.-Phys.
DR. AXEL LEINS, Dipl.-Phys.
DR. CHRISTIAN SCHLÖRB, Dipl.-Biochem.
OSWIN RIDDERBUSCH, Dipl.-Biochem.

DR. PAUL TAUCHNER, Dipl.-Chem. (Of Counsel)
DR. PETER A. RAUH, Dipl.-Chem. (Of Counsel)

PATENTANWALT - SCHWEIZ
EUROPEAN PATENT ATTORNEY
DR. WERNER BASTIAN, Dipl.-Biol.

EUROPEAN PATENT ATTORNEYS
DR. RENATE BARTH, Dipl.-Chem.
DR. URSULA HOFMANN, Dipl.-Chem.
DR. PETER EINMAYR, Dipl.-Chem.
DR. OLAF MALEK, Dipl.-Biol.
DR. ROGER ABSEHER, Biochem.
DR. DANIEL EISENBARTH, Dipl.-Biol.
DANA KRÄMER, Ph.D., Dipl.-Biochem.
KIMIO TAKAHASHI 1)
DR. ULRICH SENTNER, Dipl.-Biol.
DR. ALEXANDER SCHWENDEMANN, Dipl.-Biol.
DR. MAURIZIO DI STASIO, Dipl.-Biol.
NAMI SAEKI 1)

PATENTANWALT - DEUTSCHLAND
DR. ANDREAS M. ROBINSON, Dipl.-Biol.

RECHTSANWÄLTE
DR. JOHANN PITZ
DR. THURE SCHUBERT
DR. MATHIAS KLEESPIES, LL.M.
SIMONE SCHÄFER
PAUL KRETSCHMAR, LL.M. 2)
DR. MARCUS V. WELSER, LL.M. 2)
ACHIM BENDER
BARBARA GUGGENMOS, Dipl.-Chem.
JENNIFER CLAYTON-CHEN
DR. GEORG ANDREAS RAUH
DR. STEFANIE NABROTZKI, LL.M.
CHRISTIAN HUFNAGEL, LL.M. 3)
NILS BINGS, LL.M.

CONSULTANTS
DR. CHRISTIAN GUGERELL 4)
YOSHIKAZU ISHINO
JENNIFER L. ENMON, Ph.D., J.D. 5)
RICHARD ENMON, Ph.D., J.D. 5)

1) Japanese Patent Attorney
2) Fachanwalt für gewerblichen Rechtsschutz
3) U.S. Attorney-at-Law (New York)
4) European Patent Attorney
5) Registered U.S. Patent Attorney

MAIN OFFICE
SIEBERTSTR. 3
81675 MÜNCHEN/GERMANY

POSTAL ADDRESS:
POB 86 07 67
81634 MÜNCHEN/GERMANY

Tel.: +49-(0)89-413 04-0
Fax: +49-(0)89-413 04-111
Fax trademarks: /-400

BERLIN OFFICE
JOACHIMSTALER STR. 34
10719 BERLIN/GERMANY

Tel.: +49-(0)30-340 609-501
Fax: +49-(0)30-340 609-512

Partnerschaftsregister Amtsgericht München PR 89

BASEL OFFICE (CH)
NADELBERG 3
4051 BASEL/SWITZERLAND

Tel.: +41-(0)61 560 1490
Fax: +41-(0)61 560 1488

HR Firmennummer CH-270.9.001.271-9

E-Mail:
patents@vossiusandpartner.com
trademarks@vossiusandpartner.com

www.vossiusandpartner.com

Liste aller Partner i.S.d. PartGG:
www.vossiusandpartner.com/partner

1. INADMISSIBLE BROADENING (Articles 100(c) and 123(2) EPC)

1.1. The then Opponent alleges that the subject-matter of independent claims 1 and 5 and the claims dependent thereon is not directly and unambiguously disclosed by the application a filed thereby contravening Article 123(2) EPC.

1.2. The second medical use claims 1 and 5 comprise identical features. Claim 1 is drafted as purpose-limited product claim in accordance with the EPC 2000 and claim 5 is drafted as a Swiss-type claim in accordance with the EPC 1973.

The Opponent has divided these claims into the following features:

(1) the use of eculizumab,
(2) the treatment of a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH),
(3) intravenous administration,
(4) administration of 600 mg each week for four weeks,
(5) administration of 900 mg 1 week later,
(6) administration of 900 mg on a biweekly basis,
(7) a breakthrough in serum hemolytic activity when treated under a dosing schedule according to (4) to (6), and
(8) administration of 900 mg every 12 days.

1.2.1. In more detail, the opponent is of the view that each of features (1) and (3) requires the selection of an item from a list of equally categorized items. In other terms, three selections from three lists are allegedly required in order to arrive at features (1) and (3) thereby violating Article 123(2) EPC.

1.2.2. The Opponent furthermore purports that feature (3) has no basis in the application as filed but only the more narrow feature "intravenous infusion by injection" (see page 20, lines 4-8 of the application as filed).

1.2.3. The Opponent considers that the general specification of the applications does not describe any specific dosage regimen. The Opponent concludes that the only basis for features (4) to (8) can be found in the Examples of the application as filed. However, the Opponent contends that features (4) to (8) are an undue

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generalisation of the specific contents of the Examples and that in particular the following essential features of the Examples would have been omitted in claims 1 and 5:

(i) the PNH patients are transfusion-dependent and hemolytic

(ii) the meaning of transfusion dependency in the context of the application

(iii) the infusion time of approx. 30 min, and

(iv) the occurrence of the breakthrough between weeks 12 and 64.

1.2.4. With regard to feature (4) the Opponent further alleges that the term "600 mg each week for four weeks" only requires the administration of 600 mg once per week for four weeks, while the Examples would require that the 600 mg are administered at a time interval of exactly 7 days (i.e. weekly intervals) for four weeks.

1.2.5. Finally, the Opponent believes that it would not be clearly supported in the Examples whether the dosages according to features (5) and (6) were intravenously administered. The route of administration would not have been specified in the Examples.

1.3. <u>The new claims have a clear and unambiguous basis in the application as filed.</u>

1.3.1. Granted claim 1 reads:

> "Eculizumab for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein eculizumab is to be administered intravenously to the patient under the following dosing schedule:
> (i) 600 mg each week for four weeks;
> (ii) 900 mg 1 week later;
> (iii) 900 mg on a biweekly basis; and thereafter
> (iv) 900 mg every 12 days,
> wherein said patient exhibits breakthrough in serum hemolytic activity when treated under a dosing schedule according to items (i) to (iii)."

As will be detailed herein below, granted claim 1 and consequently also granted claim 5 has a clear and unambiguous basis in the application as filed, because

(i) all features of these claims can be directly and unambiguously derived from the Examples of the application as filed, and

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(ii) no technically essential feature of the examples has been omitted or changed.

In the following we will provide a clear and unambiguous basis for each of features (1) to (8) as classified by the Opponent.

1.3.2. *Feature (1) - use of eculizumab*

Eculizumab is the antibody which is used in the examples of the application as filed; see page 32, line 14 reading

> "The specific antibody used in the study was eculizumab."

Thus - in contrast to the allegations of the opponent - no selection from a list is required in order arrive at the anti-C5 antibody which is eculizumab. Hence, feature (1) is directly and unambiguously supported by the Examples of the application as filed.

1.3.3. *Feature (2) - treatment of a patient afflicted with PNH*

The Examples of the application as filed at page 32 start to read:

> "Eleven patients participated in therapy trials to evaluate the effects of anti-C5 antibody on PNH and symptoms associated therewith. PNH patients were transfusion-dependent and hemolytic. Patients were defined as transfusion dependent with a history of four or more transfusions within twelve months." (emphasis added)

Hence - contrary to the assertions of the opponent - no selection from a list is required in order to define the patient to be treated as patient being afflicted with PNH.

The Opponent further considers that the PNH patient has to be further defined as (i) being hemolytic and (ii) having a history of four or more transfusions within twelve months whereas these features are not reflected by the claim.

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(i) hemolytic anemia

At page 2, lines 9 to 15 of the application as filed it is described that PNH is characterized by hemolytic anemia. Hemolytic anemia is one of the characterizing symptoms of the disease PNH.

The Patentee has informed us that every individual to a very slight extent has some PNH cells, but they are present at an extremely low level and of course these individuals are not considered to be PNH patients. In a very small number of individuals these PNH clones of cells begin to expand and when they expand enough, hemolysis becomes apparent. These individuals will be diagnosed as being a PNH patient. Consequently, every individual given a clinical diagnosis of PNH will show hemolysis.

In summary, a PNH patient is inherently hemolytic. The omission of an inherent feature cannot violate Article 123(2) EPC. Compliance of Article 123(2) EPC has to be assessed from the perspective of a skilled person.

(ii) history of blood transfusions

As is evident from the above-citation from page 32 of the application as filed, the PNH patients used in the examples of the application had a history of four or more blood transfusions within twelve months. In order to judge whether this information on the PNH patients has to be considered a technical feature which cannot be omitted in claims 1 and 5 without violating Article 123(2) EPC we refer to the pertinent case law. In T 331/87 the Board developed the following general three criteria for the replacement or removal of a feature from a claim:

> "The replacement or removal of a feature from a claim may not violate Article 123(2) EPC provided the skilled person would directly and unambiguously recognise that
> (1) the feature was not explained as essential in the disclosure,
> (2) it is not, as such, indispensable for the function of the invention in the light of the technical problem it serves to solve, and
> (3) the replacement or removal requires no real modification of other features to compensate for the change (cf. point 6 of the Reasons; following Decision T 260/85, "Coaxial connector/AMP" OJ EPO 1989, 105)." (see headnote of T 331/87)

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As regards requirement (1) of the above-described three-point test, we note that nothing in the application as filed conveys the impression that only PNH patients being transfusion-dependent can be treated by eculizumab.

In view of requirement (2) we note that administration of eculizumab prevents hemolytic events by blocking the complement cascade. Since all PNH patients suffer from hemolytic anemia, all PNH patients will benefit from the claimed use of eculizumab. It is of further note that the skilled person immediately understands from the Examples of the application as filed that all PNH patients showing a complement breakthrough should be treated by 900 mg of eculizumab every 12 days. A requirement of a certain transfusion history for the treatment to be successful is not apparent.

With regard to requirement (3) Patentee asserts that all PNH patients and not only transfusion dependent PNH patients may exhibits breakthrough in serum hemolytic activity when treated under a dosing schedule according to items (i) to (iii). In more detail, the Patentee has indicated that, to the best of its knowledge, the ability to show breakthrough appears to be independent of the severity of the disease. Instead, breakthrough is related to how rapidly eculizumab is cleared from the circulation. Some patients seem to clear eculizumab at a higher rate than other patients. The severity of the disease - which may be expressed at least in part by the blood transfusion history of a PNH patient - has therefore no technical effect on the other features of granted claims 1 and 5.

It is thus our firm believe that the PNH patient in claims 1 and 5 neither has to be further defined as (i) being hemolytic nor as (ii) having a history of four or more transfusions within twelve months in order to render these claims compliant with Article 123(2) EPC.

1.3.4. *Feature (3) - administered intravenously*

In the Examples on page 32, lines 12-16 it is stated:

> "Over the course of four weeks, each of 11 patients received a weekly 600 mg intravenous infusion of anti-C5 antibody for approximately thirty

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> minutes. The specific anti-C5 antibody used in the study was eculizumab. Patients received 900 mg of eculizumab 1 week later then 900 mg on a biweekly basis." (emphasis added)

Hence, in the Examples eculizumab is administered intravenously. Again - contrary to the statements of the opponent - no selection from any list in the specification is required in order to define that eculizumab is administered intravenously.

The allegation of the Opponent that only the first dosage of weekly 600mg for four weeks has been administered intravenously makes no technical sense. As the Opposition Division knows, an application has to be read with a mind willing to understand; see, e.g., decision T 190/99. Also the prior art cited by the opponent itself shows that eculizumab is routinely administered intravenously. For example, it is stated in D4 that

> "Patients received 600mg eculizumab by intravenous infusion over 30 minutes weekly for 4 doses and then 900 mg every other week". (emphasis added)

Essentially corresponding statements can be found in D3 and D6.

Granted claims 1 and 5 refer to intravenous administration and not intravenous infusion. The skilled person knows, though, that an intravenous administration is always by a "push" - which is a one-time, rapid injection of the medication into the bloodstream – or by an "infusion" - which is a slow drip of medication into the vein over a period of time. The technical effect is in both cases that eculizumab is delivered in the blood stream. The only difference is the time frame in which the complete dose of eculizumab is administered. However, the time is not characterized as being essential in the application as filed. The indication of the time is also certainly not indispensable in order to work the invention, and varying the infusion time does not require a modification of the other features of the claim. Hence, in connection with the omittance of the intravenous time the criteria of the "three-point test" developed in T 331/87 are clearly met. Omittance of the infusion time of approx. 30 minutes does not constitute a violation of Article 123(2) EPC.

1.3.5. *Feature (7) - breakthrough in serum hemolytic activity*

The study described in the Examples of the application as filed has been initially carried out for 12 weeks and then has been extended to 64 weeks (see, for example, Table 1 or Figure 3 of the application as filed). The breakthrough in 2 out of 11 PNH patients has been observed between weeks 12 and 64 of the study (see Figure 4 of the application as filed).

It is not essential with respect to the claimed dosage regimen when a PNH patient has a complement breakthrough. The essential step is to increase the dosage from 900mg/14d to 900mg/12d once a complement breakthrough is observed. As it is described in the Examples at page 38, lines 15-17, the complement blockade was permanently restored by shortening the interval of administration - although both PNH patients likely did not show the complement breakthrough at the same time point during the 64-weeks study.

Hence, it is not technically necessary to define in granted clams 1 and 5 at which particular point in time a breakthrough is observed in a PNH patient to be treated.

1.3.6. *Features (4) to (6) and (8)*

The fact that also the dosages according to features (5) and (6) were administered intravenously has been discussed herein above in connection with feature (3).

The Opponent's interpretation of the wording of feature (4) is a mere play on words and should not attract any attention.

Beyond these points the Opponent apparently does not contest that features (4) to (6) and (8) as such can be clearly and unambiguously derived from the Examples of the application as filed. Having said that, the Opponent alleges that these features would only find support in connection with further features of the Examples. These further allegedly omitted features have been discussed herein above in connection with features (1) to (3) and (7).

As is evident from the above discussion in connection with features (1) to (3) and (7) these features do not violate Article 123(2) EPC.

1.3.7. The Opponent does not consider that the features in the dependent claims give raise to any further violation of Article 123(2) EPC. Hence, all of the granted claims comply with Article 123(2) EPC.

2. PRIORITY (Article 87 EPC)

2.1. For essentially the same reasons put forward by the Opponent in section 4 entitled "added subject-matter", the Opponent believes that the subject-matter of the claims cannot be directly and unambiguously derived from the priority application.

The Opponent concludes that the effective date of the granted claims is not the priority date of February 3, 2004 but the international filing date of February 3, 2005.

2.2. As will be shown in the following the relevant contents in the Examples of the application as filed - which form a clear and unambiguous basis for the granted claims - are also comprised in the priority document US 10/771,552; compare page 30, lines 17-18 of the priority document and page 32, lines 16-20 of the application as filed.

In more detail, page 30 of US 10/771,552 reads:

> 5 **EXAMPLES**
>
> Eleven patients participated in therapy trials to evaluate the effects of anti-C5 antibody on PNH and symptoms associated therewith. PNH patients were transfusion-dependent and hemolytic. Patients were defined as transfusion dependent with a history of four or more transfusion within twelve months. The

and

> Over the course of four weeks, each of 11 patients received a weekly 600 mg intravenous infusion of anti-C5 antibody for approximately thirty minutes. The specific anti-C5 antibody used in the study was eculizumab. Patients received 900 mg of eculizumab 1 week later then 900 mg on a bi-weekly basis. The first twelve weeks of the study constituted the pilot study. All patients participated in an extension study conducted to a total of 48 weeks.

These two passages give rise to priority for features (1) to (6).

Page 30 of US 10/771,552 reads

> 0.001). As seen in Figure 4, break-through of complement blockade resulted in hemoglobinuria, dysphagia, and increased LDH and AST. At the next dose, symptoms resolved (Fig 5) and reduction from 900mg every 14 days to 900mg every 12 days resulted in a regain of complement control which was maintained for over 9 months in both patients. This patient shows a 24 hour resolution of

and page 34 of US 10/771,552 reads

> eculizumab treatment. Two patients exhibited a breakthrough in complement activity, but complement blockade was permanently restored by reducing the dosing interval to 12 days (See, Figure 4).

These two passages give rise to priority for features (7) and (8).

Otherwise arguments in favour of clear and unambiguous support in the application as filed as detailed in section 1, *supra* apply *mutatis mutandis* for entitlement of priority.

Hence, the subject-matter of granted claims 1 and 5 has also a clear and unambiguous basis in the priority application. The priority claim is valid.

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3. NOVELTY (Articles 100(a) and 54 EPC)

3.1. The Opponent considers that the claims lack novelty in view of D1.

3.2. D1 has been published on February 5, 2004 and hence 2 days after the priority date of the patent. D1 is not prior art because the claims are entitled to the priority date; see section 2, *supra*.

4. INVENTIVE STEP (Article 100(a) and 56 EPC)

4.1. The Opponent alleges that the granted claims lack inventive step in view of D5 considered alone or in combination with any one of D2, D3, D4 or D6. The Opponent also contends that the granted claims are no inventive in view of any one of D2, D3, D4 or D6.

4.2. D5 may be considered as closest prior art in the assessment of inventive step of the granted claims. D5 describes:

> "We previously reported that eculizumab was very effective at acutely controlling intravascular hemolysis in a 3-month Pilot study of transfusion-dependent PNH patients. We now report that all 11 patients from the initial study entered an extension trial of 900mg eculizumab by i.v. infusion over 30 minutes every other week for one year. [...] Two patients experienced transient breakthroughs in complement activity associated with LDH, hemoglobinuria and mild symptoms; these resolves immediately upon next dose of eculizumab and further breakthroughs were prevented by a slight decrease in dosing interval." (emphasis added)

Details on the 3-months pilot study are, for example, described in D3, D4 and D6 (see page 53, left column). Hence, D5 (in combination with any one of D3, D4 and D6) could be seen as describing that 2 out of 11 PNH patients exhibited a complement breakthrough when treated under a dosage regimen similar, but not identical to that recited in the granted claims. D5 furthermore teaches that the complement breakthrough can be permanently prevented by a slight decrease in dosing interval.

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4.3. Objective technical problem

Independent granted claims 1 and 5 are distinguished from D5 in that

(i) the dosing interval is the administration of 900 mg eculizumab every 12 days; and

(ii) feature (5) requiring "administration of 900 mg 1 week later" is absent from D5.

Accordingly, the objective technical problem underlying the granted claims in view of D5 may be seen as the determination of the specific dosing interval which prevents further breakthroughs in patients having the prior treatment history as defined in the claims.

The solution is the administration of 900 mg eculizumab every 12 days to patients having the prior treatment history as defined in the claims.

4.4. Non-obviousness

D5 neither teaches nor suggests the time interval of administration which is designated as a "slight decrease in dosing interval". Patentee submits that the skilled person would not have arrived at the exact dose of 900 mg eculizumab every 12 days without the need of inventive skills.

This is particularly evident when considering the prior art at the time of the invention in a comprehensive manner. Pursuant to the pertinent case law, e.g. T 24/81, second headnote, in the examination of inventive step all previously published embodiments must be taken into consideration which offered a suggestion to the skilled practitioner for solving the problem addressed, even where those embodiments were not particularly emphasized.

We enclose an article of Maria Kaplan in Current Opinion on Investigational Drugs 2002, 3(7):1472-4472. This article has been cited as document D10 during examination proceedings of the opposed patent and is introduced into the present opposition proceedings as document D13.

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D13 describes at page 4, left column, fourth paragraph a Phase II trail on the treatment of RA patients with eculizumab:

> "Patients were treated with placebo, eculizumab (8 mg/kg iv) once per week for 4 weeks and then once every month (induction/monthly group); eculizumab (8mg/kg iv) one per week for 4 weeks followed by once every 2 weeks (induction/biweekly group); or eculizumab (8 mg/kg iv) once every 2 weeks (biweekly group). The results after 3 months of treatment showed that the induction/monthly group met the primary endpoint of the trial (improvement in American College of Rheumatology response criteria score (ACR) 20 after 3 months of treatment), while the induction/biweekly and biweekly groups did not statistically meet the endpoint."

Importantly, only patients receiving treatment every month, but not the patients receiving treatment every two weeks meet the endpoint of the trial – being an improvement of RA. In other words, an increase of the dose of eculizumab by increasing the dosing intervals did not have a beneficial effect. Hence, D13 shows that shortening of dosing intervals may not result in an effective treatment by eculizumab.

The inventors of the opposed patent have unexpectedly found that the 12-days period is sufficient to successfully treat PNH patients which suffer from breakthrough in serum hemolytic activity when treated under a dosing schedule according to the above-defined features (4) to (6), and at the same time is not too short such that an effective treatment by eculizumab is prevented, as observed in D13. This surprising key finding of the present invention is described at page 35, lines 5-23 of the application as filed:

> "Serum hemolytic activity in nine of the eleven patients was completely blocked throughout the 64 week treatment period with trough levels of eculizumab at equilibrium ranging from approximately 35 µg/ml to 350 µg/ml. During the extension study, 2 patients did not sustain levels of eculizumab necessary to consistently block complement. This breakthrough in serum hemolytic activity occurred in the last 2 days of the 14 day dosing interval, a pattern that was repeated between multiple doses. In one of the patients, as seen in FIG. 4, break-through of complement blockade resulted in hemoglobinuria, dysphagia, and increased LDH and AST, which correlated with the return of serum hemolytic activity. At the next dose, symptoms resolved (FIG. 5) and reduction in the dosing interval from 900 mg every 14 days to 900 mg every 12 days resulted in a regain of complement control which was maintained over the extension study to 64 weeks in both patients. This patient showed a 24 hour resolution of dysphagia and hemoglobinuria. A reduction in the dosing interval from 14 to 12 days was sufficient to maintain levels of eculizumab above 35 µg/ml and

> effectively and consistently blocked serum hemolytic activity for the remainder of the extension study for both patients." (emphasis added)

Hence, the critical point in order to consistently block serum hemolytic activity is maintaining levels of eculizumab above 35 µg/ml. Thus is achieved in accordance with the invention by the reduction of the dosing interval from 900 mg every 14 days to 900 mg every 12 days. Arriving at the 12-days period is consequently not a matter of routine but required due consideration and mindful experimentation. Applicant therefore submits that the granted claims are inventive over D5. The deficiencies of D5 cannot be cured by any one of D2, D3, D4 or D6. No prior art document teaches or suggests a 12-days dosing interval, let alone the superior efficacy in preventing complement breakthrough hemolysis in PNH patients associated with this dosing interval.

5. SUFFICIENCY OF DISCLOSURE (Articles 100(b) and 83 EPC)

5.1. Eculizumab

5.1.1. The Opponent purports that the claims lack sufficiency of disclosure, because the complete sequence of eculizumab (or h5G1.1) would neither be disclosed by the application as filed nor any one of the prior art documents cited by the Opponent.

5.1.2. The Patentee asserts that the sequence for eculizumab was publicly available prior to the priority and filing date. A sequence for eculizumab was submitted to Chemical Abstracts Services (CAS) and entered into their STN database on 14 February 1999; please see the attached copy of the CAS entry No. 219685-560-4.

5.2. The term "breakthrough in serum hemolytic activity"

5.2.1. The Opponent considers that the term "breakthrough in serum hemolytic activity" is not sufficiently disclosed by the application as filed, because it is allegedly not

> "[...] clear whether one, two, three, four of these events [breakthrough of complement blockade] are necessary and/or sufficient to characterize a

breakthrough according to the claims." (see the Opponent's Appeal Brief at section 7.2, end of second paragraph)

The Opponent concludes that the skilled person would not be able to characterize and identify a "breakthrough in serum hemolytic activity".

5.2.2. The argument put forward by the Opponent reads on a lack of clarity rather than on a lack of sufficiency of disclosure. An alleged lack of clarity is not a valid ground for opposition.

Notwithstanding we wish to submit that Figure 4 of the application as filed shows that a complement breakthrough can be identified by blood in the morning urine. Breakthrough in serum hemolytic activity which is the result of the complement activity can also be diagnosed using a blood sample (see page 35, lines 5-14 of the application as filed). As such, and for the mere sake of arguments we submit that the term "breakthrough" is clear for the skilled person and means for its determination are at the skilled person's disposal.

6. CONCLUSION

In view of the above we submit that the claims as granted fulfill the requirements of the EPC. Our request that the patent be maintained on the basis of the granted claims is therefore fully justified.

Dr. Joachim Wachenfeld
European Patent Attorney

Enclosure:
CAS entry
D13

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RN 219685-50-4 REGISTRY REGISTRY COPYRIGHT 2009 ACS on STN
RN 219685-50-4 REGISTRY
ED Entered STN: 14 Feb 1999
CN Immunoglobulin, anti-(human complement C5 .alpha.-chain) (human-mouse monoclonal 5G1.1 heavy chain), disulfide with human-mouse monoclonal 5G1.1 light chain, dimer (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Eculizumab
CN h5G1.1
CN h5G1.1VHC+h5G1.1VLC
CN Soliris
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR US Adopted Names Council (USAN)
LC STN Files: ADISINSIGHT, BIOSIS, CA, CAPLUS, CBNB, CHEMCATS, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MRCK*, PHAR, PROUSDDR, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
59 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
59 REFERENCES IN FILE CAPLUS (1907 TO DATE)

Publication Number	Title	Priority Date	Publication Date	Claims reciting "eculizumab"
EP2380907B1	METHODS AND COMPOSITIONS FOR THE TREATMENT OF ANTIBODY MEDIATED NEUROPATHIES	2006-09-05 2007-09-05	2016-11-30	6. The antibody or antigen-binding fragment thereof for use according to claim 5, wherein said antibody is eculizumab.
EP1988882B1	PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY	2006-03-02 2007-03-02	2014-12-17	17. The anti-C5 antibody for use according to claim 13, wherein said whole antibody is eculizumab. 37. The use according to claim 34, wherein said antibody fragment is pexelizumab or said whole antibody is eculizumab.
EP1755674B1	PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY	2004-05-14 2005-05-16	2014-11-19 (WO 2005/110481 published 11/24/2005)	15. The antibody to C5 for use in prolonging survival of an allograft in a recipient mammal, the use, or the antibody to C5 and the at least one immunosuppressive drug for use in prolonging survival of an allograft in a recipient mammal according to claim 10, wherein said whole antibody is eculizumab.
EP2061810B1	METHODS AND COMPOSITIONS FOR THE TREATMENT OF ANTIBODY MEDIATED NEUROPATHIES	2006-09-05 2007-09-05	2014-11-12	5. The antibody for use according to claim 1 or 2, wherein said antibody is eculizumab.
EP1720571B9	METHOD OF TREATING HEMOLYTIC DISEASE	2004-02-03 2005-02-03	2012-10-24 (A2 published 11-15-2006; WO 2005/074607A2 published 8-18-2005)	1. Eculizumab for use in treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH), wherein eculizumab is to be administered intravenously to the patient under the following dosing schedule: (i) 600 mg each week for four weeks; (ii) 900 mg 1 week later; (iii) 900 mg on a biweekly basis; and thereafter (iv) 900 mg every 12 days, wherein said patient exhibits breakthrough in serum hemolytic activity when treated under a dosing schedule according to items (i) to (iii). (All eight claims recite "eculizumab")
EP3056218A1	PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY	2004-05-14 2005-05-16 2005-05-16	2016-08-17	10. The antibody to C5 according to claim 9 wherein said whole antibody is eculizumab.
EP2910253A1	METHOD OF TREATING HEMOLYTIC DISEASE	2004-02-03 2005-02-03 2005-02-03	2015-08-26	2. The anti-C5 antibody for use according to claim 1, wherein the anti-C5 antibody is eculizumab. 9. The use according to claim 8, wherein the anti-C5 antibody is eculizumab.
EP2815767A1	PROLONGATION OF SURVIVAL OF AN ALLOGRAFT BY INHIBITING COMPLEMENT ACTIVITY	2004-05-14 2005-05-16	2014-12-24	6. The composition according to claim 3, wherein the whole antibody is eculizumab.
EP2089058A2	METHODS OF TREATING HEMOLYTIC ANEMIA	2006-11-08 2007-11-08	2009-08-19	18. The method of claim 15, wherein said antibody is eculizumab. 34. The method of claim 32, wherein said antibody is eculizumab. 40. The method of claim 37, wherein said antibody is eculizumab. 59. The method of claim 56, wherein said antibody is eculizumab. 75. The method of claim 73, wherein said antibody is eculizumab. 100. The method of claim 97, wherein said antibody is eculizumab. 116. The method of claim 114, wherein said antibody is eculizumab. 122. The method of claim 119, wherein said antibody is eculizumab. 141. The method of claim 138, wherein said antibody is eculizumab. 157. The method of claim 155, wherein said antibody is eculizumab. 163. The method of claim 160, wherein said antibody is eculizumab.
EP2013235A1	METHODS FOR THE TREATMENT OF MUSCULAR DYSTROPHY ASSOCIATED WITH DYSFERLIN-DEFICIENCY	2006-05-01	2009-01-14	6. The method of claim 1, wherein said antibody is eculizumab.
EP1881993A2	NEBULIZATION OF MONOCLONAL ANTIBODIES FOR TREATING PULMONARY DI5EASES	2005-05-11 2006-05-10	2008-01-30	7. The method of claim 1 , wherein the antibody is eculizumab or pexelizumab.

Europäisches Patentamt
European Patent Office
Office européen des brevets

Letter accompanying subsequently filed items

Representative:

Mr H. Ulrich Dörries
df-mp
Fünf Höfe
Theatinerstraße 16
80333 Munich
Germany

Phone: +49 89 2102960
Fax: +49 89 21029633
E-mail: info@df-mp.com

80298 Munich
Germany
Tel. +49(0)89 2399-0 | Fax -4465

P.O. Box 5818
2280 HV Rijswijk
Netherlands
Tel. +31(0)70 340-2040 | Fax -3016

10958 Berlin
Germany
Tel. +49(0)30 25901-0 | Fax -840

The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	16195355.9
Applicant's or representative's reference	AMG17203-AV-888

	Description of document	Original file name	Assigned file name
1	Citation for the limitation procedure	AMG17203ADV-EP888_D8.pdf	LIMDOC-1.pdf
2	Citations filed by a third party	AMG17203ADV-EP888_D9.pdf	TDOC-1.pdf
3	Observations by third parties (Art. 115 EPC)	AMG17203ADV-EP888_TPO.pdf	TIPA1-1.pdf

	Payment	
1	Method of payment	Not specified

Signatures

Place:	**Munich, Germany**
Date:	**12 December 2017**
Signed by:	**Hans Doerries 13689**
Representative name:	**H. Ulrich Dörries**
Capacity:	**(Representative)**

dfmp
Dörries Frank-Molnia & Pohlman
Patentanwälte Rechtsanwälte PartG mbB

Patents – Trademarks – Designs

Theatinerstraße 16
80333 Munich
Germany

Phone +49 89 210296-0
Fax +49 89 210296-33

info@df-mp.com
www.df-mp.com

European Patent Office
Bob-van-Benthem-Platz 1
80469 München

December 12, 2017

Third Party Observations

Application Number	16 195 355.9 - 1466
Publication Number	EP 3 167 888
Title	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
Applicant	Alexion Pharmaceuticals, Inc.
Our file reference	AMG17203ADV-EP888

Third Party Observations

Amgen Inc. would like to bring the following to the Examining Division's attention:

I. According to Alexion's own submissions, eculizumab and its structure were known in the prior art.

Alexion has submitted in the brief dated July 10, 2017 with regard to the present patent application that D1 to D5 are not novelty-destroying, because only the name, not the structure of eculizumab was known in the prior art before the priority date.

This is in stark contrast to actions and statements made by Alexion in the past:

I.1 Previous patents and patent applications filed by Alexion

Alexion has filed and obtained a significant number of other European patents with one or more claims directed to the use of "eculizumab," e.g., EP2380907B1, EP1988882B1, EP1755674B1, EP2061810B1, EP1720571B9, and also filed various patent applications, all predating the

H. Ulrich Dörries [1234]
Dr. sc. nat., Dipl.-Biol.
David Molnia [12347]
M.S. Elec. Eng., B.S. Physics
Sandra Pohlman [568]
B.S. Biology
Michael Eder [1234]
Dr. sc. nat., Dipl.-Chem.
Oliver Schulz [1234]
Dipl.-Phys.
Rainer Friedrich [1234]
Dr. rer. nat., Dipl.-Biochem.
Elisabeth Greiner [1234]
Dr. rer. nat., Mag. pharm.
Philipp Nordmeyer [1234]
LL.M., Dipl.-Phys.
Dominik Ho [1234]
Dr. rer. nat., MEng (Cornell)
Holger Schimmel [1234]
Dr. rer. nat., Dipl.-Ing.
Annette Hilgendorf [1234]
Dr. rer. nat., Dipl.-Biochem.
Solveig Moré [1234]
Dr. rer. nat., Dipl.-Biochem.
Florian Brandt [1234]
Dr. rer. nat., Dipl.-Biochem.
Andreas Brzank [1234]
Dr. rer. nat., Dipl.-Phys.
René Okoampah [1234]
Dipl.-Ing.
Julia Mössinger [1234]
Dr. rer. nat., Dipl.-Biol.
Judith Hesse [8]
LL.M.
Helena Bertelsmeier [8]
LL.M.
Barbara Englert [1234]
Dr. rer. nat., Dipl.-Phys.

1 European Patent Attorney
2 European Trademark Attorney
3 European Design Attorney
4 Patentanwalt
5 Solicitor (England & Wales)
6 U.S. Patent Attorney
7 U.S. Patent Agent
8 Rechtsanwalt

Partnerschaftsregister des AG München
PR-Nr. 1278

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: March 28, 2018
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/642,096

Confirmation No.: 7606

Filed: July 5, 2017

Art Unit: 1644

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

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the U.S. Patent and Trademark Office is hereby directed to the documents listed on the attached PTO/SB/08. In accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant submits herewith copies of the non-patent literature references.

It is respectfully requested that the documents listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the documents be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited documents are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any documents herein be construed *per se* as a representation that such document is prior art. Moreover,

Applicant understands the Examiner will make an independent evaluation of the cited documents.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits (37 C.F.R. § 1.97(b)(3)). Applicant believes no fee is due with this statement.

Dated: March 28, 2018

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15642096
Filing Date	2017-07-05
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN5

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	1	Termination of opposition proceedings of European Patent No. 1720571, dated April 13, 2018, 16 pages.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15642096
	Filing Date	2017-07-05
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2018-04-27
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	32462656
Application Number:	15642096
International Application Number:	
Confirmation Number:	7606
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT
First Named Inventor/Applicant Name:	Leonard BELL
Customer Number:	133485
Filer:	Jill R. Gorny Sloper/Anita Costa
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN5
Receipt Date:	27-APR-2018
Filing Date:	05-JUL-2017
Time Stamp:	14:11:14
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	2018-04-27_IDSTRANS_AXJ-114BUSCN5_4846-9623-6131_v1.pdf	24905 4270b1b1f7dd236a9ef2c845c98da66a59e43b7c	no	2
Warnings:					

Information:					
2	Non Patent Literature	EPOPPDEC.pdf	480652 30762af63e0afcaef76c4b518b3d6f1c167f02c0	no	16
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	IDS_02.pdf	79163 7c66185c62a5b408102e62942a44439b81e0582d	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
			Total Files Size (in bytes):	584720	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: April 27, 2018
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN5
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Leonard Bell *et al.*

Application No.: 15/642,096

Confirmation No.: 7606

Filed: July 5, 2017

Art Unit: 1644

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

Examiner: J. L. Rogers

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (SIDS)

Dear Sir:

In compliance with 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the U.S. Patent and Trademark Office is hereby directed to the document listed on the attached PTO/SB/08. In accordance with 37 C.F.R. § 1.98(a)(2)(i)-(iv), Applicant submits herewith a copy of the non-patent literature reference.

It is respectfully requested that the document listed on the PTO/SB/08 be expressly considered by the Examiner during the prosecution of this application, and that the document be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The filing of this Information Disclosure Statement is not to be interpreted as a representation that the cited document is material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of the document herein be construed

per se as a representation that such document is prior art. Moreover, Applicant understands the Examiner will make an independent evaluation of the cited document.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits (37 C.F.R. § 1.97(b)(3)). Applicant believes no fee is due with this statement.

Dated: April 27, 2018

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Datum/Date
18.04.18

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
C412290EP APPR	05712607.0 / 1720571
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
ALEXION PHARMACEUTICALS, INC.	

Appeal number: T1897/14-3.3.04

Closure of the appeal proceedings
Withdrawal of the appeal/application/opposition by the sole appellant

The

☑ appeal(s) ☐ opposition(s)

☐ application

of the appellant has been withdrawn by letter dated 29.03.18 and received on 29.03.18 .

The Board has instructed the Registrar to notify all concerned that the appeal proceedings are accordingly closed without a substantive decision.

The appeal fee will be reimbursed pursuant to Rule 103(2)(a) EPC.

By order of the Board of Appeal
The Registrar Danielle Hampe
Tel.: 089 / 2399 - 3341

Annex(es):/

Registered letter

EPO Form 3324

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Boards of Appeal

The Registry

Name: P. Cremona
Tel.: 089 / 2399 - 3341

Date: 06.04.18

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
APPR	05712607.0 / 1720571
Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire	
ALEXION PHARMACEUTICALS, INC.	

Appeal number: T1897/14-3.3.04

EPA/EPO/OEB Formblatt/Form/Formulaire: 3017

Empfangsbescheinigung über den Zugang des vorstehend bezeichneten Schriftstücks
Acknowledgement of receipt of the document specified above
Récépissé du document spécifié ci-dessus

Unter Bezugnahme auf die Mitteilung im ABl. EPA 7/2010, 377 wird gebeten, die Empfangsbescheinigung mit Empfangsdatum und Unterschrift zu versehen und **umgehend** an das EPA zurückzusenden:

With reference to the Notice in OJ EPO 7/2010, 377, you are requested to date and sign the acknowledgement of receipt and return it to the EPO **immediately:**

Conformément au communiqué paru au JO OEB 7/2010, 377, vous êtes prié d'indiquer sur le récépissé la date de réception du document, de signer le récépissé et de le renvoyer **sans délai** à l' OEB:

- **über die Online-Dienste des EPA** (als Anlage zu EPA Form 1038) / **through EPO Online Services** (as annex to EPO Form 1038) / **par les services en ligne de l'OEB** (en tant que pièce jointe au formulaire OEB 1038),
- **per Fax / by fax / par téléfax (+49 (0) 89 2399-4465 or +31 (0)70 340-3016)**
- oder per Post / or by post / ou par courrier

Empfangen am / Received on / Reçu le:

13. 4. 18

Unterschrift / Signature:

Empfangsberechtigter/authorised recipient/
le destinataire ou la personne dûment mandatée

Rücksende-Adresse / Return address / Adresse de retour
(Umschlag / envelope / enveloppe ISO C4 / DL / C6/C5 / C6)

Beschwerdekammern des
Europäischen Patentamts
Richard-Reitzner-Allee 8
85540 HAAR
DEUTSCHLAND

Rücksende-Adresse / Return address / Adresse de retour

Received at the EPO on Apr 13, 2018 10:48:30. Page 1 of 1
Duration: 04.13.2018 10:47:05 AM - 04.13.2018 10:48:30 AM. This page 1 of 1 was completed at 04.13.2018 10:48:30 AM

Samsung Bioepis Exhibit No. 1002
Page 1152

Europäisches Patentamt
European Patent Office
Office européen des brevets

Termination of opposition proceedings of patent no. 05712607.0 - 1116/ 1720571 with revocation of the patent 13.04.18

I. Findings

1. The opposition proceedings are terminated for the following reason:
   The patent was revoked

   REVO 01.07.14

   The time limit pursuant to Article 108 EPC has expired.
   No appeal or application pursuant to Article 112 EPC has been filed.

   REVO 2 and DEAD coded and Form 2362 despatched.

2. Fees situation:

OPPO04	010	00625522	12.03.13	EUR	745,00
NOAP04	011	00116739	08.09.14	EUR	1 860,00
CLMS(2)	015	00571629	01.09.06	EUR	765,00

   Checked for correct fee payment. Refund(s) made on ...../... .

3. Any models still to hand were returned on ....n/a..... .

4. Enter "DEAD" and dispose of paper file

13.04.2018 ..... Date

Bertoni, Sara ..... Formalities officer

SB51929

EPO Form 2358.2 02.15

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Date
06.04.18

Zeichen/Reference/Référence	Anmeldung Nr./Application No./Demande n°//Patent Nr./Patent No./Brevet n°
APPR	05712607.0 / 1720571

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
ALEXION PHARMACEUTICALS, INC.

Appeal number: T1897/14-3.3.04

Cancellation

1. ☑ The oral proceedings appointed for 03.05.18 have been cancelled.

2. ☐ The oral proceedings appointed for

have been rescheduled to: at .

will now be in Room No.

The other provisions in the summons of 27.07.17 remain unchanged.

The Registrar P. Cremona
Tel.: 089 / 2399 - 3341

Annex(es): ☑ Acknowledgement of receipt - EPO Form 3936

Registered letter with advice of delivery

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

J A Kemp
14 South Square
Gray's Inn
London WC1R 5JJ
ROYAUME UNI

Datum / Date
05.04.2018

Zeichen/Reference/Référence	Anmeldung Nr. / Application No. / Demande n°. // Patent Nr. / Patent No. / Brevet n°.
APPR	05712607.0 // 1720571
Anmelder / Applicant / Demandeur // Patentinhaber / Proprietor / Titulaire	
ALEXION PHARMACEUTICALS, INC.	

Appeal number: **T1897/14-3.3.04**

Communication of the Board of Appeal

The Rapporteur R. Morawetz
The Registrar P. Cremona
Tel.: 089 / 2399 - 3341

Beschwerdekammern des Europäischen Patentamts
Boards of Appeal of the European Patent Office
Chambres de recours de l'Office européen des brevets

Registered letter

This document: 7 page(s) including this page

Annex(es):

Communication text

FAX: 089 413 04 111 (29 March 2018)

1. This communication is sent pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA). Any opinions expressed are provisional and not binding on the board in arriving at its decision (Article 17(2) RPBA).

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2. The purpose of this communication is to set out some of the issues to be considered during the oral proceedings.

3. An opposition was filed against the patent. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and 100 (c) EPC. The opponent withdrew its opposition with letter dated 7 October 2013 and thus ceased to be a party to the proceedings.

4. The opposition division continued the opposition proceedings of its own volition. It decided that neither the main request nor the auxiliary request before it met the requirements of Article 56 EPC and revoked the patent.

5. The appeal of the patent proprietor (hereinafter "appellant") lies against this decision.

6. The board adopts the numbering of the documents as set out in point 1 of the decision under appeal (documents D1 to D15). Documents D16 to D19 were submitted by the appellant with its statement of grounds of appeal.

7. The appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, alternatively, on the basis of the auxiliary request, both as submitted with the statement of grounds of appeal. These claim requests correspond to the claim requests underlying the decision under appeal.

8. At present the board has the following comments on the claim requests on file.

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Main request

Article 56 EPC - claim 1

9. The subject-matter of claim 1 relates to a four-stage dosing schedule for treating a patient afflicted with paroxysmal nocturnal hemoglobinuria (PNH) with the anti-C5 antibody eculizumab.

10. The opposition division held that the subject-matter of claim 1 of the main request lacked an inventive step over the teaching of document D5 as closest prior art when combined with the disclosure of document D6 (see decision under appeal, points 2.10 to 2.27).

11. The appellant did not dispute that document D5 was the closest prior art. According to the appellant the differences between the teaching of document D5 and the claimed subject-matter was twofold: (i) document D5 was silent about the dosage schedule applied prior to the bi-weekly administration of 900 mg and (ii) document D5 was silent about the feature of administering 900 mg every 12 days (see statement of grounds of appeal, point 1.3).

According to the appellant the problem to be solved was the provision of a complete eculizumab dosage regimen which is capable of preventing complement breakthroughs in all PNH patients (ibid.).

12. The appellant submitted that the opposition division had applied an "ex post facto" analysis in selecting document D6 as secondary reference (see statement of grounds of appeal, point 1.4.2), that optimising the eculizumab dosing schedule was not a matter of routine (ibid., point 1.5.1), and that document D5 failed to render decreasing the dosing interval from 14 days to 12 days obvious (ibid., point 1.5.3).

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13. At present, the board is not convinced by the arguments submitted by the appellant.

14. Document D5 reports the results obtained in an extension trial, after the patients had completed a pilot trial. Thus, document D5 discloses that "*we previously reported that eculizumab was very effective at acutely controlling intravascular hemolysis in a 3-month Pilot study of transfusion-dependent PNH patients. We now report that all 11 patients from the initial study entered an extension trial of 900 mg eculizumab by i.v. infusion over 30 minutes every other week for one year. To date all patients remain on eculizumab, completing between 11 and 15 months of therapy*" (see abstract, page 509, lines 5 to 8).

15. In the board's view, the skilled person faced with the problem of having to provide a complete eculizumab dosage regimen and knowing from document D5 that the patients receiving 900 mg every other week during the extension study were on a pilot study before would be motivated to look for the dosage regimen used in the pilot study.

16. Documents D2, D3 and D6 all relate to initial studies carried out in PNH patients which patients are said to take part in an extension study. Thus, document D2 reports that "*patients received 600 mg of eculizumab each week for four weeks, after which the dose was switched to 900 mg every two weeks. Ten patients have completed the 12-week treatment, and all choose to enter a 12-month extension trial*" (see second and first paragraph from bottom). Document D3 reports that "*eleven transfusion-dependent PNH patients have completed a 3-month pilot study receiving 600 mg eculizumab by intravenous infusion over 30 min weekly for four doses and then 900 mg every other week (...) all patients have continued on eculizumab in an*

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extension study" (see page 87, abstract, lines 5 to 8 and lines 28 to 30). Document D6 discloses "*Eleven transfusion-dependent PNH patients have completed an open-label pilot study of eculizumab. Patients received 600 mg eculizumab by intravenous infusion over 30 min weekly for four doses, followed by 900 mg 1 week later, and then 900 mg every other week for the remainder of the trial. All 11 patients completed the study and are currently participating in an open-label extension study*" (see page 197, abstract, lines 8 to 15).

17. Documents D2 and D3 thus disclose the same dosage regimen (600 mg eculizumab weekly for four doses and then 900 mg every other week) while the dosage regimen disclosed in document D6 contains an extra step compared to the dosage regimen disclosed in documents D2 and D3 (600 mg eculizumab weekly for four doses, followed by 900 mg 1 week later, and then 900 mg every other week) and is thus more detailed.

18. In the board's opinion, the skilled person faced with the problem of having to provide a complete dosing regimen and faced with the very similar disclosures in documents D2, D3 and D6 which apparently relate to one and the same pilot study would choose the most comprehensive dosage regimen, i.e. the one disclosed in document D6. No ex post facto considerations are involved in this choice.

19. The appellant relied on documents D13, D15, D7, D16, D17, D14 to support its argument that the skilled person would have proceeded very cautiously when either increasing the dose or reducing the dose of eculizumab (see statement of grounds of appeal, point 1.5.1).

20. The board notes that documents D14, D15, D16, D17 were not available before the priority date of the patent and could thus not have influenced the skilled person's

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attitude.

21. Appellant's arguments based on documents D7 and D13 fail because document D6 discloses that the dosage regimen is well tolerated "*with no patients reporting a serious adverse event*" (see page 197, abstract, lines 15 to 18).

22. As regards the second difference (see point 11), the board notes that document D5 already discloses that "*two patients experienced transient breakthroughs in complement activity associated with increased LDH, hemoglobinuria and mild symptoms; these resolved immediately upon next dose of eculizumab and further breakthroughs were prevented by a slight decrease in the dosing interval*" (see abstract, page 510a, lines 8 to 12).

23. Document D5 thus discloses that a slight decrease of the dosing interval solves the problem of complement breakthrough. All that the skilled person thus needed to do was to maintain the dose (900 mg) and decrease the dosing interval from "every other week" to slightly less than that until complement breakthrough was prevented. Since the skilled person already knew from document D5 that this would give the desired result, the actual determination of the appropriate dosing interval, i.e. every 12 days, would appear to be a matter of routine devoid of inventive activity.

Auxiliary request

Article 56 EPC - claim 1

24. The opposition division held that the feature "*wherein cell lysis is reduced below 20% of normal serum complement activity when treated under a dosing schedule according to items (i) to (iv)*" was at best

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another read-out to confirm the same resolution of breakthrough already recorded in document D5.

25. The appellant submitted that the effective inhibition of haemolytic activity was a key advantage being associated with the subject-matter claimed in the main and auxiliary requests and that this advantage was expressly incorporated in the main claim of the auxiliary request (ibid., point II).

26. At present, the board fails to see how this line of reasoning addresses the reasons given in the decision under appeal, it appears rather to confirm the point made by the opposition division. In any case, since the subject-matter claimed in the main request is at present considered to be obvious, the board fails to see how the inclusion of an effect associated with a dosage regimen which is considered to be obvious can render the claimed subject-matter inventive.

Concluding remarks

27. Should the appellant choose to file further written submissions, then attention is drawn to Article 114(2) EPC and Articles 13(1) and 13(3) RPBA.

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Beschwerdekammern
Boards of Appeal
Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Appeal number: T1897/14-3.3.04

Order

Oral proceedings to be held on 03.05.18

☑ are cancelled.

☐ are rescheduled for at hours

Room N°

Munich, 03.04.18

The Chairwoman G. Alt

Europäisches Patentamt
European Patent Office
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Acknowledgement of receipt

We hereby acknowledge receipt of the following submission by the proprietor:

Submission number	6191091	
Application number	EP05712607.0	
Patent number	EP1720571	
Date of receipt	29 March 2018	
Your reference	C412290EP	
Proprietor	Alexion Pharmaceuticals, Inc.	
Title	METHOD OF TREATING HEMOLYTIC DISEASE	
Documents submitted	package-data.xml ep-oppo.pdf (2 p.)	ep-opposition-data.xml OTHER-1.PDF\Withdraw the Appeal C412290EP PXT.PDF (1 p.)
Submitted by	CN=Elizabeth Davenport 55598	
Method of submission	Online	
Date and time receipt generated	29 March 2018, 16:49 (CEST)	
Message Digest	5D:0B:34:04:C2:8E:7F:73:6F:82:BB:60:1A:18:5E:B6:61:51:2C:B6	

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

/European Patent Office/

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Submission in opposition proceedings

Representative:

J A Kemp
811
14 South Square
Gray's Inn
London Greater London WC1R 5JJ
United Kingdom

Phone: +44 20 3077 8600
Fax: +44 20 7430 1000
E-mail: mail@jakemp.com

80298 Munich
Germany
Tel. +49(0)89 2399-0 | Fax -4465

P.O. Box 5818
NL-2280 HV Rijswijk
Netherlands
Tel. +31(0)70 340-2040 | Fax -3016

10958 Berlin
Germany
Tel. +49(0)30 25901-0 | Fax -840

- representing the proprietor(s):	Alexion Pharmaceuticals, Inc.
Proprietor/representative's reference	C412290EP

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.	EP1720571
Application No.	EP05712607.0
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	13 June 2012
Title of the invention	METHOD OF TREATING HEMOLYTIC DISEASE
Proprietor of the patent	Alexion Pharmaceuticals, Inc.

Documents attached:

	Description of document	Original file name	Assigned file name
1	Any annexes (other than citation) to an opposition letter - Request to withdraw appeal	Withdraw the Appeal C412290EP PXT.PDF	OTHER-1.PDF

Signatures

Place:	
Date:	**29 March 2018**
Signed by:	**Elizabeth Davenport 55598**
Association:	**J A Kemp**
Representative name:	**DAVENPORT, Elizabeth**
Capacity:	**(Representative)**

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J A • K E M P

BY ONLINE FILING

The European Patent Office
Bayerstrasse 34
(entrance via Zollstrasse 3)
80335 Munich
Germany

29 March 2018

Dear Sirs

Appeal No. T1897/14-3.3.04
Opposition to European Patent No. 1720571
(Application No. 05712607.0)
ALEXION PHARMACEUTICALS, INC.
Our Ref: C412290EP PXT

I hereby withdraw the Appeal filed by Alexion Pharmaceuticals Inc.

Yours faithfully

Electronically Signed
DR PAMELA M TUXWORTH
ASSOCIATION NO. 811

PATENT ATTORNEYS • TRADE MARK ATTORNEYS
LONDON • OXFORD • CAMBRIDGE • PARIS • MUNICH

14 South Square, Gray's Inn, London WC1R 5JJ
T +44 20 3077 8600 **F** +44 20 7430 1000
mail@jakemp.com **www.jakemp.com**

A list of our partners is available at our principal place of business at the address above. Regulated by IPREG

ERBITUX™

Rx only

(Cetuximab)

For intravenous use only.

WARNING

Infusion Reactions: Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX. Severe infusion reactions are characterized by rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and hypotension (see **WARNINGS** and **ADVERSE REACTIONS**). Severe infusion reactions require immediate interruption of the ERBITUX infusion and permanent discontinuation from further treatment. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

DESCRIPTION

ERBITUX™ (Cetuximab) is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). ERBITUX is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions and has an approximate molecular weight of 152 kDa. ERBITUX is produced in mammalian (murine myeloma) cell culture.

ERBITUX is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous, Cetuximab particulates. Each single-use, 50-mL vial contains 100 mg of Cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and Water for Injection, USP.

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CLINICAL PHARMACOLOGY

General

ERBITUX binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor alpha. Binding of ERBITUX to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum.

In vitro assays and *in vivo* animal studies have shown that ERBITUX inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of ERBITUX were observed in human tumor xenografts lacking EGFR expression. The addition of ERBITUX to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

Human Pharmacokinetics

ERBITUX administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m^2. ERBITUX clearance (CL) decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, it appeared to plateau. The volume of the distribution (Vd) for ERBITUX appeared to be independent of dose and approximated the vascular space of 2-3 L/m^2.

Following a 2-hour infusion of 400 mg/m^2 of ERBITUX, the maximum mean serum concentration (Cmax) was 184 ?g/mL (range: 92-327 ?g/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m^2 produced a mean Cmax of 140 ?g/mL (range 120-170 ?g/mL). Following the recommended dose regimen (400 mg/m^2 initial dose/250 mg/m^2 weekly dose), ERBITUX concentrations reached steady-state levels by the third weekly infusion with mean peak and trough

concentrations across studies ranging from 168 to 235 and 41 to 85 ? g/mL, respectively. The mean half-life was 114 hours (range 75-188 hours).

Special Populations

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates including race, gender, age, and hepatic and renal function on ERBITUX pharmacokinetics.

Female patients had a 25% lower intrinsic ERBITUX clearance than male patients. Similar efficacy and safety were observed for female and male patients in the clinical trials; therefore, dose modification based on gender is not necessary. None of the other covariates explored appeared to have an impact on ERBITUX pharmacokinetics.

ERBITUX has not been studied in pediatric populations.

CLINICAL STUDIES

The efficacy and safety of ERBITUX alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). ERBITUX was further evaluated as a single agent in a third clinical trial (57 patients). Safety data from 111 patients treated with single agent ERBITUX was also evaluated. All trials studied patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

Randomized, Controlled Trial

A multicenter, randomized, controlled clinical trial was conducted in 329 patients randomized to receive either ERBITUX plus irinotecan (218 patients) or ERBITUX monotherapy (111 patients). In both arms of the study, ERBITUX was administered as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly until disease progression or unacceptable toxicity. All patients received a 20-mg test dose on Day 1. In the ERBITUX plus irinotecan arm, irinotecan was added to ERBITUX using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly times four doses every 6 weeks. An Independent Radiographic Review Committee (IRC), blinded to the treatment arms, assessed both the progression on prior irinotecan and the response to protocol treatment for all patients.

Of the 329 randomized patients, 206 (63%) were male. The median age was 59 years (range 26-84), and the majority was Caucasian (323, 98%). Eighty-eight percent of patients had baseline Karnofsky Performance Status ?80. Fifty-eight percent of patients had colon cancer and 40% rectal cancer. Approximately two-thirds (63%) of patients had previously failed oxaliplatin treatment.

The efficacy of ERBITUX plus irinotecan or ERBITUX monotherapy was evaluated in all randomized patients.

Analyses were also conducted in two pre-specified subpopulations: irinotecan refractory and irinotecan and oxaliplatin failures. The irinotecan refractory population was defined as randomized patients who had received at least two cycles of irinotecan-based chemotherapy prior to treatment with ERBITUX, and had independent confirmation of disease progression within 30 days of completion of the last cycle of irinotecan-based chemotherapy.

The irinotecan and oxaliplatin failure population was defined as irinotecan refractory patients who had previously been treated with and failed an oxaliplatin-containing regimen.

The objective response rates (ORR) in these populations are presented in Table 1.

Table 1: Objective Response Rates per Independent Review

Populations	ERBITUX + Irinotecan		ERBITUX Monotherapy		Difference (95% CI[a])	
	n	ORR (%)	n	ORR (%)	%	p-value CMH[b]
All Patients	218	22.9	111	10.8	12.1 (4.1 - 20.2)	0.007
? Irinotecan-Oxaliplatin Failure	80	23.8	44	11.4	12.4 (-0.8, 25.6)	0.09
? Irinotecan Refractory	132	25.8	69	14.5	11.3 (0.1 - 22.4)	0.07

[a]95% confidence interval for the difference in objective response rates.
[b]Cochran-Mantel-Haenszel test.

The median duration of response in the overall population was 5.7 months in the combination arm and 4.2 months in the monotherapy arm. Compared with patients randomized to ERBITUX alone, patients randomized to ERBITUX and irinotecan experienced a significantly longer median time to disease progression (see Table 2).

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Table 2: Time to Progression per Independent Review

Populations	ERBITUX + Irinotecan (median)	ERBITUX Monotherapy (median)	Hazard Ratio (95% CI[a])	Log-rank p-value
All Patients	4.1 mo	1.5 mo	0.54 (0.42 □0.71)	<0.001
? Irinotecan-Oxaliplatin Failure	2.9 mo	1.5 mo	0.48 (0.31 - 0.72)	<0.001
? Irinotecan Refractory	4.0 mo	1.5 mo	0.52 (0.37 - 0.73)	<0.001

[a]Hazard ratio of ERBITUX + irinotecan: ERBITUX monotherapy with 95% confidence interval.

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Single-Arm Trials

ERBITUX, in combination with irinotecan, was studied in a single-arm, multicenter, open-label clinical trial in 138 patients with EGFR-expressing metastatic colorectal cancer who had progressed following an irinotecan containing regimen. Patients received a 20-mg test dose of ERBITUX on day 1, followed by a 400-mg/m^2 initial dose, and 250 mg/m^2 weekly until disease progression or unacceptable toxicity. Patients received the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m^2 every 3 weeks or 125 mg/m^2 weekly times four doses every 6 weeks. Of 138 patients enrolled, 74 patients had documented progression to irinotecan as determined by an IRC. The overall response rate was 15% for the overall population and 12% for the irinotecan failure population. The median durations of response were 6.5 and 6.7 months, respectively.

ERBITUX was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with EGFR-expressing metastatic colorectal cancer who progressed following an irinotecan-containing regimen. Of 57 patients enrolled, 28 patients had documented progression to irinotecan. The overall response rate was 9% for the all treated group and 14% for the irinotecan failure group. The median times to progression were 1.4 and 1.3 months, respectively. The median duration of response was 4.2 months for both groups.

EGFR Expression and Response

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit. Specimens were scored

based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

INDICATIONS AND USAGE

ERBITUX, used in combination with irinotecan, is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy.

ERBITUX administered as a single agent is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy.

The effectiveness of ERBITUX is based on objective response rates (see **CLINICAL STUDIES**). Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with ERBITUX.

CONTRAINDICATIONS

None.

WARNINGS

Infusion Reactions (See BOXED WARNINGS: Infusion Reactions, ADVERSE REACTIONS: Infusion Reactions, and DOSAGE AND ADMINISTRATION: Dose Modifications)

Severe infusion reactions occurred with the administration of ERBITUX in approximately 3% (17/633) of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of ERBITUX despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. Caution must be exercised with every ERBITUX infusion, as there were patients who experienced their first severe infusion reaction during later infusions.

Severe infusion reactions require the immediate interruption of ERBITUX therapy and permanent discontinuation from further treatment. Appropriate medical therapy

including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of ERBITUX and by continued use of antihistamine medications (eg, diphenhydramine) in subsequent doses (see **DOSAGE AND ADMINSTRATION: Dose Modifications**).

Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 633 (<0.5%) patients with advanced colorectal cancer receiving ERBITUX. Interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one case. Two patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving ERBITUX in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with ERBITUX and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

In the event of acute onset or worsening pulmonary symptoms, ERBITUX therapy should be interrupted and a prompt investigation of these symptoms should occur. If ILD is confirmed, ERBITUX should be discontinued and the patient should be treated appropriately.

Dermatologic Toxicity (See ADVERSE REACTIONS: Dermatologic Toxicity and DOSAGE AND ADMINISTRATION: Dose Modifications)

In cynomolgus monkeys, ERBITUX, when administered at doses of approximately 0.4 to 4 times the weekly human exposure (based on total body surface area), resulted in dermatologic findings, including inflammation at the injection site and desquamation of the external integument. At the highest dose level, the epithelial mucosa of the nasal passage, esophagus, and tongue were similarly affected, and degenerative changes in the renal tubular epithelium occurred. Deaths due to sepsis were observed in 50% (5/10) of the animals at the highest dose level beginning after approximately 13 weeks of treatment.

In clinical studies of ERBITUX, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (eg, blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 88% (560/633) of all treated patients, and was severe (Grade 3 or 4) in 12% (79/633) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported.

Patients developing dermatologic toxicities while receiving ERBITUX should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future ERBITUX infusions should be instituted in case of severe acneform rash (see **DOSAGE AND ADMINISTRATION**, Table 4). Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

PRECAUTIONS

General

ERBITUX therapy should be used with caution in patients with known hypersensitivity to Cetuximab, murine proteins, or any component of this product.

It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving ERBITUX as sunlight can exacerbate any skin reactions that may occur.

EGF Receptor Testing

Patients enrolled in the clinical studies were required to have immunohistochemical evidence of positive EGFr expression using the DakoCytomation EGFr pharmDx test kit. Assessment for EGFR expression should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Refer to the DakoCytomation test kit package insert for full instructions on assay performance. (See **CLINICAL STUDIES: EGFR Expression and Response**.)

Drug Interactions

A drug interaction study was performed in which ERBITUX was administered in combination with irinotecan. There was no evidence of any pharmacokinetic interactions between ERBITUX and irinotecan.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to ERBITUX were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sample timing, the incidence of antibody development in patients receiving ERBITUX has not been adequately determined. The incidence of antibodies to ERBITUX was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-ERBITUX antibodies were detected in 5% (28 of 530) of evaluable patients. In patients positive for anti-ERBITUX antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to ERBITUX and the safety or antitumor activity of the molecule.

The observed incidence of anti-ERBITUX antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-ERBITUX antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ERBITUX with the incidence of antibodies to other products may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to test ERBITUX for carcinogenic potential. No mutagenic or clastogenic potential of ERBITUX was observed in the *Salmonella-Escherichia coli* (Ames) assay or in the *in vivo* rat micronucleus test. A 39-week toxicity study in cynomolgus monkeys receiving 0.4 to 4 times the human dose of ERBITUX (based on total body surface area) revealed a tendency for impairment of menstrual cycling in treated female monkeys, including increased incidences of irregularity or absence of cycles, when compared to control animals, and beginning from

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week 25 of treatment and continuing through the 6 week recovery period. Serum testosterone levels and analysis of sperm counts, viability, and motility were not remarkably different between ERBITUX-treated and control male monkeys. It is not known if ERBITUX can impair fertility in humans.

Pregnancy Category C

Animal reproduction studies have not been conducted with ERBITUX. However, the EGFR has been implicated in the control of prenatal development and may be essential for normal organogenesis, proliferation, and differentiation in the developing embryo. In addition, human IgG1 is known to cross the placental barrier; therefore ERBITUX has the potential to be transmitted from the mother to the developing fetus. It is not known whether ERBITUX can cause fetal harm when administered to a pregnant woman or whether ERBITUX can affect reproductive capacity. There are no adequate and well-controlled studies of ERBITUX in pregnant women. ERBITUX should only be given to a pregnant woman, or any woman not employing adequate contraception if the potential benefit justifies the potential risk to the fetus. All patients should be counseled regarding the potential risk of ERBITUX treatment to the developing fetus prior to initiation of therapy. If the patient becomes pregnant while receiving this drug, she should be apprised of the potential hazard to the fetus and/or the potential risk for loss of the pregnancy.

Nursing Mothers

It is not known whether ERBITUX is secreted in human milk. Since human IgG1 is secreted in human milk, the potential for absorption and harm to the infant after ingestion is unknown. Based on the mean half-life of ERBITUX after multiple dosing of 114 hours [range 75-188 hours] (see **CLINICAL PHARMACOLOGY: Human Pharmacokinetics**), women should be advised to discontinue nursing during treatment with ERBITUX and for 60 days following the last dose of ERBITUX.

Pediatric Use

The safety and effectiveness of ERBITUX in pediatric patients has not been established.

Geriatric Use

Of the 633 patients who received ERBITUX with irinotecan or ERBITUX monotherapy in four advanced colorectal cancer studies, 206 patients (33%) were 65 years of age or

older. No overall differences in safety or efficacy were observed between these patients and younger patients.

ADVERSE REACTIONS

Except where indicated, the data described below reflect exposure to ERBITUX in 633 patients with advanced metastatic colorectal cancer. ERBITUX was studied in combination with irinotecan (n=354) or as monotherapy (n=279). Patients receiving ERBITUX plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for over 6 months), and patients receiving ERBITUX monotherapy received a median of 7 doses (with 26/279 [9%] treated for over 6 months). The population had a median age of 59 and was 60% male and 91% Caucasian. The range of dosing for patients receiving ERBITUX plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving ERBITUX monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with ERBITUX were:

- Infusion reaction (3%) (See **BOXED WARNINGS, WARNINGS,** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Dermatologic toxicity (1%) (See **WARNINGS** and **DOSAGE AND ADMINISTRATION: Dose Modifications**);
- Interstitial lung disease (0.5%) (See **WARNINGS**);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving ERBITUX plus irinotecan, 2% in patients receiving ERBITUX monotherapy;
- Diarrhea (6%) in patients receiving ERBITUX plus irinotecan, 0% in patients receiving ERBITUX monotherapy.

Thirty-seven (10%) patients receiving ERBITUX plus irinotecan and 14 (5%) patients receiving ERBITUX monotherapy discontinued treatment primarily because of adverse events.

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The most common adverse events seen in 354 patients receiving ERBITUX plus irinotecan were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 279 patients receiving ERBITUX monotherapy were acneform rash (90%), asthenia/malaise (49%), fever (33%), nausea (29%), constipation (28%), and diarrhea (28%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in Table 3 are based on the experience of 354 patients treated with ERBITUX plus irinotecan and 279 patients treated with ERBITUX monotherapy.

Table 3: Incidence of Adverse Events (? 10%) in Patients with Advanced Colorectal Carcinoma

	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=279)	
Body System Preferred Term[1]	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise[2]	73	16	49	10
Abdominal Pain	45	8	25	7
Fever[3]	34	4	33	0
Pain	23	6	19	5
Infusion Reaction[4]	19	3	25	2
Infection	16	1	11	1
Back Pain	16	3	11	3
Headache	14	2	25	3
Digestive				
Diarrhea	72	22	28	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	25	3
Constipation	30	2	28	1

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Table 3: Incidence of Adverse Events (? 10%) in Patients with Advanced Colorectal Carcinoma

Body System Preferred Term[1]	ERBITUX plus Irinotecan (n=354)		ERBITUX Monotherapy (n=279)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Stomatitis	26	2	11	<1
Dyspepsia	14	0	7	0
Hematic/Lymphatic				
Leukopenia	25	17	1	0
Anemia	16	5	10	4
Metabolic/Nutritional				
Weight Loss	21	0	9	1
Peripheral Edema	16	1	10	<1
Dehydration	15	6	9	2
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	9	0
Respiratory				
Dyspnea[3]	23	2	20	7
Cough Increased	20	0	10	1
Skin/Appendages				
Acneform Rash[5]	88	14	90	10
Alopecia	21	0	5	0
Skin Disorder	15	1	5	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	10	<1
Conjunctivitis	14	1	7	<1

[1] Adverse events that occurred (toxicity Grades 1 through 4) in ? 10% of patients with refractory colorectal carcinoma treated with ERBITUX plus irinotecan or in ? 10% of patients with refractory colorectal carcinoma treated with ERBITUX monotherapy.

[2] Asthenia/malaise is defined as any event described as "asthenia", "malaise", or "somnolence"

[3] Includes cases reported as infusion reaction.

[4] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction", or any event occurring on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever" or "dyspnea"

[5] Acneform rash is defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis"

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Infusion Reactions (see BOXED WARNING: Infusion Reactions)

In clinical trials, severe, potentially fatal infusion reactions were reported. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving ERBITUX plus irinotecan and 2% of patients receiving ERBITUX monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving ERBITUX plus irinotecan and 23% of patients receiving ERBITUX monotherapy. (See **WARNINGS: Infusion Reactions** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

In the clinical studies described above, a 20-mg test dose was administered intravenously over 10 minutes prior to the loading dose to all patients. The test dose did not reliably identify patients at risk for severe allergic reactions.

Dermatologic Toxicity and Related Disorders

Non-suppurative acneform rash described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin", or "exfoliative dermatitis" was observed in patients receiving ERBITUX plus irinotecan or ERBITUX monotherapy. One or more of the dermatological adverse events were reported in 88% (14% Grade 3) of patients receiving ERBITUX plus irinotecan and in 90% (10% Grade 3) of patients receiving ERBITUX monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back, but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (eg, blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days. (See **WARNINGS: Dermatologic Toxicity** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

A related nail disorder, occurring in 14% of patients (0.3% Grade 3), was characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

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Use with Radiation Therapy

In a study of 21 patients with locally advanced squamous cell cancer of the head and neck, patients treated with ERBITUX, cisplatin, and radiation had a 95% incidence of rash (19% Grade 3). The incidence and severity of cutaneous reactions with combined modality therapy appears to be additive, particularly within the radiation port. The addition of radiation to ERBITUX therapy in patients with colorectal cancer should be done with appropriate caution.

OVERDOSAGE

Single doses of ERBITUX higher than 500 mg/m^2 have not been tested. There is no experience with overdosage in human clinical trials.

DOSAGE AND ADMINISTRATION

The recommended dose of ERBITUX, in combination with irinotecan or as monotherapy, is 400 mg/m^2 as an initial loading dose (first infusion) administered as a 120-minute IV infusion (maximum infusion rate 5 mL/min). The recommended weekly maintenance dose (all other infusions) is 250 mg/m^2 infused over 60 minutes (maximum infusion rate 5 mL/min). Premedication with an H_1 antagonist (eg, 50 mg of diphenhydramine IV) is recommended. Appropriate medical resources for the treatment of severe infusion reactions should be available during ERBITUX infusions. (See **WARNINGS: Infusion Reactions**.)

Dose Modifications

Infusion Reactions

If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%.

ERBITUX should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions. (See **WARNINGS** and **ADVERSE REACTIONS.)**

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Dermatologic Toxicity and Related Disorders

If a patient experiences severe acneform rash, ERBITUX treatment adjustments should be made according to Table 4. In patients with mild and moderate skin toxicity, treatment should continue without dose modification. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Table 4: ERBITUX Dose Modification Guidelines

Severe Acneform Rash	ERBITUX	Outcome	ERBITUX Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue ERBITUX
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 200 mg/m^2
		No Improvement	Discontinue ERBITUX
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce dose to 150 mg/m^2
		No Improvement	Discontinue ERBITUX
4th occurrence	Discontinue ERBITUX		

Preparation for Administration

DO NOT ADMINISTER ERBITUX AS AN IV PUSH OR BOLUS.

ERBITUX must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

ERBITUX is supplied as a 50-mL, single-use vial containing 100 mg of Cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous Cetuximab particulates. **DO NOT SHAKE OR DILUTE.**

ERBITUX CAN BE ADMINISTERED VIA INFUSION PUMP OR SYRINGE PUMP.

Infusion Pump:

? Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).

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? Fill ERBITUX into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.

? Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.

? Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).

? Affix the infusion line and prime it with ERBITUX before starting the infusion.

? Maximum infusion rate should not exceed 5 mL/min.

? Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

? Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).

? Place the syringe into the syringe driver of a syringe pump and set the rate.

? Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).

? Connect up the infusion line and start the infusion after priming the line with ERBITUX.

? Repeat procedure until the calculated volume has been infused.

? Use a new needle and filter for each vial.

? Maximum infusion rate should not exceed 5 mL/min.

? Use 0.9% saline solution to flush line at the end of infusion.

ERBITUX should be piggybacked to the patient's infusion line.

Following the ERBITUX infusion, a 1-hour observation period is recommended.

HOW SUPPLIED

ERBITUX? (Cetuximab) is supplied as a single-use, 50-mL vial containing 100 mg of Cetuximab as a sterile, preservative-free, injectable liquid. Each carton contains one ERBITUX vial (NDC 66733-948-23).

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Stability and Storage

Store vials under refrigeration at 2? C to 8? C (36? F to 46? F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0?C. This product contains no preservatives. Preparations of ERBITUX in infusion containers are chemically and physically stable for up to 12 hours at 2? C to 8? C (36? F to 46? F) and up to 8 hours at controlled room temperature (20? C to 25? C; 68? F to 77? F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2? to 8? C. Discard any unused portion of the vial.

US Patent No. 6,217,866

ERBITUX? is a trademark of ImClone Systems Incorporated.

Manufactured by ImClone Systems Incorporated, Branchburg, NJ 08876
Distributed and Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543

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xxxxxx Issued _____

CEA-Scan®
(Arcitumomab) 8/99

For the Preparation of Technetium Tc 99m Arcitumomab.
Sterile, Non-Pyrogenic, Lyophilized Powder for Intravenous Use Only.

DESCRIPTION

CEA-Scan® is a radiodiagnostic agent consisting of a murine monoclonal antibody Fab′ fragment, Arcitumomab, formulated to be labeled with Technetium Tc 99m. The active component, Arcitumomab, is a Fab′ fragment generated from IMMU-4, a murine IgG_1 monoclonal antibody produced in murine ascitic fluid supplied to Immunomedics, Inc., by Charles River Laboratories. IMMU-4 is purified from the ascitic fluid and is digested with pepsin to produce $F(ab')_2$ fragments and subsequently reduced to produce the 50,000-dalton Arcitumomab. Each vial contains the non-radioactive materials necessary to prepare one patient dose. CEA-Scan® is a sterile, lyophilized formulation, containing 1.25 mg of Arcitumomab and 0.29 mg stannous chloride per vial, with potassium sodium tartrate tetrahydrate, sodium acetate trihydrate, sodium chloride, acetic acid, glacial, hydrochloric acid, and sucrose. The imaging agent, Technetium Tc 99m CEA-Scan®, Technetium Tc 99m Arcitumomab, is formed by reconstitution of the contents of the CEA-Scan® vial with 30 mCi of Tc 99m sodium pertechnetate in 1 ml of Sodium Chloride for Injection, USP. The resulting solution is pH 5-7 and for intravenous use only. Following administration, the labeled antibody can be visualized by common nuclear medicine instrumentation.

Physical Characteristics of Technetium Tc 99m

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.[2] The principal photon that is useful for detection and imaging is listed in the following table.

Principal Radiation Emission Data

Radiation	Mean % Per Disintegration	Energy (keV)
Gamma-2	89.07	140.5

External Radiation

The specific gamma ray constant for Technetium Tc 99m is 0.78 R/mCi-hr at 1 cm. The first half-value thickness of lead (Pb) for Technetium Tc 99m is 0.017 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in the following table. For example, the use of 0.25 cm of Pb will decrease the external radiation exposure by a factor of about 1000.

Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Coefficient of Attentuation
0.017	**0.5**
0.08	**10^{-1}**
0.16	**10^{-2}**
0.25	**10^{-3}**
0.33	**10^{-4}**

To correct for physical decay of this radionuclide, the fractions that remain at selected time intervals after the time of calibration are shown in the following table.

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Physical Decay Chart: Technetium Tc 99m Half-Life 6.02 Hours			
Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501	18	0.130

*Calibration Time

CLINICAL PHARMACOLOGY

IMMU-4 is reactive with carcinoembryonic antigen (CEA), a tumor-associated antigen the expression of which is increased in a variety of carcinomas, particularly of the gastrointestinal tract, as well as in fetal gastrointestinal tissues and in certain inflammatory states (e.g., Crohn's disease, inflammatory bowel disease, post-radiation therapy to the bowel), and can be shed and detected in the serum.[3,4] Assays of serum levels of circulating CEA are performed to obtain prognostic information following potentially curative surgical resection and as an adjunct to monitoring for recurrent disease in patients who have undergone curative resection of colorectal cancer.[5] Many cross-reactive, but genetically distinct, CEA variants have been described in the literature, including nonspecific cross-reactive antigen (NCA) and meconium antigen (MA).

IMMU-4 is specific for the classical 200,000-dalton CEA that is found predominantly on the cell membrane. The IMMU-4 antibody does not demonstrate cross-reactivity with NCA or with MA.[6] The Technetium Tc 99m CEA-SCAN® product complexes circulating CEA (less than 50% complexation was observed with plasma CEA levels up to 2000 ng/ml, and is not detectable at serum CEA levels below 250 ng/ml) and binds to CEA on the cell surface.

Use of the Fab′ fragment minimizes induction of human anti-mouse antibody (HAMA). Of over 400 patients evaluated, less than 1% of the patients were sensitized, as demonstrated by lack of induction of HAMA reactive with mouse-IgG-fragment[7,8] (See ADVERSE REACTIONS.) The pharmacokinetics of the Fab′ fragment (as compared to intact immunogloblin) minimizes liver metabolism and the Fab′ fragment clears rapidly from the blood.[9] Pharmacokinetic studies were performed after the intravenous administration of the product. At 1, 5 and 24 hours after infusion, the blood levels were 63%, 23%, and 7% of the injected dose (percent injected dose/liter blood), respectively. The initial half-life was approximately one hour; the terminal half-life was 13 ± 4 hours, with 28% of the radiolabel excreted in the urine over the first 24 hours after administration.

CLINICAL STUDIES

CEA-Scan® (Arcitumomab) was evaluated for imaging efficacy and safety in four clinical trials, two of which were Phase 3, one in patients with known disease[8] and the other in patients with occult disease.[8] These imaging studies were conducted to evaluate the presence, location and extent of colorectal cancer, primarily in the liver and extrahepatic abdominal and pelvic regions.[8] Patients eligible for these studies had no prior exposure to murine proteins or murine antibody products. The imaging protocol in both studies was the same. Whole-body planar images were to be obtained at 2-5 hours and 18-24 hours post-injection, with acquisition of 300K counts per view during the initial planar views and 200K counts per view for the late planar images. The protocols required Single-Photon Emission Computed Tomography (SPECT) images of the head, thorax, abdomen and pelvis at 2-5 hours post-injection.

Performance Characteristics in Patients with Evidence of Disease Detected by Standard Modalities:

An open-label, multi-center, single arm trial designed to evaluate the safety and efficacy of Technetium Tc 99m CEA-SCAN® was performed in patients with histologically confirmed colorectal cancer and evidence of primary and/or metastatic disease detected by physical examination, colonoscopy, and/or standard radiologic studies. A total of 222 patients received a 1-mg dose of the antibody labeled with 20-30 mCi of Technetium Tc 99m. The primary analysis of imaging performance and potential clinical utility focused on

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the 122 patients in whom surgical/histopathological evaluation was performed. In patients with at least one site of recurrent or metastatic colorectal cancer identified by standard diagnostic modalities [SDM] (in 95% of patients, this was CT), CEA-Scan® showed an imaging sensitivity of 78% (90/115), a specificity of 86% (6/7), an accuracy of 79% (96/122), a positive predictive value of 99% (90/91), and a negative predictive value of 19% (6/31). When used in conjunction with SDM (identification of potentially malignant lesions by SDM and/or CEA-Scan®), the combination showed an imaging sensitivity of 97% (111/115), a specificity of 29% (2/7), an accuracy of 93% (113/122), a positive predictive value of 96% (111/116), and a negative predictive value of 33% (2/6).

While a formal study exclusively for patients with primary presentation of cancer of the colon or rectum has not been performed, 23 such patients were included in this study. The primary tumor was visualized in 18 of 23 patients by CEA-Scan®. In addition, 11 of these patients had metastatic disease identified at surgery. CEA-Scan® correctly identified at least one metastatic lesion in each of the 11 patients, including 10 patients who had liver metastases.

Performance Characteristics in Patients with Negative or Equivocal Evidence of Disease on Standard Diagnostic Studies:

A single-arm, open-label, multi-center clinical trial designed to evaluate the safety and efficacy of CEA-Scan® (Arcitumomab) for detection of malignant lesions was performed in patients with a history of colorectal carcinoma and presumptive evidence of recurrence or metastasis, primarily due to an elevated and/or rising serum CEA level and negative or equivocal findings on standard radiologic evaluation (CT, MRI, ultrasound). The presence or absence of tumor in one or more sites was determined by histological confirmation from "second-look" surgery, biopsy or laparoscopy, in 88 patients.

Of these 88 patients, 63 had histologically-confirmed malignant lesions. Of these 63, 40 patients had malignant lesions identified on the CEA-Scan® (sensitivity 63%). In four of these 40 patients, reevaluation of the most recent CT scans revealed evidence of disease. Of the 25 patients in whom surgical exploration was negative, CEA-Scan® incorrectly identified a site of disease in 11 (specificity 56%). In this population, the predictive value of a positive CEA-Scan® was 78% (40/51) and the predictive value of a negative CEA-Scan® was 38% (14/37). These data are presented in Table 1.

Table 1
88 Surgically Evaluated Patients with Occult Disease*

		CEA-Scan®		
		Negative	Recurrence	TOTAL
Surgical Findings	No disease	14	11	25
	Recurrence	23	40	63
	TOTAL	37	51	88

*By definition SDM were negative or equivocal for entry; however on review, 4 patients had positive findings on CT scan

Imaging Performance by Region Based Upon Combined Results of the Phase 3 Studies:

The data from the Phase 3 studies were combined to provide an integrated assessment of the imaging characteristics of CEA-Scan® in the abdomen, pelvis, and liver (Table 2).

Table 2
Sensitivity and Specificity of CEA-Scan® (per lesion analysis)

		Abdomen	Liver	Pelvis	Overall
CEA-Scan®	Sensitivity	44/96 (46%)	132/211 (63%)	62/103 (60%)	240/419 (57%)
	Specificity	95/112 (85%)	96/107 (90%)	69/93 (74%)	262/314 (83%)

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In general, CEA-Scan® was more sensitive and less specific in the abdomen and pelvis than CT[8]; however, direct comparisons of the performance characteristics of SDM to CEA-Scan® are difficult to interpret, since the results of SDM were entry criteria for both Phase 3 protocols.

Complementarity Analyses Based Upon Combined Results of the Phase 3 Trials:
Analysis of the complementary use of CEA-Scan® with SDMs showed that lesions identified in this population by both CT and CEA-Scan® were significantly more likely to be confirmed as cancer at surgery (positive predictive value (PPV) = 146/150, 97%) than the group of all lesions identified by CT scan (PPV = 200/233, 86%) or all lesions identified by CEA-Scan® (PPV = 240/292, 83%). When the scan results were discordant for the presence of a lesion and when both were negative in a region, the frequency with which tumor was found was lower (see Table 3).

Table 3
Lesions* Detected by CT and/or CEA-Scan® in Surgically Explored Patients

Radiologic Findings		Surgical Findings: Sites without tumor at surgery	Surgical Findings: Histologically confirmed tumor†	Total
CT Negative	CEA-Scan® Negative	233	125 (35%)	358
	CEA-Scan® Positive	48	94 (66%)	142
CT Positive	CEA-Scan® Negative	29	54 (65%)	83
	CEA-Scan® Positive	4	146 (97%)	150
Total		314	419	

* Negative lesions derived from number of potential sites of involvement per region explored
□ Percentage of patients with histologically confirmed malignant lesions

In the detection of liver metastases, when added to CT scan evaluation, CEA-Scan®(Arcitumomab) indicated the presence of liver metastases in 18 additional patients of whom 10 actually had liver metastases. Thus, addition of CEA-Scan® increased sensitivity from 55/83 (66%) to 65/83 (78%), but decreased specificity from 113/126 (89%) to 105/126 (83%).

Resectability Analysis:
After the studies were completed and analyzed, criteria were developed to assess the potential for curative resection (based on scans and/or surgical findings), and the data were reanalyzed to assess the role of CEA-Scan® in the pre-surgical evaluation of patients for possible curative resection of recurrent or metastatic disease. A patient or diagnostic scan was scored as resectable (R) if there were $\leq$4 lesions in the liver or only 1 region of abdominal or pelvic involvement, non-resectable (NR) if there were >4 liver lesions or 2 or more regions of involvement, and negative (N) if there was no evidence of disease. The patient assessment was based upon surgical exploration or procedures and pathologic findings.[10]

If lesions were considered present when identified by either CT or CEA-Scan®, CEA-Scan® in combination with CT correctly classified a greater percentage of patients with resectable disease (66% vs. 47%) and a greater percentage of patients with non-resectable disease (47% vs. 19%) compared with CT alone. However, adding CEA-Scan® to CT scan increased the frequency of incorrect identification of disease, among those patients with no disease at surgery, from 15% of patients to 32% of patients. Comparative data regarding the predictive values of CT and of CT plus CEA-Scan® for the absence of metastatic disease, the presence of resectability or of non-resectable disease are provided in Table 4. The predictive value of the combination of the two scans for the absence of malignant disease (i.e., both

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negative studies) was greater than for CT alone (67% vs. 38%), whereas the predictive value of findings of resectable or non-resectable disease on CT alone were similar to those of the combination.

Table 4
Comparison of Resectability Determinations in 209 Surgically Explored Subjects According to CT and CT plus CEA-Scan®

Surgical Findings	CT scan Findings			Percentage Correct by Surgical findings	CT plus CEA-Scan‡			Percentage Correct by Surgical findings
	Negative	Resectable	Non-resect		Negative	Resectable	Non-resect	
Negative	**40**	7	0	**40/47 (85%)**	**32**	**12**	**3**	**32/47 (68%)**
Resect.	38	**42**	7	**42/89* (47%)**	**8**	**59**	**18**	**59/89* (66%)**
Non-resect.	28	26	**14**	**14/73* (19%)**	**8**	**27**	**34**	**34/73* (47%)**
Percentage Correct by Scan result †	**40/106 (38%)**	**42/77* (55%)**	**14/26* (54%)**		**32/48 (67%)**	**59/102* (58%)**	**34/59* (58%)**	

*Denominators include some subjects with the "correct" resectability assessment based upon incorrect scan findings
†The percentage of scans for which the resectability status was correct, which is analogous to predictive value for resectability status
‡Lesions identified by either SDM and/or CEA-Scan® were considered positive

Based on the data obtained in the resectability analysis (Tables 4 & 6), the management paradigm (Table 5) was developed to evaluate the potential utility of CEA-Scan® as an adjunct to CT in the resectability analysis.. As noted in the paradigm, when CT and CEA-Scan® were discordant, the CEA-Scan®, by itself, was not to be relied upon.

Table 5 Management Paradigm Evaluated

Imaging Result	Course of Action†
CT + CEA-Scan® concordant for resectability	Operate
CT + CEA-Scan® concordant for non-resectability	Do not operate
CT + CEA-Scan® concordant for absence of disease	Wait and repeat evaluation in 2-3 months
CT+ CEA-Scan® discordant for resectability	Biopsy critical lesion(s) or perform additional study
CT + CEA-Scan® discordant for absence of disease	Biopsy unconfirmed lesion(s)

†The management of any individual should be based on all the available information.

Among the 209 patients with surgical exploration and/or biopsy of lesions, 106 (51%) had CT and CEA-Scan® findings which were concordant, i.e., CT and CEA-Scan® identified the lesions in the same location with similar extent of involvement or both failed to identify any evidence of disease. When CEA-Scan® and CT were concordant, 29 of 31 (94%) patients without disease, 29 of 37 (78%) patients with resectable disease, and 17 of 38 (45%) of patients with non-resectable disease were correctly identified. The predictive value of concordant SDM and CEA-Scan® for absence of disease was 64% (29/45; 95% confidence interval = 50-78%), for the presence of resectable disease was 66% (29/44; 95% CI=52-80%), and for the presence of non-resectable disease was 100% (17/17; 95% CI= 80-100%) [see Table 6].

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Table 6 Resectability Determination when CT and CEA-Scan® are Concordant† (n=106)			
Surgical Findings	Concordant CT and CEA-Scan® Findings (n=106)		
	Negative	Resectable	Non-resect
Negative (n=31)	29	2	0
Resectable (n=37)	8	29	0
Non-resectable (n=38)	8	13	17
Total	45	44	17

†CT and CEA-Scan® identified the lesions in the same location with similar extent of involvement or both failed to identify any evidence of disease.

Readministration

Forty-four patients received two injections of CEA-Scan® at a median interval for 11.5 months (range 6-27 months). No serious adverse events and no evidence of HAMA to CEA-Scan® (HAMA <74 ng/mL of ImmuSTRIP fragment assay) were reported following the second injection. Paired imaging studies from the first and second administration were available for 35 of the 44 subjects. In 9% (3/35) of patients, the second imaging studies revealed a change in the pattern of CEA-Scan® distribution which differed from that typically seen after the first injection; specifically, there was more rapid clearance of radiotracer from the blood pool and increased localization of radiotracer in the kidneys. There are insufficient data to determine the etiology for the differences observed and this is under current investigation. The ability of CEA-Scan® to detect the presence, location, and extent of tumor in patients with this pattern of altered biodistribution is not known.

INDICATIONS

CEA-Scan® (Arcitumomab) is indicated, in conjunction with standard diagnostic evaluations (e.g., additional imaging evaluation), for detection of the presence, location and extent of recurrent and/or metastatic colorectal carcinoma involving the liver, extrahepatic abdomen and pelvis in patients with a histologically confirmed diagnosis of colorectal carcinoma. CEA-Scan® provides additional information in patients with no evidence of disease by standard diagnostic modalities (SDM) in whom recurrence or metastasis is suspected based upon elevated or rising serum CEA, and in patients with evidence of metastatic or recurrent disease on SDM. A retrospective analysis suggests that these data can be useful in the evaluation of patients in whom surgical intervention (biopsy, exploratory laparotomy and surgical resection) is under consideration.

CEA-Scan® is not indicated for the differential diagnosis of suspected colorectal carcinoma or as a screening tool for colorectal cancer. CEA-Scan® is not intended for readministration or for assessment of response to treatment. (see PRECAUTIONS)

CONTRAINDICATIONS

CEA-Scan® should not be administered to patients who are hypersensitive to products of murine origin or to Technetium Tc 99m.

WARNINGS

Anaphylactic and other hypersensitivity reactions can occur following administration of mouse protein to patients. Although serious reactions of this type have not been observed in clinical trials after CEA-Scan® administration, medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of this agent.

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PRECAUTIONS

General

CEA-Scan® is to be interpreted in conjunction with standard diagnostic modalities. A negative or positive CEA-Scan® by itself should not be utilized in the diagnostic evaluation of colorectal cancer. Discordant results are substantially less predictive than concordant results.

CEA-Scan® should not be used as a screening test for colorectal cancer.

There is limited experience with readministration of CEA-Scan® (see CLINICAL STUDIES).

The components of CEA-Scan® are sterile and non-pyrogenic. It is essential to follow preparation directions carefully and to adhere to strict aseptic procedures during preparation of Technetium Tc 99m CEA-SCAN®. The contents of the vial are intended only for use in the preparation of Technetium Tc 99m CEA-SCAN® and are not to be administered directly to patients.

The contents of the vial before preparation are not radioactive. However, after Tc 99m pertechnetate is added, adequate shielding of the preparation must be maintained. Appropriate safety measures should be used to minimize radiation exposure to clinical personnel and patients, consistent with proper patient management.

Radiopharmaceuticals should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides.

Imaging Interpretation

General

There are limited data to determine the imaging characteristics and efficacy of the CEA-Scan® (Arcitumomab) in detection of lesions outside of the abdominopelvic cavity.[7,8]

Areas of potential false-positive readings, particularly with planar imaging, may be observed near the major bloodpool organs (heart, major vessels, etc.) at very early imaging times, near the sites of antibody fragment metabolism (kidneys and urinary bladder), and in the intestines and gallbladder. Late imaging may also aid in the evaluation of suspected normal bowel activity.

With regard to imaging of tumor near the kidneys or urinary bladder, it is advisable to have the patient void urine prior to acquisition of imaging data to decrease bladder activity. Careful SPECT imaging near the kidneys and bladder has been helpful.

Porta Hepatis Region

Precise localization of lesions in the region of the porta hepatis has been difficult. Lesions within the porta hepatis region may be present within the liver or the portal nodes. At the time of surgical exploration, such lesions (which if nodal would preclude resection of hepatic metastases) should be explored first.

False-Positive Lesions

There were 52 false-positive lesions observed in 41 patients from a total of 209 surgically explored subjects in the two pivotal trials. Thirty-five of these lesions were in occult disease patients. Of the 52 false-positive lesions, 11 were observed in the liver, 17 in the extra-hepatic abdomen, and 24 in the pelvis. A pathological correlate to the lesions was infrequently documented; these included granulomas in the liver (1 instance), adhesions with or without suture granulomas (4 cases), surgical incision site (1 case). Descriptions of false-positive lesions within the abdomen were suggestive of colonic activity in several cases.

Hot, Rimmed, and Cold Lesions

Only hot or rimmed lesions should be considered as positive for tumor. Lesions that are rimmed or cold usually fill in as hot or rimmed, respectively, with time.[8,9] Often, large lesions, due to poor vascularization or central necrosis, will appear to be cold.

Information for Patients

Murine monoclonal antibodies are foreign proteins, and their administration can induce human anti-mouse antibodies (HAMA). While limited data exist concerning the clinical significance of HAMA, the presence of HAMA may interfere with murine antibody-based immunoassays (e.g., serum CEA assays), could compromise the efficacy of *in vitro* or *in vivo* diagnostic or therapeutic murine antibody-based agents, and may increase the risk of adverse reactions. For these reasons, patients should be informed that the use of this product could affect the future use of other murine-based products, including CEA-Scan®, and they

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should be advised to discuss prior use of murine-based antibody products with their physicians. (see Heterologous Protein Administration)

Heterologous Protein Administration
The presence of HAMA and human anti-mouse fragment antibodies has been reported in patients before and after receiving CEA-Scan® (<1% of patients develop HAMA to the antibody fragment). While hypersensitivity reactions to CEA-Scan® have not been observed to date, it is possible that such reactions could occur, resulting in anaphylactic shock, serum sickness or death. In addition, patients who have previously received murine monoclonal antibody products are more likely to have HAMA. When considering the use of the CEA-Scan® in patients who have previously received murine antibody-based products, physicians should be aware of the potential for HAMA to increase the risk of allergic reactions and to alter clearance and biodistribution. The quality or sensitivity of the imaging study may then be compromised.

Drug/Laboratory Test Interactions
The presence of HAMA in serum may interfere with two-site murine antibody-based immunoassays, such as assays for CEA and CA-125. If HAMA is known or suspected to be present, the clinical laboratory should be notified that interference may occur.

CEA-Scan® may interfere with serum assays for assessment of serum levels of CEA. Therefore, any determination of serum CEA should be made prior to injection with CEA-Scan®. Assays for serum CEA should not be performed within 7 days after injection of CEA-Scan®.

No data are available on possible drug interactions. Do not mix or administer CEA-Scan® with other products. Sufficient time should be allowed for clearance and radioactive decay before and after the use of this product and other products using radionuclides.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed to evaluate the carcinogenic or mutagenic potential of Technetium Tc 99m Arcitumomab or to determine its effects on fertility in males or females.

Pregnancy - Category C
Animal reproduction studies have not been conducted with CEA-Scan®. It is also not known whether it can cause fetal harm or affect reproductive capacity when administered to a pregnant woman. CEA-Scan® should be used during pregnancy only if, in the opinion of the physician, the information to be gained justifies the potential risk to the fetus. Examinations using a radiopharmaceutical in a woman of child-bearing capability should be performed during the first 8-10 days following the onset of menses, if possible.

Lactation
Before administering a radioactive medicinal product to a mother who is breast-feeding, consideration should be given whether the investigation could be reasonably delayed until the mother has ceased breast-feeding. If the use of the product is deemed to be clinically indicated, breast-feeding should be interrupted, the expressed milk discarded, and formula feedings substituted for breast-feeding.

Pediatric Use
Safety and diagnostic accuracy in persons under 21 years of age have not been established.

ADVERSE REACTIONS
In the patients studied with CEA-Scan®, one patient each developed the following minor self-limiting adverse effects: transient eosinophilia, nausea, bursitis, urticaria, generalized itching, headache, upset stomach and fever. Out of a total of over 500 patients receiving the product to date, there has been a single report of an apparent grand mal epileptic seizure in a severely hypertensive patient that was □possibly related□ to CEA-Scan® infusion.

Over 400 patients who have received CEA-Scan® have been evaluated for HAMA by Immunomedics using ELISA methodology. Fewer than 1% of the patients showed an elevation of HAMA levels to fragment after being injected with CEA-Scan®. If the physician suspects HAMA based on an adverse reaction or

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altered biodistribution pattern, and deems that a HAMA assay is clinically warranted, he/she should telephone Immunomedics, Inc., at 800 327-7211, between 8:30 a.m. and 5:00 p.m. Eastern Standard Time, for information on procedures to be followed for submission of patient serum for assessment of HAMA directed against mouse monoclonal antibody fragments.

OVERDOSAGE

Intravenous infusion of intact IgG and $F(ab')_2$ of IMMU-4 in doses of up to 25 mg or Arcitumomab at doses up to 10 mg have not shown any serious adverse reaction.

DOSAGE AND ADMINISTRATION

CEA-Scan® is reconstituted with sodium pertechnetate Tc 99m solution prior to use. (See section on Preparation of Technetium-Labeled CEA-Scan® [Arcitumomab].) The recommended adult dose is a single dose of 1 mg of Arcitumomab labeled with 20 to 30 mCi of Technetium Tc 99m. Following dilution of the Technetium Tc 99m CEA-SCAN® with 1 ml of Sodium Chloride Injection, USP, the dose is administered as a 2-ml intravenous injection. Alternately, the contents of the vial may be diluted to a total volume of 30 ml with isotonic Sodium Chloride Injection, USP. Intravenous infusion of Technetium Tc 99m CEA-SCAN® diluted to 30 ml with Sodium Chloride Injection, USP, should be performed over a period of 5 to 20 minutes.

CEA-Scan® can be injected five minutes after reconstitution and should be used within 4 hours following reconstitution. Use of the product more than 4 hours after reconstitution may adversely affect imaging quality. The reconstituted preparation can be kept at room temperature prior to infusion. The preparation is sterile, non-pyrogenic and contains no bacteriostatic preservative.

Immediately prior to administration, the patient dose should be measured in a dose calibrator. Prior to patient administration, radiochemical purity must be ^{3}90% by Instant Thin Layer Chromatography (ITLC). The solution should be inspected visually; if there is particulate matter or discoloration, the preparation should be discarded and the manufacturer should be notified.

Immunoscintigraphy, using planar and Single-Photon Emission Computed Tomography (SPECT) techniques, should be performed at two to five hours after injection; selected additional views may be obtained up to 24 hours (as indicated by earlier imaging).

Radiation Dosimetry

Radiation dosimetry for individual organs is provided below. The values were calculated according to Medical Internal Radiation Dosimetry (MIRD). Data represent the mean of ten patients, with the exception of kidney (nine patients), ovary (eight patients) and testes (two patients).

Summary of Normal Organ Dosimetry (µGy/MBq)

Technetium Tc 99m CEA-Scan®

Organ	Mean	± SD
Bladder	16.6	3.6
Kidney	100.3	31.7
Spleen	15.9	4.5
Liver	10.4	2.9
Red Marrow	9.9	2.0
Lung	7.7	1.9
Ovary	7.7	1.5
Total Body	4.6	0.8
Testes	4.5	0.6

Effective dose equivalent 13.1 µSv/MBq
Effective dose 9.1 µSv/MBq

Guidelines for Safe Preparation and Handling

Read complete directions thoroughly before starting the preparation procedure. All procedures should be conducted using aseptic technique and standard precautions for handling radionuclides.

Preparation of Technetium Tc 99m CEA-SCAN®

1. Required Materials, Not Supplied

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a. Technetium Tc 99m, oxidant-free
b. 2, 1-ml shielded, sterile syringes
c. Alcohol (or germicidal) swabs
d. Lead shield for 3-ml vial
e. Sodium Chloride for Injection, USP
f. 10-µl pipette
g. Silica gel impregnated glass fiber strips, 1 x 9 cm
h. Acetone
i. Chromatography jar
j. Gamma counter
k. Dose calibrator
l. Counting tubes
m. Sterile 1- and 2-ml disposable syringes

2. The container for Arcitumomab does not contain preservatives. It is important that the user adhere to strict aseptic procedures during the preparation, withdrawal and administration of the CEA-Scan® product.
3. Obtain 25 to 30 mCi sodium pertechnetate Tc 99m in Sodium Chloride Injection, USP, at a concentration of 30 mCi/ml. With in-house generators: in a 2-ml vial, dilute 25-30 mCi of sodium pertechnetate Tc 99m to a final concentration of 30 mCi/ml with Sodium Chloride Injection, USP. Draw up 1 ml of sodium pertechnetate into a 1-ml shielded syringe (with a permanently affixed needle).
4. Inject 25-30 mCi of sodium pertechnetate Tc 99m in 1 ml into a shielded vial of Arcitumomab to resuspend the contents.
5. Swirl and shake the vial for approximately 30 seconds making sure all sodium pertechnetate Tc 99m is in contact with the antibody. Allow the labeling reaction to proceed for at least five minutes. Add 1 ml of Sodium Chloride Injection, USP, in order to facilitate easy removal. Remove the entire contents of the vial. Assay the product in a suitable dose calibrator.
6. After radiolabeling the antibody, remove a small aliquot and use approximately 1 µL without further dilution for the analysis of free technetium in the sample by Instant Thin Layer Chromatography (ITLC). To minimize any oxidation, the ITLC should be performed as soon as possible after removal of the sample. Determine the radiochemical purity by Instant Thin Layer Chromatography on silica gel impregnated glass fiber strips, 1 x 9 cm, using acetone as the solvent, to ensure that levels of free technetium meet the specifications of less than 10%. When the solvent front is within 1 cm of the top of the strip, remove it, cut it in half and place each half into a glass tube. Count each tube in a gamma scintillation counter, dose calibrator or radiochromatogram analyzer. Calculate the percent free technetium as follows:

$$\% \text{ Free Technetium} = \frac{\text{Activity in top half of strip}}{\text{Total Activity}} \times 100$$

7. Based on the activity measured in the activity calibrator, withdraw a sufficient amount of the product to provide the desired activity (20-30 mCi of Technetium Tc 99m. Technetium Tc 99m CEA-SCAN® can be used after five minutes and should be used within four hours after preparation. Technetium Tc 99m CEA-SCAN® can be stored at room temperature after radiolabeling.
8. Prior to administration, the solution should be inspected visually for particulate matter and discoloration. If either appear, the vial should be discarded and the manufacturer notified.

Image Acquisition

Planar imaging of the pelvis and abdomen, at two to five hours post-injection with at least 500K counts per view, should be made. Image acquisition in analogue and/or digital word-mode with a 128 x 128 matrix is recommended.

SPECT of the pelvis and abdomen at two to five hours post-injection should also be acquired. SPECT acquisition parameters recommended are: 60 projections in a 360° step-and-shoot technique, 30 seconds per view in a 64 x 64 matrix. Data processing by filtered back-projection and reconstruction in three planes (transaxial, coronal and sagittal) is recommended. Where it is desired to evaluate possible non-specific activity, later imaging may be advisable.

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If late imaging is performed (up to 24 hours post-injection), intestinal and gall bladder activity may interfere with true tumor imaging. Therefore, such late images should be compared to those made at earlier times (two to five hours) and interpreted conservatively. Occasionally, bowel and gallbladder activity also may be visualized on the early images.

Due to excretion of the labeled fragment in the urine, the patient should urinate prior to imaging of the pelvis in order to decrease bladder activity.

HOW SUPPLIED

Package containing one (1) vial, with a single-use dose of 1.25 mg lyophilized Arcitumomab. The product should not be used beyond the expiration date printed on the label.

Storage

Store at 2°-8° C. Do not freeze.

Following reconstitution and radiolabeling, the material can be held at room temperature and must be used within four hours following reconstitution.

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Covered by one or more U.S. Patents:
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4,818,709
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Immunomedics, Inc.
300 American Road
Morris Plains, NJ 07950

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Ibritumomab Tiuxetan

ZEVALIN®

Kits for the Preparation of Indium-111 (In-111) Ibritumomab Tiuxetan (In-111 ZEVALIN) and Yttrium-90 (Y-90) Ibritumomab Tiuxetan (Y-90 ZEVALIN)

In-111 Ibritumomab Tiuxetan and Y-90 Ibritumomab Tiuxetan are components of the ZEVALIN therapeutic regimen (See Description).

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WARNINGS

Fatal Infusion Reactions: Deaths have occurred within 24 hours of Rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. These fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first Rituximab infusion (See WARNINGS and ADVERSE REACTIONS). Patients who develop severe infusion reactions should have Rituximab, In-111 ZEVALIN, and Y-90 ZEVALIN infusions discontinued and receive medical treatment.

Prolonged and Severe Cytopenias: Y-90 ZEVALIN administration results in severe and prolonged cytopenias in most patients. The ZEVALIN therapeutic regimen should not be administered to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve (See ADVERSE REACTIONS and CLINICAL STUDIES).

Dosing

- The prescribed, measured, and administered dose of Y-90 ZEVALIN should not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq).
- Y-90 ZEVALIN should not be administered to patients with altered biodistribution as determined by imaging with In-111 ZEVALIN.

In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides.

DESCRIPTION

ZEVALIN

ZEVALIN□ (Ibritumomab Tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody Ibritumomab and the linker-chelator tiuxetan [N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-

propyl]-[N-[2-bis(carboxymethyl)amino]-2-(methyl)-ethyl]glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for Indium-111 or Yttrium-90. The approximate molecular weight of Ibritumomab Tiuxetan is 148 kD.

The antibody moiety of ZEVALIN is Ibritumomab, a murine IgG_1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Ibritumomab is produced in Chinese hamster ovary cells and is composed of two murine gamma 1 heavy chains of 445 amino acids each and two kappa light chains of 213 amino acids each.

ZEVALIN Therapeutic Regimen

The ZEVALIN therapeutic regimen is administered in two steps: Step 1 includes one infusion of Rituximab preceding In-111 ZEVALIN. Step 2 follows Step 1 by seven to nine days and consists of a second infusion of Rituximab followed by Y-90 ZEVALIN.

ZEVALIN□ is supplied as two separate and distinctly labeled kits that contain all of the non-radioactive ingredients necessary to produce a single dose of In-111 ZEVALIN and a single dose of Y-90 ZEVALIN, both essential components of the ZEVALIN therapeutic regimen. Indium-111 chloride and Rituximab must be ordered separately from the ZEVALIN kit. Yttrium-90 Chloride Sterile Solution is supplied by MDS Nordion when the Y-90 ZEVALIN kit is ordered.

ZEVALIN Kits

Each of the two ZEVALIN kits contains four vials that are used to produce a single dose of either In-111 ZEVALIN or Y-90 ZEVALIN, as indicated on the outer container label:

(1) One (1) ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present.

(2) One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate trihydrate in 2 mL of Water for Injection; a sterile, pyrogen-free, clear, colorless

solution; no preservative present.

(3) One (1) Formulation Buffer Vial containing 750 mg of Albumin (Human), 76 mg of sodium chloride, 21 mg of sodium phosphate dibasic heptahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber colored solution; no preservative present.

(4) One (1) empty Reaction Vial, sterile, pyrogen-free.

Physical/Radiochemical Characteristics of In-111

Indium-111 decays by electron capture, with a physical half-life of 67.3 hours (2.81 days).[1] The product of radioactive decay is nonradioactive cadmium-111. Radiation emission data for In-111 are summarized in Table 1.

Table 1.
Principal In-111 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	90.2	171.3
Gamma-3	94.0	245.4

External Radiation

The exposure rate constant for 37 MBq (1 mCi) of In-111 is 8.3 x 10^{-4} C/kg/hr (3.2 R/hr) at 1 cm. Adequate shielding should be used with this gamma-emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of In-111, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 2.

Table 2.
Physical Decay Chart: In-111
Half-life 2.81 Days (67.3 Hours)

Calibration Time (Hrs.)	Fraction Remaining
-48	1.64
-42	1.54
-36	1.45
-24	1.28
-12	1.13
-6	1.06
0	1.00
6	0.94
12	0.88
24	0.78
36	0.69
42	0.65
48	0.61

Physical/Radiochemical Characteristics of Y-90

Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days).[1] The product of radioactive decay is non-radioactive zirconium-90. The range of beta particles in soft tissue (?$_{90}$) is 5 mm. Radiation emission data for Y-90 are summarized in Table 3.

Table 3.
Principal Y-90 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta minus	100	750-935

External Radiation

The exposure rate for 37 MBq (1 mCi) of Y-90 is 8.3 x 10^{-3} C/kg/hr (32 R/hr) at the mouth of an open Y-90 vial. Adequate shielding should be used with this beta-emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of Y-90, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 4.

Table 4.
Physical Decay Chart: Y-90
Half-life 2.67 Days (64.1 Hours)

Calibration Time (Hrs.)	Fraction Remaining	Calibration Time (Hrs.)	Fraction Remaining
-36	1.48	0	1.00
-24	1.30	1	0.99
-12	1.14	2	0.98
-8	1.09	3	0.97
-7	1.08	4	0.96
-6	1.07	5	0.95
-5	1.06	6	0.94
-4	1.04	7	0.93
-3	1.03	8	0.92
-2	1.02	12	0.88
-1	1.01	24	0.77
0	1.00	36	0.68

CLINICAL PHARMACOLOGY

General Pharmacology

Ibritumomab Tiuxetan binds specifically to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35).[2, 3] The apparent affinity (K_D) of Ibritumomab Tiuxetan for the CD20 antigen ranges between approximately 14 to 18 nM. The CD20 antigen is expressed on pre-B and mature B lymphocytes and on > 90% of B-cell non-Hodgkin's lymphomas (NHL).[4, 5] The CD20 antigen is not shed from the cell surface and does not internalize upon antibody binding.[6]

Mechanism of Action: The complementarity-determining regions of Ibritumomab bind to the CD20 antigen on B lymphocytes. Ibritumomab, like Rituximab, induces apoptosis in CD20+ B-cell lines *in vitro*.[6] The chelate tiuxetan, which tightly binds In-111 or

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Y-90, is covalently linked to the amino groups of exposed lysines and arginines contained within the antibody. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells.[7]

Normal Human Tissue Cross-Reactivity: Ibritumomab Tiuxetan binding was observed *in vitro* on lymphoid cells of the bone marrow, lymph node, thymus, red and white pulp of the spleen, and lymphoid follicles of the tonsil, as well as lymphoid nodules of other organs such as the large and small intestines. Binding was not observed on the nonlymphoid tissues or gonadal tissues (see **CLINICAL PHARMACOLOGY, Radiation Dosimetry**)

Pharmacokinetics / Pharmacodynamics

Pharmacokinetic and biodistribution studies were performed using In-111 ZEVALIN (5 mCi [185 MBq] In-111, 1.6 mg Ibritumomab Tiuxetan). In a study designed to assess the need for pre-administration of unlabeled antibody, only 18% of known sites of disease were imaged when In-111 ZEVALIN was administered without unlabeled Ibritumomab. When preceded by unlabeled Ibritumomab (1.0 mg/kg or 2.5 mg/kg), In-111 ZEVALIN detected 56% and 92% of known disease sites, respectively.

In pharmacokinetic studies of patients receiving the ZEVALIN therapeutic regimen, the mean effective half-life for Y-90 activity in blood was 30 hours, and the mean area under the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over 7 days, a median of 7.2% of the injected activity was excreted in urine.

In clinical studies, administration of the ZEVALIN therapeutic regimen resulted in sustained depletion of circulating B cells. At four weeks, the median number of circulating B cells was zero (range, 0-1084 cell/mm^3). B-cell recovery began at approximately 12 weeks following treatment, and the median level of B cells was within the normal range (32 to 341 cells/mm^3) by 9 months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell

depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range 13-3990 mg/dL) after treatment and recovered to normal values by 6-month post therapy.

Radiation Dosimetry

Estimations of radiation-absorbed doses for In-111 ZEVALIN and Y-90 ZEVALIN were performed using sequential whole body images and the MIRDOSE 3 software program.[8, 9] The estimated radiation absorbed doses to organs and marrow from a course of the ZEVALIN therapeutic regimen are summarized in Table 5. Absorbed dose estimates for the lower large intestine, upper large intestine, and small intestine have been modified from the standard MIRDOSE 3 output to account for the assumption that activity is within the intestine wall rather than the intestine contents.

Table 5.
Estimated Radiation Absorbed Doses From Y-90 ZEVALIN and In-111 ZEVALIN

	Y-90 ZEVALIN mGy/MBq		In-111 ZEVALIN mGy/MBq	
Organ	**Median**	**Range**	**Median**	**Range**
Spleen[1]	9.4	1.8 - 14.4	0.9	0.2 - 1.2
Testes[1]	9.1	5.4 - 11.4	0.6	0.4 - 0.8
Liver[1]	4.8	2.3 - 8.1	0.7	0.3 - 1.1
Lower Large Intestinal Wall[1]	4.8	3.1 □8.2	0.4	0.2 - 0.6
Upper Large Intestinal Wall[1]	3.6	2.0 □6.7	0.3	0.2 - 0.6
Heart Wall[1]	2.8	1.5 - 3.2	0.4	0.2 - 0.5
Lungs[1]	2.0	1.2 - 3.4	0.2	0.1 - 0.4
Small Intestine[1]	1.4	0.8 □2.1	0.2	0.1 - 0.3
Red Marrow[2]	1.3	0.7 - 1.8	0.2	0.1 - 0.2
Urinary Bladder Wall[3]	0.9	0.7 - 2.1	0.2	0.1 - 0.2
Bone Surfaces[2]	0.9	0.5 - 1.2	0.2	0.1 - 0.2
Ovaries[3]	0.4	0.3 - 0.5	0.2	0.2 - 0.2
Uterus[3]	0.4	0.3 - 0.5	0.2	0.1 - 0.2

Adrenals[3]	0.3	0.0 - 0.5	0.2	0.1 - 0.3
Brain[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Breasts[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Gallbladder Wall[3]	0.3	0.0 - 0.5	0.3	0.1 - 0.4
Muscle[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Pancreas[3]	0.3	0.0 - 0.5	0.2	0.1 - 0.3
Skin[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Stomach[3]	0.3	0.0 - 0.5	0.1	0.1 - 0.2
Thymus[3]	0.3	0.0 - 0.5	0.1	0.1 - 0.2
Thyroid[3]	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Kidneys[1]	0.1	0.0 - 0.2	0.2	0.1 - 0.2
Total Body[3]	0.5	0.2 - 0.7	0.1	0.1 - 0.2

1 Organ region of interest
2 Sacrum region of interest [10]
3 Whole body region of interest

CLINICAL STUDIES

The safety and efficacy of the ZEVALIN therapeutic regimen were evaluated in two multi-center trials enrolling a total of 197 subjects. The ZEVALIN therapeutic regimen was administered in two steps (see DOSAGE and ADMINISTRATION). The activity and toxicity of a variation of the ZEVALIN therapeutic regimen employing a reduced dose of Y-90 ZEVALIN was further defined in a third study enrolling a total of 30 patients who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3).

Study 1 was a single arm study of 54 patients with relapsed follicular lymphoma refractory to Rituximab treatment. Patients were considered refractory if their last prior treatment with Rituximab did not result in a complete or partial response, or if time to disease progression (TTP) was < 6 months. The primary efficacy endpoint of the study was the overall response rate (ORR) using the International Workshop Response Criteria (IWRC).[11] Secondary efficacy endpoints included time to disease progression (TTP)

and duration of response (DR). In a secondary analysis comparing objective response to the ZEVALIN therapeutic regimen with that observed with the most recent treatment with Rituximab, the median duration of response following the ZEVALIN therapeutic regimen was 6 vs. 4 months. Table 6 summarizes efficacy data from this study.

Study 2 was a randomized, controlled, multicenter study comparing the ZEVALIN therapeutic regimen to treatment with Rituximab. The trial was conducted in 143 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL. A total of 73 patients received the ZEVALIN therapeutic regimen, and 70 patients received Rituximab given as an IV infusion at 375 mg/m^2 weekly times 4 doses. The primary efficacy endpoint of the study was to determine the ORR using the IWRC[11] (see Table 6). The ORR was significantly higher (80% vs. 56%, p = 0.002) for patients treated with the ZEVALIN therapeutic regimen. The secondary endpoints, duration of response and time to progression, were not significantly different between the two treatment arms.

Table 6.
Summary of Efficacy Data[1]

	Study 1	Study 2	
	ZEVALIN therapeutic regimen N = 54	**ZEVALIN therapeutic regimen N = 73**	**Rituximab N = 70**
Overall Response Rate (%)	74	80	56
Complete Response Rate (%)	15	30	16
CRu Rate[2] (%)	0	4	4
Median DR[3,4] (Months) [Range[5]]	6.4 [0.5-24.9+]	13.9 [1.0-30.1+]	11.8 [1.2-24.5]
Median TTP[3,6] (Months) [Range[5]]	6.8 [1.1-25.9+]	11.2 [0.8-31.5+]	10.1 [0.7-26.1]

[1]IWRC: International Workshop response criteria
[2]CRu: Unconfirmed complete response
[3]Estimated with observed range.
[4]Duration of response: interval from the onset of response to disease progression.
[5]□+□indicates an ongoing response.
[6]Time to Disease Progression: interval from the first infusion to disease progression.

Study 3 was a single arm study of 30 patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL who had mild thrombocytopenia (platelet count

100,000 to 149,000 cells/mm^3). Excluded from the study were patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were considered to have impaired bone marrow reserve if they had any of the following: prior myeloablative therapy with stem cell support; prior external beam radiation to > 25% of active marrow; a platelet count <100,000 cells/mm^3; or neutrophil count <1,500 cells/mm^3. In this study, a modification of the ZEVALIN therapeutic regimen with a lower specific activity Y-90 ZEVALIN dose [(Y-90 ZEVALIN at 0.3 mCi/kg (11.1 MBq/kg)] was used. Objective, durable clinical responses were observed [67% ORR (95% CI: 48-85%), 11.8 months median DR (range: 4-17 months)] and resulted in a greater incidence of hematologic toxicity (see ADVERSE REACTIONS) than in Studies 1 and 2.

INDICATIONS AND USAGE

ZEVALIN, as part of the ZEVALIN therapeutic regimen (see DOSAGE AND ADMINISTRATION), is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma. Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or refractory patient population is based on overall response rates (see CLINICAL STUDIES). The effects of the ZEVALIN therapeutic regimen on survival are not known.

CONTRAINDICATIONS

The ZEVALIN therapeutic regimen is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product, including Rituximab, yttrium chloride, and indium chloride.

WARNINGS (SEE BOXED WARNING)

Altered Biodistribution: Y-90 ZEVALIN should not be administered to patients with altered biodistribution of In-111 ZEVALIN. The expected biodistribution of In-111 ZEVALIN includes easily detectable uptake in the blood pool areas on the first day image, with less activity in the blood pool areas on the second or third day image;

moderately high to high uptake in normal liver and spleen during the first day and the second or third day image; and moderately low or very low uptake in normal kidneys, urinary bladder, and normal bowel on the first day image and the second or third day image. Altered biodistribution of In-111 ZEVALIN can be characterized by diffuse uptake in normal lung more intense than the cardiac blood pool on the first day image or more intense than the liver on the second or third day image; kidneys with greater intensity than the liver on the posterior view of the second or third day image; or intense areas of uptake throughout the normal bowel comparable to uptake by the liver on the second or third day images.

Severe Infusion Reactions (See PRECAUTIONS, Hypersensitivity): The ZEVALIN therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These severe reactions typically occur during the first Rituximab infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of Rituximab, In-111 ZEVALIN, or Y-90 ZEVALIN administration. The most severe manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. **Because the ZEVALIN therapeutic regimen includes the use of Rituximab, see also prescribing information for RITUXAN (Rituximab).**

Cytopenias (See ADVERSE REACTIONS, Hematologic Events):
The most common severe adverse events reported with the ZEVALIN therapeutic regimen were thrombocytopenia (61% of patients with platelet counts <50,000 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count (ANC) <1,000 cells/mm^3) in patients with ≥150,000 platelets/mm^3 prior to treatment. Both incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000 cells/mm^3). For all patients, the median time to nadir was 7-9 weeks and the median duration of cytopenias was 22-35 days. In <5% of cases, patients experienced severe cytopenia that extended beyond the prospectively defined protocol treatment period of 12

weeks following administration of the ZEVALIN therapeutic regimen. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anti-cancer therapy, or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions.

Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in a minority of patients in clinical studies. Careful monitoring for and management of cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3 months after use of the ZEVALIN therapeutic regimen are necessary. Caution should be exercised in treating patients with drugs that interfere with platelet function or coagulation following the ZEVALIN therapeutic regimen and patients receiving such agents should be closely monitored.

The ZEVALIN therapeutic regimen should not be administered to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve, e.g., prior myeloablative therapies; platelet count <100,000 cells/mm^3; neutrophil count <1,500 cells/mm^3; hypocellular bone marrow (≤15% cellularity or marked reduction in bone marrow precursors); or to patients with a history of failed stem cell collection.

Secondary Malignancies: Out of 349 patients treated with the ZEVALIN therapeutic regimen, three cases of acute myelogenous leukemia and two cases of myelodysplastic syndrome have been reported following the ZEVALIN therapeutic regimen (see ADVERSE REACTIONS).

Pregnancy Category D: Y-90 ZEVALIN can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Creutzfeldt-Jakob disease (CJD): This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS

The ZEVALIN therapeutic regimen is intended as a single course treatment. The safety and toxicity profile from multiple courses of the ZEVALIN therapeutic regimen or of other forms of therapeutic irradiation preceding, following, or in combination with the ZEVALIN therapeutic regimen have not been established.

Radionuclide Precautions: The contents of the ZEVALIN kit are not radioactive. However, during and after radiolabeling ZEVALIN with In-111 or Y-90, care should be taken to minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

Hypersensitivity: Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of ZEVALIN. Patients who have received murine proteins should be screened for human anti-mouse antibodies (HAMA). Patients with evidence of HAMA have not been studied and may be at increased risk of allergic or serious hypersensitivity reactions during ZEVALIN therapeutic regimen administrations.

Immunization: The safety of immunization with live viral vaccines following the ZEVALIN therapeutic regimen has not been studied. Also, the ability of patients who received the ZEVALIN therapeutic regimen to generate a primary or anamnestic humoral response to any vaccine has not been studied.

Laboratory Monitoring: Complete blood counts (CBC) and platelet counts should be obtained weekly following the ZEVALIN therapeutic regimen and should continue until levels recover. CBC and platelet counts should be monitored more frequently in patients who develop severe cytopenia, or as clinically indicated.

Drug Interactions: No formal drug interaction studies have been performed with ZEVALIN. Due to the frequent occurrence of severe and prolonged thrombocytopenia, the potential benefits of medications which interfere with platelet function and/or anticoagulation should be weighed against the potential increased risks of bleeding and hemorrhage. Patients receiving medications that interfere with platelet function or coagulation should have more frequent laboratory monitoring for thrombocytopenia. In addition, the transfusion practices for such patients may need to be modified given the increased risk of bleeding.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of the ZEVALIN therapeutic regimen, or to determine its effects on fertility in males or females. However, radiation is a potential carcinogen and mutagen. The ZEVALIN therapeutic regimen results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There have been no studies to evaluate whether the ZEVALIN therapeutic regimen causes hypogonadism, premature menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential risk that the ZEVALIN therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the ZEVALIN therapeutic regimen.

Pregnancy Category D: SEE WARNINGS.

Nursing Mothers: It is not known whether ZEVALIN is excreted in human milk. Because human IgG is excreted in human milk and the potential for ZEVALIN exposure

in the infant is unknown, women should be advised to discontinue nursing and formula feeding should be substituted for breast feedings (see CLINICAL PHARMACOLOGY).

Geriatric Use: Of 349 patients treated with the ZEVALIN therapeutic regimen in clinical studies, 38% (132 patients) were age 65 years and over, while 12% (41 patients) were age 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use: The safety and effectiveness of the ZEVALIN therapeutic regimen in children have not been established.

ADVERSE REACTIONS

Safety data, except where indicated, are based upon 349 patients treated in 5 clinical studies with the ZEVALIN therapeutic regimen (see DOSAGE AND ADMINISTRATION). Because the ZEVALIN therapeutic regimen includes the use of Rituximab, also see prescribing information for RITUXAN (Rituximab).

The most serious adverse reactions caused by the ZEVALIN therapeutic regimen include infections (predominantly bacterial in origin), allergic reactions (bronchospasm and angioedema), and hemorrhage while thrombocytopenic (resulting in deaths). In addition, patients who have received the ZEVALIN therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion reactions have occurred following the infusion of Rituximab. Please refer to the BOXED WARNINGS and WARNINGS sections for detailed descriptions of these reactions.

The most common toxicities reported were neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity. Table 7 lists adverse events that occurred in ≥ 5% of patients. A more

372 detailed description of the incidence and duration of hematologic toxicities, according to
373 baseline platelet count (as an indicator of bone marrow reserve) is provided in Table 8,
374 Hematologic Toxicity.

Table 7.
Incidence of Adverse Events in ≥ 5 % of Patients Receiving the ZEVALIN therapeutic regimen [1]
(N = 349)

	All Grades %	Grade 3/4 %
Any Adverse Event	**99**	**89**
Body as a Whole	**80**	**12**
Asthenia	43	3
Infection	29	5
Chills	24	<1
Fever	17	1
Abdominal Pain	16	3
Pain	13	1
Headache	12	1
Throat Irritation	10	0
Back Pain	8	1
Flushing	6	0
Cardiovascular System	**17**	**3**
Hypotension	6	1
Digestive System	**48**	**3**
Nausea	31	1
Vomiting	12	0
Diarrhea	9	<1
Anorexia	8	0
Abdominal enlargement	5	0
Constipation	5	0
Hemic and Lymphatic System	**98**	**86**
Thrombocytopenia	95	63
Neutropenia	77	60
Anemia	61	17
Ecchymosis	7	<1
Metabolic and Nutritional Disorders	**23**	**3**
Peripheral Edema	8	1
Angioedema	5	<1
Musculoskeletal System	**18**	**1**
Arthralgia	7	1
Myalgia	7	<1
Nervous System	**27**	**2**
Dizziness	10	<1
Insomnia	5	0
Respiratory System	**36**	**3**
Dyspnea	14	2
Increased Cough	10	0
Rhinitis	6	0
Bronchospasm	5	0
Skin and Appendages	**28**	**1**
Pruritus	9	<1
Rash	8	<1
Special Senses	**7**	**<1**
Urogenital System	**6**	**<1**

[1] Adverse events were followed for a period of 12 weeks following the first Rituximab infusion of the ZEVALIN therapeutic regimen

Note: All adverse events are included, regardless of relationship.

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The following adverse events (except for those noted in Table 7) occurred in between 1 and 4% of patients during the treatment period: urticaria (4%), anxiety (4%), dyspepsia (4%), sweats (4%), petechia (3%), epistaxis (3%), allergic reaction (2%), and melena (2%).

Severe or life-threatening adverse events occurred in 1-5% of patients (except for those noted in Table 7) consisted of pancytopenia (2%), allergic reaction (1%), gastrointestinal hemorrhage (1%), melena (1%), tumor pain (1%), and apnea (1%). The following severe or life threatening events occurred in <1% of patients: angioedema, tachycardia, urticaria, arthritis, lung edema, pulmonary embolus, encephalopathy, hematemesis, subdural hematoma, and vaginal hemorrhage.

Hematologic Events: Hematologic toxicity was the most frequently observed adverse event in clinical trials. Table 8 presents the incidence and duration of severe hematologic toxicity for patients with normal baseline platelet count (= 150,000 cells/mm^3) treated with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3) at baseline who were treated with a modified ZEVALIN therapeutic regimen that included a lower specific activity Y-90 ZEVALIN dose at 0.3 mCi/kg (11.1 MBq/kg).

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Table 8.
Severe Hematologic Toxicity

	ZEVALIN therapeutic regimen using 0.4 mCi/kg Y-90 Dose (14.8 MBq/kg)	Modified ZEVALIN therapeutic regimen using 0.3 mCi/kg Y-90 dose (11.1 MBq/kg)
ANC		
Median nadir (cells/mm^3)	800	600
Per Patient Incidence ANC <1000 cells/mm^3	57%	74%
Per Patient Incidence ANC <500 cells/mm^3	30%	35%
Median Duration (Days)* ANC <1000 cells/mm^3	22	29
Platelets		
Median nadir (cells/mm^3)	41,000	24,000
Per Patient Incidence Platelets <50,000 cells/mm^3	61%	78%
Per Patient Incidence Platelets <10,000 cells/mm^3	10%	14%
Median Duration (Days)# Platelets <50,000 cells/mm^3	24	35

*Median duration of neutropenia for patients with ANC <1000 cells/mm^3 (Date from last laboratory value showing ANC =1000 cells/mm^3 to date of first laboratory value following nadir showing ANC =1000 cells/mm^3, censored at initiation of next treatment ordeath)

Median duration of thrombocytopenia for patients with platelets <50,000 cells/mm^3 (Date from last laboratory value showing platelet count =50,000 cells/mm^3 to date of first laboratory value following nadir showing platelet count =50,000 cells/mm^3, censored at initiation of next treatment or death)

Median time to ANC nadir was 62 days, to platelet nadir was 53 days, and to hemoglobin nadir was 68 days. Information on growth factor use and platelet transfusions is based on 211 patients for whom data were collected. Filgrastim was given to 13% of patients and erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood cell transfusions to 20%.

Infectious Events: During the first 3 months after initiating the ZEVALIN therapeutic regimen, 29% of patients developed infections. Three percent of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract

infection. Life threatening infections were reported for 2% of patients that included sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with ZEVALIN, 6% of patients developed infections. Two percent of patients had serious infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis. One percent of patients had life threatening infections that included bacterial pneumonia, respiratory disease, and sepsis.

Secondary Malignancies: A total of 2% of patients developed secondary malignancies following the ZEVALIN therapeutic regimen. One patient developed a Grade 1 meningioma, three developed acute myelogenous leukemia, and two developed a myelodysplastic syndrome. The onset of a second cancer was 8-34 months following the ZEVALIN therapeutic regimen and 4 to 14 years following the patients' diagnosis of NHL.

Immunogenicity: Of 211 patients who received the ZEVALIN therapeutic regimen in clinical trials and who were followed for 90 days, there were eight (3.8%) patients with evidence of human anti-mouse antibody (HAMA) (n=5) or human anti-chimeric antibody (HACA) (n=4) at any time during the course of the study. Two patients had low titers of HAMA prior to initiation of the ZEVALIN therapeutic regimen; one remained positive without an increase in titer while the other had a negative titer post-treatment. Three patients had evidence of HACA responses prior to initiation of the ZEVALIN therapeutic regimen; one had a marked increase in HACA titer while the other two had negative titers post-treatment. Of the three patients who had negative HAMA or HACA titers prior to the ZEVALIN therapeutic regimen, two developed HAMA in absence of HACA titers, and one had both HAMA and HACA positive titers post-treatment. Evidence of immunogenicity may be masked in patients who are lymphopenic. There has not been adequate evaluation of HAMA and HACA at delayed timepoints, concurrent with the recovery from lymphopenia at 6-12 months, to establish whether masking of the immunogenicity at early timepoints occurs. The data reflect the percentage of patients

whose test results were considered positive for antibodies to Ibritumomab or Rituximab using kinetic enzyme immunoassays to Ibritumomab and Rituximab. The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling and concomitant medications. Comparisons of the incidence of HAMA/HACA to the ZEVALIN therapeutic regimen with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

Doses as high as 0.52 mCi/kg (19.2 MBq/kg) of Y-90 ZEVALIN were administered in ZEVALIN therapeutic regimen clinical trials and severe hematological toxicities were observed. No fatalities or second organ injury resulting from overdosage administrations were documented. However, single doses up to 50 mCi (1850 MBq) of Y-90 ZEVALIN, and multiple doses of 20 mCi (740 MBq) followed by 40 mCi (1480 MBq) of Y-90 ZEVALIN were studied in a limited number of subjects. In these trials, some patients required autologous stem cell support to manage hematological toxicity.

DOSAGE AND ADMINISTRATION

The ZEVALIN therapeutic regimen is administered in two steps: Step 1 includes a single infusion of 250 mg/m^2 Rituximab (not included in the ZEVALIN kits) preceding a fixed dose of 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN administered as a 10 minute IV push. Step 2 follows step 1 by seven to nine days and consists of a second infusion of 250 mg/m^2 of Rituximab prior to 0.4 mCi/kg of Y-90 ZEVALIN administered as a 10 minute IV push.

Rituximab Administration: NOTE THAT THE DOSE OF RITUXIMAB IS LOWER WHEN USED AS PART OF THE ZEVALIN THERAPEUTIC REGIMEN, AS COMPARED TO THE DOSE OF RITUXIMAB WHEN USED AS A SINGLE AGENT. DO NOT ADMINISTER RITUXIMAB AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur (see

WARNINGS). Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of Rituximab.

ZEVALIN Therapeutic Regimen Dose Modification in Patients with Mild Thrombocytopenia: The Y-90 ZEVALIN dose should be reduced to 0.3 mCi/kg (11.1 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000 cells/mm^3.

Two separate and distinctly-labeled kits are ordered for the preparation of a single dose each of In-111 ZEVALIN and Y□90 ZEVALIN. In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides. **Changing the ratio of any of the reactants in the radiolabeling process may adversely impact therapeutic results. In-111 ZEVALIN and Y-90 ZEVALIN should not be used in the absence of the Rituximab pre-dose.**

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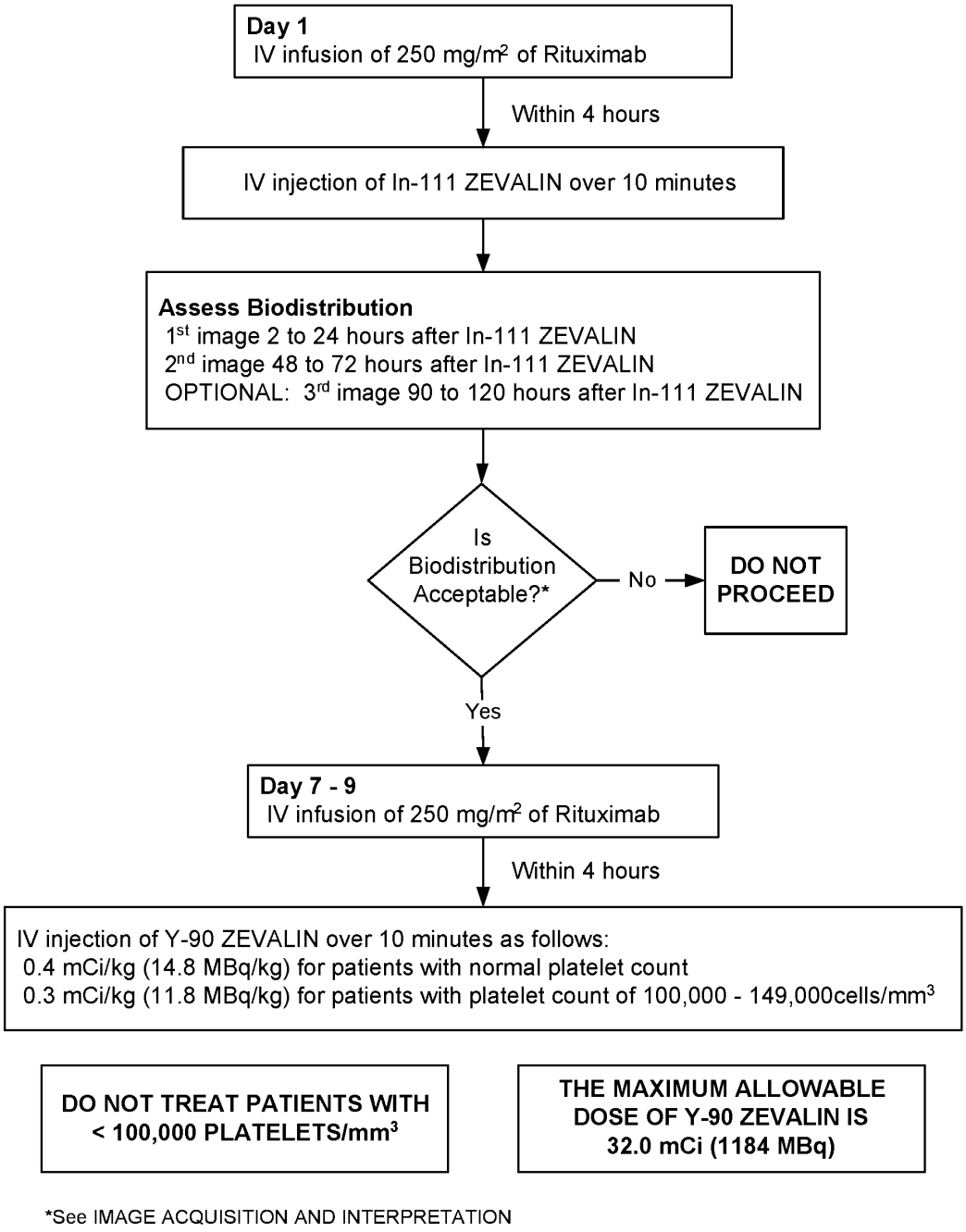
Overview of Dosing Schedule:



ZEVALIN Therapeutic Regimen Administration

Step 1:

First Rituximab Infusion: Rituximab at a dose of 250 mg/m^2 should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

In-111 ZEVALIN Injection: Within 4 hours following completion of the Rituximab dose, 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN is injected intravenously (I.V.) over a period of 10 minutes.

Step 2:

Step 2 of the ZEVALIN therapeutic regimen is initiated seven to nine days following Step 1 administrations.

Second Rituximab Infusion: Rituximab at a dose of 250 mg/m^2 is administered I.V. at an initial rate of 100 mg/hr (50 mg/hr if infusion related events were documented during the first Rituximab administration) and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr, as tolerated.

Y-90 ZEVALIN Injection:

Within 4 hours following completion of the Rituximab dose, Y-90 ZEVALIN at a dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with a platelet count >150,000 cells/mm^3, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with a platelet count of 100,000-149,000 cells/mm^3 is injected intravenously (I.V.) over a period of 10 minutes. Precautions should be taken to avoid extravasation. A free flowing I.V. line should be established prior to Y-90 ZEVALIN injection. Close monitoring for evidence of extravasation during the injection of Y-90 ZEVALIN is required. If any signs or

symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. **The prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight. Do not give Y-90 ZEVALIN to patients with a platelet count <100,000/mm^3 (see WARNINGS).**

DIRECTIONS FOR PREPARATION OF RADIOLABELED ZEVALIN.

A. PREPARATION OF THE IN-111 ZEVALIN DOSE

GENERAL:

Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure. Important, significant differences exist in the preparation of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of In-111.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and during the determination of radiochemical purity of In-111 ZEVALIN. Appropriate shielding should be used during radiolabeling, and use of a syringe shield is recommended during administration to the patient. The radiolabeling of ZEVALIN shall be done according to the following directions.

Required materials not supplied in the kit:

A. Indium-111 Chloride Sterile Solution (In-111 Chloride) from Amersham Health, Inc. or Mallinckrodt, Inc.

B. Three sterile 1 mL syringes

C. One sterile 3 mL syringe

D. Two sterile 10 mL syringes with 18-20 G needles

E. Instant thin-layer chromatographic silica gel strips

F. 0.9% sodium chloride aqueous solution for the chromatography solvent

G. Developing chamber for chromatography

H. Suitable radioactivity counting apparatus

I. Filter, 0.22 micrometer, low-protein-binding

J. Vial and syringe shield

Method:

1. Sterile, pyrogen-free In-111 chloride must be used for the preparation of In-111 ZEVALIN. The use of high purity In-111 chloride manufactured by Amersham Health, Inc. or Mallinckrodt, Inc. is required.

2. Before radiolabeling, allow contents of the refrigerated carton to reach room temperature. Note: The ZEVALIN vial contains a protein solution that may develop translucent particulates. These particulates will be removed by filtration prior to administration.

3. Clean the rubber stoppers of all of the vials in the kit and the In-111 chloride vial with a suitable alcohol swab and allow to air dry.

4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to room temperature). To avoid the buildup of excessive pressure during the procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.

5. Prior to initiating the radiolabeling reaction, determine the amount of each component needed according to the directions below:

a. Calculate the volume of In-111 chloride that is equivalent to 5.5 mCi based on the activity concentration of the In-111 chloride stock.

b. The volume of 50 mM sodium acetate solution needed is 1.2 times the volume of In-111 chloride solution determined in step 5.a., above. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)

c. Calculate the volume of Formulation Buffer needed to bring the Reaction Vial contents to a final volume of 10 mL. This is the volume of Formulation Buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example, if volumes of 0.5 mL of In-111 chloride, 0.6 mL of sodium acetate and 1.0 mL of ZEVALIN were used, then the amount of formulation buffer would be 10-(0.5 + 0.6 + 1.0) = 7.9 mL.

6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM of sodium acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

7. Transfer 5.5 mCi of In-111 chloride to the Reaction Vial with a sterile 1 mL syringe. Mix the two solutions and coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

8. With a sterile 3 mL syringe, transfer 1.0 mL of ZEVALIN (Ibritumomab Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by gentle inversion or rolling. **Do not shake or agitate the vial contents, since this will cause foaming and denaturation of the protein.**

9. Allow the labeling reaction to proceed at room temperature for 30 minutes. Allowing the labeling reaction to proceed for a longer or shorter time may result in inadequate labeling.

10. **Immediately** after the 30-minute incubation period, using a sterile 10 mL syringe with a large bore needle (18 G - 20 G), transfer the calculated volume of Formulation Buffer from step 5.c. to the Reaction Vial. Gently add the Formulation Buffer down the side of the Reaction Vial. If necessary, to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not shake or agitate the vial contents. Avoid foaming.

11. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration, and affix these labels to the reaction vial and shielded reaction vial container.

12. Calculate the volume required for an In-111 ZEVALIN dose of 5 mCi. Withdraw the required volume from the Reaction Vial contents into a sterile 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The syringe should contain the dose of In-111 ZEVALIN to be administered to the patient. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume added, and the date and time of expiration, and affix these labels to the syringe and shielded unit dose container.

13. Determine Radiochemical purity. See Section C: Procedure for Determining Radiochemical Purity Section that follows DIRECTIONS FOR PREPARATION OF THE Y-90 ZEVALIN DOSE.

14. Indium-111 ZEVALIN should be stored at 2 - 8°C (36-46°F) until use and administered within 12 hours of radiolabeling.

15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen Administration: Step 1

16. Discard vials, needles and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

B. PREPARATION OF THE Y-90 ZEVALIN DOSE

GENERAL:

Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure. Important, significant differences exist in the preparation of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Y-90.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized in the preparation and during the determination of radiochemical purity of Y-90 ZEVALIN. Appropriate shielding should be used during radiolabeling, and use of a syringe shield is recommended during administration to the patient. The radiolabeling of ZEVALIN shall be done according to the following directions.

Required materials not supplied in the kit:

A. Yttrium-90 Chloride Sterile Solution from MDS Nordion (shipped directly from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit)

B. Three sterile 1 mL syringes

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C. One sterile 3 mL syringe

D. Two sterile 10 mL syringes with 18-20 G needles

E. Instant thin-layer chromatographic silica gel strips (ITLC-SG)

F. 0.9% sodium chloride aqueous solution for the chromatography solvent

G. Suitable radioactivity counting apparatus

H. Developing chamber for chromatography

I. Filter, 0.22 micrometer, low-protein-binding

J. Vial and syringe shield

Method:

1. Sterile, pyrogen-free Y-90 chloride must be used for the preparation of Y-90 ZEVALIN. The use of high purity Y-90 chloride manufactured by MDS Nordion is required.

2. Before radiolabeling, allow the contents of the refrigerated carton to reach room temperature. Note: The ZEVALIN vial contains a protein solution that may develop translucent particulates. These particulates will be removed by filtration prior to administration.

3. Clean the rubber stoppers of all of the vials in the kit and the Y-90 chloride vial with a suitable alcohol swab and allow to air dry.

4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to room temperature). To avoid the buildup of excessive pressure during the procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.

5. Prior to initiating the radiolabeling reaction, determine the amount of each component needed according to the directions below:

a. Calculate the volume of Y-90 chloride that is equivalent to 40 mCi based on the activity concentration of the Y-90 chloride stock.

b. The volume of 50 mM sodium acetate solution needed is 1.2 times the volume of Y-90 chloride solution determined in step 5.a., above. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)

c. Calculate the volume of Formulation Buffer needed to bring the Reaction Vial contents to a final volume of 10 mL. This is the volume of Formulation Buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example if the volumes were 0.5 mL of Y-90 chloride, 0.6 mL of sodium acetate and 1.3 mL of ZEVALIN, then the amount of formulation buffer would be 10-(0.5 + 0.6 + 1.3) = 7.6 mL.

6. With a sterile 1 mL syringe, transfer the calculated volume 50 mM of sodium acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

7. Transfer 40 mCi of Y-90 chloride to the Reaction Vial with a sterile 1 mL syringe. Mix the two solutions and coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

8. With a sterile 3 mL syringe, transfer 1.3 mL of ZEVALIN (Ibritumomab Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by gentle inversion or rolling. **Do not shake or agitate the vial contents, since this will cause foaming and denaturation of the protein.**

9. Allow the labeling reaction to proceed at room temperature for 5 minutes. Allowing the labeling reaction to proceed for a longer or shorter time may result in inadequate labeling.

10. **Immediately** after the 5-minute incubation period, using a sterile 10 mL syringe with a large bore needle (18 G - 20 G), transfer the calculated volume of Formulation Buffer from step 5.c. to the Reaction Vial, terminating incubation. Gently add the Formulation Buffer down the side of the Reaction Vial. If necessary to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not shake or agitate the vial contents. Avoid foaming.

11. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume, and the date and time of expiration and affix these labels to the reaction vial and shielded reaction vial container.

12. Calculate the volume required for a Y-90 ZEVALIN dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with normal platelet count, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet count of 100,000 - 149,000 cells/mm^3. **The prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight.** Withdraw the required volume from the Reaction Vial contents into a sterile 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Y-90. The syringe should contain the dose of Y-90 ZEVALIN to be administered to the patient, and should be within 10% of the actual prescribed dose of Y-90 ZEVALIN, not to exceed a maximum dose of 32.0 mCi. Do not exceed ± 10% of the prescribed dose. Using the supplied labels, record the patient identification, the date and time of preparation, the total activity and volume added, and the date

and time of expiration and affix these labels to the syringe and shielded unit dose container.

13. Determine Radiochemical Purity. See Section C: Procedure for Determining Radiochemical Purity Section that follows these DIRECTIONS FOR PREPARATION OF THE Y-90 ZEVALIN DOSE.

14. Yttrium-90 ZEVALIN should be stored at 2 - 8°C (36-46°F) until use and administered within 8 hours of radiolabeling.

15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen Administration: Step 2.

16. Discard vials, needles and syringes in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

Yttrium-90 ZEVALIN is suitable for administration on an outpatient basis. Beyond the use of vial and syringe shields for preparation and injection, no special shielding is necessary.

C. PROCEDURE FOR DETERMINING RADIOCHEMICAL PURITY (RCP)
The following procedure should be used for both In-111 ZEVALIN and Y-90 ZEVALIN:

A. At room temperature, place a small drop of either In-111 ZEVALIN or Y-90 ZEVALIN at the origin of an ILTC-SG strip.
B. Place the ITLC-SG strip into a chromatography chamber with the origin at the bottom and the solvent front at the top. Allow the solvent (0.9% NaCl) to migrate at least 5 cm from the bottom of the strip. Remove the strip from the chamber and cut the strip in half. Count each half of the ITLC-SG strip for one-minute (CPM) with a suitable counting apparatus.

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C. Calculate the percent RCP as follows:

$$\% \text{ RCP} = \frac{\text{CPM bottom half}}{\text{CPM bottom half} + \text{CPM top half}} \text{ X } 100$$

D. If the radiochemical purity is <95%, the ITLC procedure should be repeated. If repeat testing confirms that radiochemical purity is <95%, the preparation should not be administered.

IMAGE ACQUISITION AND INTERPRETATION

The biodistribution of In-111 ZEVALIN should be assessed by a visual evaluation of whole body planar view anterior and posterior gamma images at 2 - 24 hours and 48 □72 hours after injection. To resolve ambiguities, a third image at 90 □120 hours may be necessary. Images should be acquired using a large field of view gamma camera equipped with a medium energy collimator. The gamma camera should be calibrated using the 171 and 245 keV photopeaks for In-111 with a 15% □20% symmetric window. Using a 256 x 1024 computer acquisition matrix, the scan speed should be 10 cm/min for the first scan, 7 cm/min for the second scan, and 5 cm/min for the optional third scan.

The radiopharmaceutical is expected to be easily detectable in the blood pool areas at the first time point, with less activity in the blood pool on later images. Moderately high to high uptake is seen in the normal liver and spleen, with low uptake in the lungs, kidneys, and urinary bladder. Localization to lymphoid aggregates in the bowel wall has been reported. Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor-bearing areas in normal organs may be seen as areas of increased or decreased intensity.

If a visual inspection of the gamma images reveals an altered biodistribution, the patient should not proceed to the Y-90 ZEVALIN dose. The patient may be considered to have an altered biodistribution if the blood pool is not visualized on the first image indicating rapid clearance of the radiopharmaceutical by the reticuloendothelial system to the liver, spleen, and/or marrow. Other potential examples of altered biodistribution may include

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diffuse uptake in the normal lungs or kidneys more intense than the liver on the second or third image.

During ZEVALIN clinical development, individual tumor radiation absorbed dose estimates as high as 778 cGy/mCi have been reported. Although solid organ toxicity has not been directly attributed to radiation from adjacent tumors, careful consideration should be applied before proceeding with treatment in patients with very high tumor uptake next to critical organs or structures.

HOW SUPPLIED

The In-111 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with In-111. The Y-90 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with Y-90.

The kit for the preparation of a single dose of In-111 ZEVALIN includes four vials: one ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one empty Reaction vial and four identification labels.

The kit for the preparation of a single dose of Y-90 ZEVALIN includes four vials: one ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one empty Reaction vial and four identification labels.

The contents of all vials are sterile, pyrogen-free and contain no preservatives.

The Indium-111 Chloride Sterile Solution (In-111 Chloride) must be ordered separately from either Amersham Health, Inc. or Mallinckrodt, Inc. at the time the In-111 ZEVALIN kit is ordered. The Yttrium-90 Chloride Sterile Solution will be shipped directly from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit.

Storage

Store at 2 -8°C (36-46°F). Do not freeze.

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Complement-specific antibodies: Designing novel anti-inflammatories

LOUIS A. MATIS & SCOTT A. ROLLINS

Immunobiology Program, Alexion Pharmaceuticals, Inc., 25 Science Park, Suite 360, New Haven, Connecticut 06511, USA

Correspondence should be addressed to L.A.M.

The immunoglobulin variable gene repertoire generates enormous diversity through both combinatorial and somatic mutational mechanisms. Consequently, it has the capacity to produce high-affinity, exquisitely specific antibodies to a vast number of potential antigenic targets. Also, the constant domains of antibody molecules can harness effector mechanisms of the humoral and cellular immune systems *in vivo*[1]. Thus, monoclonal antibodies hold great promise for application to a wide range of diagnostic and therapeutic clinical settings, as evidenced by the current clinical use of monoclonal antibody-derived products in transplantation[2], myocardial revascularization[3] and tumour imaging[4].

Antibody engineering

Recent advances in the molecular engineering of immunoglobulin genes have further broadened the potential utility of monoclonal antibody-based therapeutics. For example, Fab fragments, as well as covalently linked single-chain fragments consisting of the heavy and light chain variable regions (scFvs), have been derived that retain the specificity and affinity of the original intact antibody[1,5]. These smaller molecules display distinct properties, such as reduced serum half-life and enhanced tissue penetration, which may be particularly useful for certain clinical situations such as tumour imaging and therapy, or for the treatment of acute inflammation. In addition, they are amenable to modifications, such as covalent linkage to genes encoding toxins, enzymes or cytokines, or to the incorporation of dual specificity or catalytic function, which can impart novel functional properties to these monoclonal antibody-derived molecules[1,6–8]. Further, advances in combinatorial library and phage display technology may allow the recapitulation *in vitro* of the natural processes of selection and repertoire maturation to yield high-affinity, functionally useful antibodies without the requirement for immunization and hybridoma production[5].

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Chronic application of monoclonal antibody therapy requires 'humanization' to prevent a host immune response from developing. Current methods to accomplish this include complementarity-determining region (CDR) grafting, or replacement of the hypervariable loops of a human antibody with those of the murine monoclonal antibody of desired specificity, selection by phage display[9], or potentially using HumAb mice, in which endogenous Ig loci have been inactivated by mutation and then replaced by large segments of human immunoglobulin genomic loci[10,11].

Complement and inflammation

Complement proteins represent an attractive target for the development of monoclonal antibody-based anti-inflammatory therapeutics. The complement system is composed of more than 20 serum proteins that interact in a precise series of enzymatic cleavage and membrane binding events leading to the generation of products with immunoprotective, immunoregulatory, and pro-inflammatory properties[12].

Complement can be activated through either of two distinct enzymatic cascades, referred to as the classical and alternative pathways (Fig. 1). The classical pathway is generally initiated by the interaction of C1q with antibody/antigen complexes, whereas the alternative pathway is initiated by deposition of C3b on a variety of substrates including bacterial lipopolysaccharide and cell membranes. The formation of C3b is necessary for the amplification and progression of the complement cascade through both pathways. It is the primary opsonin for many pathogenic microorganisms and, in addition, promotes the clearance as well as solubilization of immune complexes.

Both the classical and alternative pathways converge at C5, which is cleaved to form products with multiple proinflammatory effects (see Fig. 1). C5a is the most potent anaphylatoxin, inducing alterations in smooth muscle and vascular tone, as well as vascular permeability[12]. It is also a powerful 'chemotaxin' and activator of both neutrophils and monocytes. C5a-mediated cellular activation can significantly amplify inflammatory responses by inducing the release of multiple additional inflammatory mediators, including hydrolytic enzymes, cytokines, arachidonic acid metabolites and reactive oxygen species. C5 cleavage also leads to the formation of C5b-9, or the membrane attack complex (MAC). There is now strong evidence that the MAC may play an important role in inflammation in addition to its role as a lytic pore-forming complex, as it also stimulates the release of many of the same proinflammatory molecules as C5a and promotes thrombosis following deposition on platelets and endothelium[13].

Complement in disease

With improved methodology for the detection of activated components in inflamed tissue and biological fluids, the complement system has been increasingly implicated as contributing to the pathogenesis of numerous disease states (see table)[14]. These include immunological diseases characterized by antibody-mediated classical pathway activation, as well as vascular inflammatory conditions in which the alternative pathway is induced after reperfusion of ischaemic tissue. Distinct mechanisms of complement activation are associated with some diseases, such as Alzheimer's disease, since the β-amyloid protein has been shown to bind to C1q directly and thereby to activate the classical pathway *in vitro*[15]. In many conditions there is evidence for simultaneous activation of both classical and alternative pathways.

Modelling anti-C5 therapy

Because activation of C5 represents a critical step in the inflammatory cascade and as there are no known naturally existing molecules that uniquely block C5 activation, the C5 molecule represents an attractive target for development of a monoclonal antibody-based complement inhibitor. Therapeutic inhibition of the complement cascade at C5 would block the formation of the potent inflammatory mediators C5a and C5b-9 via both the classical and alternative pathways, while preserving the patient's

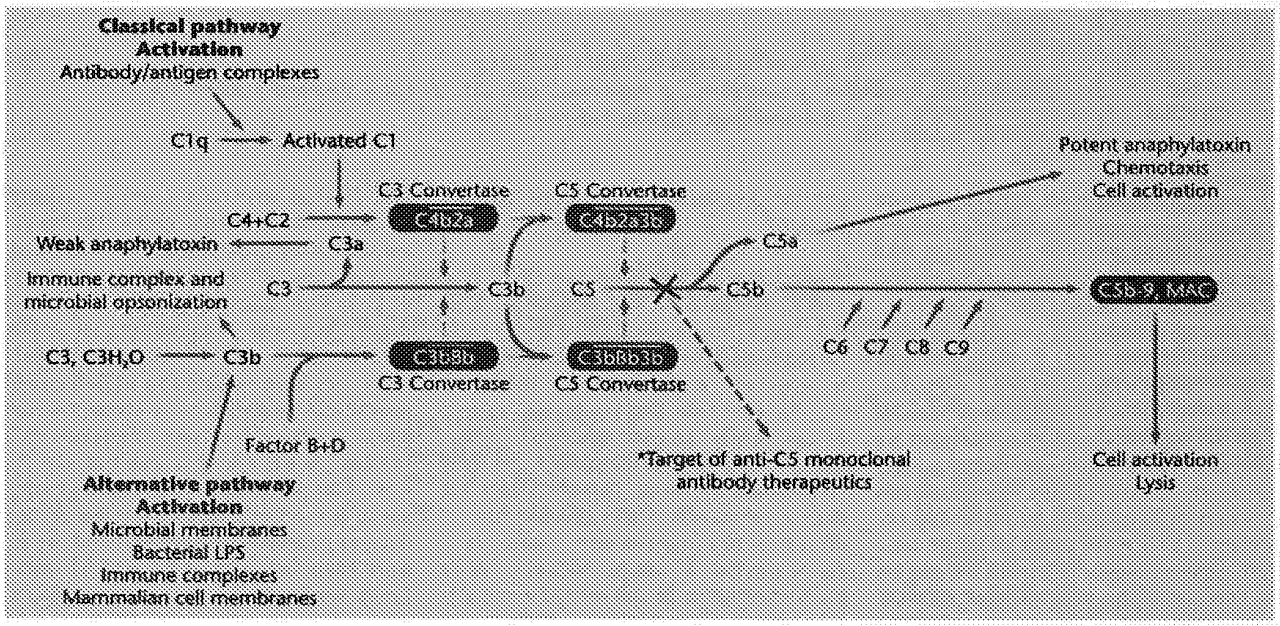

Fig. 1 Components of the complement cascade.

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ability to generate the critical immunoprotective and immunoregulatory functions of C3b-mediated opsonization and immune clearance. Therefore, we have developed recombinant C5-specific monoclonal antibodies and their engineered derivatives as soluble anti-inflammatory biopharmaceuticals. The principle of anti-C5 monoclonal antibody therapy of inflammatory disease has been examined in several preclinical models. Using a monoclonal antibody specific for mouse C5, we have shown that systemic anti-C5 monoclonal antibody administration efficiently inhibited complement *in vivo* (inhibiting serum haemolytic activity for as long as six to seven days after a single intravenous injection), and that treatment with anti-C5 monoclonal antibody was therapeutically effective in two distinct models of immune complex nephritis and autoimmune disease (Y. Wang *et al.*, manuscript in preparation). In these models, continuous treatment with anti-C5 monoclonal antibody for up to six months was not associated with any negative side effects. In murine collagen-induced arthritis, anti-C5 monoclonal antibody therapy not only prevented the onset of disease, but, most importantly, was also highly effective in ameliorating the course of established arthritis[16]. In an *ex vivo* model of cardiopulmonary bypass (CPB)-induced inflammation, administration of a prototype anti-human C5 monoclonal antibody completely blocked C5a and C5b-9 generation in whole human blood, as well as both the platelet and leukocyte activation that normally occur during CPB[17]. Thus, anti-C5 monoclonal antibody therapy effectively modulated inflammatory responses in both *in vivo* and *ex vivo* models.

Diseases associated with complement activation[1]

Renal	Rheumatological	Neurological
Lupus nephritis	Lupus arthritis	Cerebral lupus
Membranoproliferative GN	Rheumatoid arthritis	Guillian-Barré syndrome
Membranous nephritis	Sjögren's syndrome	Alzheimer's disease
IgA nephropathy	Behçet's syndrome	Multiple sclerosis
	Systemic sclerosis	Myasthenia gravis
Vascular/pulmonary	**Biocompatibility**	**Dermatological**
Atherosclerosis	Post-CPB inflammation	Vasculitis
Myocardial infarction	Haemodialysis	Pemphigus
Stroke	Catheter reactions	Bullous pemphigoid
ARDS	Platelet storage	Phototoxic reactions
Reperfusion injury	Transplant rejection	Thermal burns
Allergy	**Infection**	**Other**
Anaphylaxis	Septic shock	Inflammatory bowel disease
Asthma	Viral infection	Thyroiditis
Skin reactions	Bacterial infection	Infertility
		PNH
		Haemolytic anaemia

[1]Disease association with complement activation has been demonstrated by the presence of activated complement components in biological fluids and/or deposition of activated complement components in diseased tissue. GN, glomerulonephritis; ARDS, adult respiratory distress syndrome; CPB, cardiopulmonary bypass; PNH, paroxysmal nocturnal haemoglobinuria.

Recombinant anti-C5 antibodies

To generate a human C5-specific monoclonal antibody for clinical development, mice were immunized with purified human C5 and candidate monoclonals were screened in high throughput *in vitro* assays for their ability to block both C5a and C5b-9 generation via the classical and alternative pathways. From this effort a highly potent anti-C5 monoclonal antibody was derived with very high affinity (K_d < 100 pM), capable of blocking complement activation at monoclonal antibody/C5 molar ratios as low as 0.5:1. The genes encoding the variable regions of this monoclonal antibody have been cloned and several recombinant forms have been engineered. Both recombinant Fab and scFv variants have been derived and shown to bind C5 with similar affinity and to block C5 activation at the same molar ratio as the intact antibody. In addition, humanized recombinant anti-C5 monoclonal antibody and scFv that retain the binding affinity and complement inhibitory activity of their murine counterparts have been produced by CDR grafting (M. Evans, manuscript in preparation).

The ability of an scFv derivative of a C5-specific monoclonal antibody to inhibit complement *in vivo* was tested by generating and administering intravenously a C5-specific scFv cross-reactive with primate complement[18]. This scFv-inhibited serum complement haemolytic activity for up to 2 hours following administration of a single intravenous bolus, consistent with the more rapid clearance of scFvs relative to intact monoclonal antibodies. C5 inhibition by an intravenously administered scFv also demonstrated that the functional domains of the immunoglobulin constant region were not required for complement inhibition *in vivo*. The efficacy and pharmacokinetic profile of the anti-C5 scFv suggest that it may be a useful anti-inflammatory agent in acute settings such as CPB or ischaemia/reperfusion injury associated with myocardial infarction.

In summary, we have shown that inhibition of C5 activation with high-affinity monoclonal antibodies represents a novel and potentially safe and effective approach to ameliorate inflammation in a variety of clinical settings. The potent anti-C5 activity of the scFv molecule further suggests that it may be possible to define minimal peptide sequences that retain C5 inhibitory activity, and thereby ultimately design orally available small molecule peptidomimetics. With recent advances in antibody engineering, monoclonal antibody-based therapeutic approaches appear to be well poised to achieve their anticipated clinical potential.

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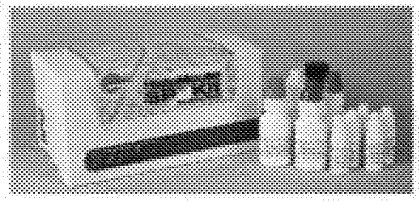
ON THE MARKET

KITS



Immunohistochemistry detection kit for researchers using rodent models in research.

The HistoMouse SP kit from Zymed Laboratories is designed to **detect mouse primary antibodies on mouse tissue and cells** immunologically, without causing background staining (resulting from the anti-mouse secondary antibody binding to endogenous mouse IgG in the sample). Zymed's approach is said to block the endogenous mouse IgG in the tissue. The new kit contains blocker, biotinylated secondary antibody, streptavidin–horseradish peroxidase, the AEC substrate system, counterstain and mounting solution. It can be used to detect mouse, rabbit, rat and guinea pig primary antibodies on mouse or rat tissue and cells.
Reader Service No. 150
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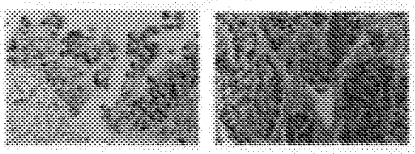
ANTIBODIES

Available from Kamiya Biomedical — an **anti-angiotensin-converting enzyme** (ACE) monoclonal antibody (clone 9B9). ACE has been implicated in many diseases, including infection with the human immunodeficiency virus, myocardial infarction, hypertension, sarcoidosis, restenosis, cardiomyopathy, stroke and diabetes. The monoclonal antibody reacts specifically with ACE of human, monkey, rat, hamster, cat and guinea pig origin. It can be used in immunohistochemistry, immunoprecipitation, immunoassays, radioimmunoimaging, antibody–drug targeting to the lung, and in the estimation of lung vessel injury in animal models.
Reader Service No. 151
Tel. (+1) 805-374-1380
Fax (+1) 805-374-1385

Neurotrophic factors, receptor and antibodies.

Both **human and recombinant rat ciliary neurotrophic factor** (CNTF) can be obtained from R&D Systems. The activities of these CNTF proteins have been measured in a human erythroleukaemic cell line (TF-1) bioassay as well as by their ability to support the survival and neurite outgrowth of cultured embryonic chick dorsal root ganglia. In addition, R&D Systems offers two **anti-CNTF antibodies** — a polyclonal and a monoclonal anti-human CNTF. **Soluble gp130 protein** and both **monoclonal and polyclonal anti-human gp130 antibodies** are available. The anti-gp130 antibodies block the cell-surface human gp130-mediated bioactivities induced by IL-6, IL-11, LIF and OSM, in addition to CNTF.
Reader Service No. 152
Tel. (+44) (0) 1235-531074
Fax (+44) (0) 1235-533420

A total of nine new antibodies are available from Transduction Laboratories for the **study of proteins involved in cell adhesion**. The catenins (α-, β- and γ-) are cytoplasmic proteins that bind to the highly conserved cytoplasmic tail of the E-cadherin (also known as uvomorulin) molecule. The cadherins are transmembrane adhesion molecules that are found along with catenins at adherens junctions (zonula adherens). These junctions are thought to be critical for cell–cell adhesion, signal transmission between neighbouring cells, and for anchoring the actin cytoskeleton. Antibodies to P-cadherin, cadherin-5, cadherin-11 and desmoglein are also available. All four can be used in western blotting and immunocytochemistry with a variety of species. Antibodies to E-cadherin, α-catenin and β-catenin can also be used under native conditions in immunoprecipitation. Completing the line-up are antibodies against L1 glycoprotein for cell adhesion studies in neuronal cells.
Reader Service No. 153
Tel. (+1) 606-277-1399
Fax (+1) 606-276-2251



Rb (Ab-5) staining of formalin-fixed, paraffin-embedded normal human bladder after thermal pretreatment, left, and MIB-1 (Ab-1) staining of highly proliferative lung tumour.

Oncogene Science recently announced the availability of two new **antibodies directed against the Rb tumour suppressor gene protein** (p105). Rb (Ab-5), clone LM95.1, is said to stain formalin-fixed, paraffin-embedded human tissues and will immunoblot the Rb protein. Rb (Ab-6), clone AF11, on the other hand, will react with the Rb protein from a

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By taking advantage of a radiation-inducible promoter, it is possible to control, both spatially and temporally, gene transcription. Hallahan *et al.* (pages 786–791) have linked such a promoter to the tumour necrosis factor-α (TNF-α) gene and demonstrate an increased ability to treat, *in vivo*, xenografted mouse tumours. Shown is the immunohistochemical detection of TNF-α seen as granular intracytoplasmic staining within the human epithelial tumour cells.

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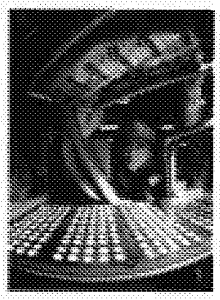

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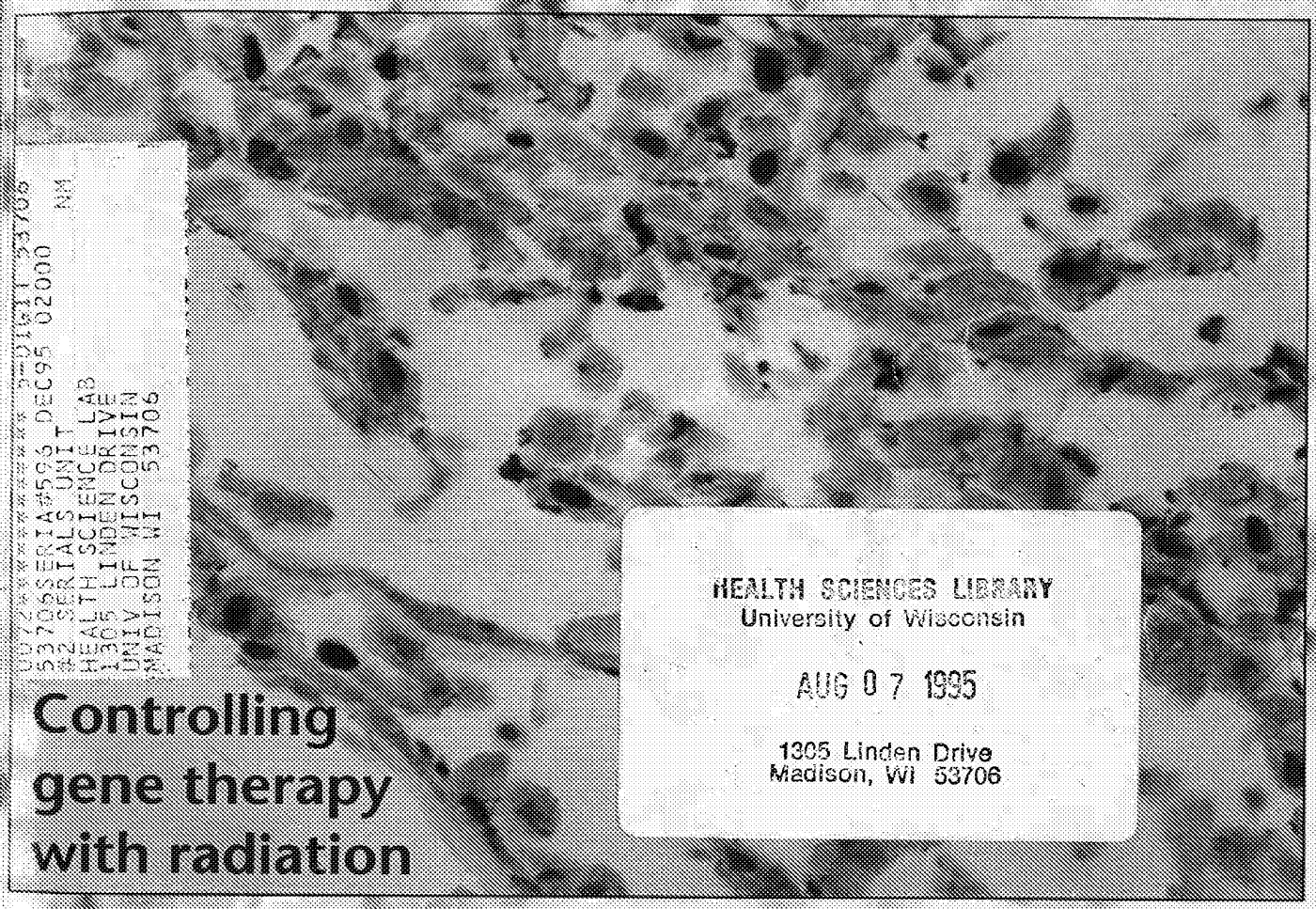

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SYNAGIS® (PALIVIZUMAB)
for Intramuscular Administration

DESCRIPTION: Synagis® (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Palivizumab is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L gene K104 with Jκ-4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process which involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis® (palivizumab) is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis® (palivizumab) is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis® (palivizumab) is to be administered by intramuscular injection only. Upon reconstitution, Synagis® (palivizumab) contains the following excipients: 47 mM histidine, 3.0 mM glycine and 5.6% mannitol and the active ingredient, palivizumab, at a concentration of 100 milligrams per mL solution. The reconstituted solution should appear clear or slightly opalescent.

CLINICAL PHARMACOLOGY: *Mechanism of Action:* Synagis® (palivizumab) exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis® (palivizumab) (5). Synagis® (palivizumab) serum concentrations of = 40 μg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis® (palivizumab) was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, palivizumab significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In studies in adult volunteers Synagis® (palivizumab) had a pharmacokinetic profile similar to a human IgG1 antibody in regard to the volume of distribution and the half-life (mean 18 days). In pediatric patients less than 24 months of age, the mean half-life of Synagis® (palivizumab) was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ±SD 30 day trough serum drug concentrations of 37 ±21 μg/mL after the first injection, 57 ±41 μg/mL after the second injection, 68 ±51 μg/mL after the third injection and 72 ±50 μg/mL after the fourth injection (7). In pediatric patients given Synagis® (palivizumab) for a second season, the mean ±SD serum concentrations following the first and fourth injections were 61 ±17 μg/mL and 86 ±31μg/mL, respectively.

CLINICAL STUDIES: The safety and efficacy of Synagis® (palivizumab) were assessed in a randomized, double-blind, placebo-controlled trial (IMpact-RSV Trial) of RSV disease prophylaxis among high-risk pediatric patients (7). This trial, conducted at 139 centers in the United States, Canada and the United Kingdom, studied patients = 24 months of age with bronchopulmonary dysplasia (BPD) and patients with premature birth (= 35 weeks gestation) who were = 6 months of age at study entry. Patients with uncorrected congenital heart disease were excluded from enrollment. In this trial, 500 patients were randomized to receive five monthly placebo injections and 1,002 patients were randomized to receive five monthly injections of 15 mg/kg of Synagis® (palivizumab). Subjects were randomized into the study from November 15 to December 13, 1996, and were followed for safety and efficacy for 150 days. Ninety-nine percent of all subjects

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completed the study and 93% received all five injections. The primary endpoint was the incidence of RSV hospitalization.

RSV hospitalizations occurred among 53 of 500 (10.6%) patients in the placebo group and 48 of 1002 (4.8%) patients in the Synagis® (palivizumab) group, a 55% reduction ($p<0.001$). The reduction of RSV hospitalization was observed both in patients enrolled with a diagnosis of BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] Synagis® [palivizumab]) and patients enrolled with a diagnosis of prematurity without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] Synagis® [palivizumab]). The reduction of RSV hospitalization was observed throughout the course of the RSV season.

Among secondary endpoints, the incidence of ICU admission during hospitalization for RSV infection was lower among subjects receiving Synagis® (palivizumab) (1.3%) than among those receiving placebo (3.0%), but there was no difference in the mean duration of ICU care between the two groups for patients requiring ICU care. Overall, the data do not suggest that RSV illness was less severe among patients who received Synagis® (palivizumab) and who required hospitalization due to RSV infection than among placebo patients who required hospitalization due to RSV infection. Synagis® (palivizumab) did not alter the incidence and mean duration of hospitalization for non-RSV respiratory illness or the incidence of otitis media.

INDICATIONS AND USAGE: Synagis® (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD) and infants with a history of prematurity (≤ 35 weeks gestational age). (See *Clinical Studies* section)

CONTRAINDICATIONS: Synagis® (palivizumab) should not be used in pediatric patients with a history of a severe prior reaction to Synagis® (palivizumab) or other components of this product.

WARNINGS: Very rare cases of anaphylaxis (<1 case per 100,000 patients) have been reported following re-exposure to Synagis (palivizumab) [see Adverse Reactions, Post-Marketing Experience]. Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to palivizumab. If a severe hypersensitivity reaction occurs, therapy with palivizumab should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of palivizumab. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.**

PRECAUTIONS: *General:* Synagis® (palivizumab) is for intramuscular use only. As with any intramuscular injection, Synagis® (palivizumab) should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis® (palivizumab) have not been demonstrated for treatment of established RSV disease.

The single-use vial of Synagis® (palivizumab) does not contain a preservative. Injections should be given within 6 hours after reconstitution.

Drug Interactions: No formal drug-drug interaction studies were conducted. In the IMpact-RSV trial, the proportions of patients in the placebo and Synagis® (palivizumab) groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

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Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not performed.

Pregnancy: Pregnancy Category C: Synagis® (palivizumab) is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis® (palivizumab) can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS: In the combined pediatric prophylaxis studies of pediatric patients with BPD or prematurity involving 520 subjects receiving placebo and 1168 subjects receiving 5 monthly doses of Synagis® (palivizumab), the proportions of subjects in the placebo and Synagis® (palivizumab) groups who experienced any adverse event or any serious adverse event were similar.

Most of the safety information was derived from the IMpact-RSV trial. In this study, Synagis® (palivizumab) was discontinued in five patients: two because of vomiting and diarrhea, one because of erythema and moderate induration at the site of the fourth injection, and two because of pre-existing medical conditions which required management (one with congenital anemia and one with pulmonary venous stenosis requiring cardiac surgery). Seizures were reported in 0.6% of the placebo group and 0.4% of the Synagis® group. Deaths in study patients occurred in five of 500 placebo recipients and four of 1,002 Synagis® (palivizumab) recipients. Sudden infant death syndrome was responsible for two of these deaths in the placebo group and one death in the Synagis® (palivizumab) Adverse events which occurred in more than 1% of patients receiving Synagis® (palivizumab) in the IMpact-RSV study for which the incidence in the Synagis® (palivizumab) group was 1% greater than in the placebo group are shown in Table 1.

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Table 1. Adverse Events Occurring in IMpact-RSV Study at Greater Frequency in the Synagis® (palivizumab) Group

% of patients with:	Placebo n = 500	Synagis® (palivizumab) n = 1,002
upper respiratory infection	49.0%	52.6%
otitis media	40.0%	41.9%
rhinitis	23.4%	28.7%
rash	22.4%	25.6%
pain	6.8%	8.5%
hernia	5.0%	6.3%
SGOT increased	3.8%	4.9%
Pharyngitis	1.4%	2.6%

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Other adverse events reported in more than 1% of the Synagis® (palivizumab) group included: fever, cough, wheeze, bronchiolitis, pneumonia, bronchitis, asthma, croup, dyspnea, sinusitis, apnea, failure to thrive, nervousness, diarrhea, vomiting, and gastroenteritis, SGPT increase, liver function abnormality, study drug injections site reaction, conjunctivitis, viral infection, oral monilia, fungal dermatitis, eczema, seborrhea, anemia and flu syndrome. The incidence of these adverse events was similar between the Synagis® (palivizumab) and placebo groups.

Immunogenicity

In the Mpact-RSV trial, the incidence of anti-palivizumab antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis® (palivizumab) group. In pediatric patients receiving Synagis® (palivizumab) for a second season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in Synagis® (palivizumab) serum concentrations.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis® (palivizumab) in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis® (palivizumab) with the incidence of antibodies to other products may be misleading.

Post-Marketing Experience

The following adverse reactions have been identified and reported during post-approval use of Synagis® (palivizumab). Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Based on experience in over 400,000 patients who have received Synagis® (>2 million doses), rare severe acute hypersensitivity reactions have been reported on initial or subsequent exposure. Very rare cases of anaphylaxis (<1 case per 100,000 patients) have also been reported following re-exposure. None of the reported hypersensitivity reactions were fatal. Hypersensitivity reactions may include dyspnea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis® (palivizumab) is unknown.

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis® (palivizumab) are similar in character and frequency to those after the initial five doses.

OVERDOSAGE: No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis® (palivizumab) at a dose of 50 mg/kg.

DOSAGE AND ADMINISTRATION: The recommended dose of Synagis® (palivizumab) is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

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Synagis® (palivizumab) should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = [patient weight (kg) x 15 mg/kg ÷ 100 mg/mL of Synagis® (palivizumab)]. Injection volumes over 1 mL should be given as a divided dose.

Preparation for Administration:

- To reconstitute, remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent.
- Both the 50 mg and 100 mg vials contain an overfill to allow the withdrawal of 50 milligrams or 100 milligrams respectively when reconstituted following the directions described below.
- Slowly add 0.6 mL of sterile water for injection to the 50 mg vial or add 1.0 mL of sterile water for injection to the 100 mg vial. The vial should be gently swirled for 30 seconds to avoid foaming. DO NOT SHAKE VIAL.
- Reconstituted Synagis® (palivizumab) should stand at room temperature for a minimum of 20 minutes until the solution clarifies.
- Reconstituted Synagis® (palivizumab) does not contain a preservative and should be administered within 6 hours of reconstitution.

To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. Do not reuse syringes and needles.

HOW SUPPLIED: Synagis® (palivizumab) is supplied in single use vials as lyophilized powder to deliver either 50 milligrams or 100 milligrams when reconstituted with sterile water for injection.

50 mg vial NDC 60574-4112-1
Upon reconstitution the 50 mg vial contains 50 milligrams Synagis® (palivizumab) in 0.5 mL.

100 mg vial NDC 60574-4111-1
Upon reconstitution the 100 mg vial contains 100 milligrams Synagis® (palivizumab) in 1.0 mL.

Upon receipt and until reconstitution for use, Synagis® (palivizumab) should be stored between 2 and 8°C (35.6° and 46.4°F) in its original container. Do not freeze. Do not use beyond the expiration date.

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® Synagis (palivizumab) is a registered trademark of MedImmune, Inc.

Manufactured by:

MedImmune, Inc.
Gaithersburg, MD 20878
U.S. Govt. License No. 1252
(1-877-633-4411)

Co-Marketed by:

ROSS Ross Products Division
Abbott Laboratories, Inc.
Columbus, OH 43215-1724

Rev. date: December 2, 1999

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WARNING

Campath should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

- **Hematologic Toxicity:** Serious and, in rare instances fatal, pancytopenia/ marrow hypoplasia, autoimmune idiopathic thrombocytopenia, and autoimmune hemolytic anemia have occurred in patients receiving Campath therapy. **Single doses of Campath greater than 30 mg or cumulative doses greater than 90 mg per week should not be administered because these doses are associated with a higher incidence of pancytopenia.**

- **Infusion Reactions:** Campath can result in serious infusion reactions. Patients should be carefully monitored during infusions and Campath discontinued if indicated. (See DOSAGE AND ADMINISTRATION.) **Gradual escalation to the recommended maintenance dose is required at the initiation of therapy and after interruption of therapy for 7 or more days.**

- **Infections, Opportunistic Infections:** Serious, sometimes fatal bacterial, viral, fungal, and protozoan infections have been reported in patients receiving Campath therapy. Prophylaxis directed against *Pneumocystis carinii* pneumonia (PCP) and herpes virus infections has been shown to decrease, but not eliminate, the occurrence of these infections.

Campath® (ALEMTUZUMAB)

DESCRIPTION

Campath® (Alemtuzumab) is a recombinant DNA-derived humanized monoclonal antibody (Campath-1H) that is directed against the 21-28 kD cell surface glycoprotein, CD52. CD52 is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and tissues of the male reproductive system. The Campath-1H antibody is an IgG1 kappa with human variable framework and constant regions, and complementarity-determining regions from a murine (rat) monoclonal antibody (Campath-1G). The Campath-1H antibody has an approximate molecular weight of 150 kD.

Campath is produced in mammalian cell (Chinese hamster ovary) suspension culture in a medium containing neomycin. Neomycin is not detectable in the final product. Campath is a sterile, clear, colorless, isotonic pH 6.8-7.4 solution for injection. Each single use ampoule of Campath

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contains 30 mg Alemtuzumab, 24.0 mg sodium chloride, 3.5 mg dibasic sodium phosphate, 0.6 mg potassium chloride, 0.6 mg monobasic potassium phosphate, 0.3 mg polysorbate 80, and 0.056 mg disodium edetate. No preservatives are added.

CLINICAL PHARMACOLOGY

General:

Alemtuzumab binds to CD52, a non-modulating antigen that is present on the surface of essentially all B and T lymphocytes, a majority of monocytes, macrophages, and NK cells, and a subpopulation of granulocytes. Analysis of samples collected from multiple volunteers has not identified CD52 expression on erythrocytes or hematopoetic stem cells. The proposed mechanism of action is antibody-dependent lysis of leukemic cells following cell surface binding. Campath-1H Fab binding was observed in lymphoid tissues and the mononuclear phagocyte system. A proportion of bone marrow cells, including some $CD34^+$ cells, express variable levels of CD52. Significant binding was also observed in the skin and male reproductive tract (epididymis, sperm, seminal vesicle). Mature spermatozoa stain for CD52, but neither spermatogenic cells nor immature spermatozoa show evidence of staining.

Human Pharmacokinetics:

The pharmacokinetic profile of Alemtuzumab was studied in a multicenter rising-dose trial in non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Campath was administered once weekly for a maximum of 12 weeks. Following intravenous infusions over a range of doses, the maximum serum concentration (C_{max}) and the area under the curve (AUC) showed relative dose proportionality. The overall average half-life ($t_{1/2}$) over the dosing interval was about 12 days. The pharmacokinetic profile of Campath administered as a 30 mg intravenous infusion three times per week was evaluated in CLL patients. Peak and trough levels of Campath rose during the first few weeks of treatment, and appeared to approach steady state by approximately week 6, although there was marked inter-patient variability. The rise in serum Campath concentration corresponded with the reduction in malignant lymphocytosis.

CLINICAL STUDIES

The safety and efficacy of Campath were evaluated in a multicenter, open-label, noncomparative study (Study 1) of 93 patients with B-cell chronic lymphocytic leukemia (B-CLL) who had been previously treated with alkylating agents and had failed treatment with fludarabine. Fludarabine failure was defined as lack of an objective partial (PR) or complete (CR) response to at least one fludarabine-containing regimen, progressive disease (PD) while on fludarabine treatment, or relapse within 6 months of the last dose of fludarabine. Patients were gradually escalated to a maintenance dose of Campath 30 mg intravenously three times per week for 4 to 12 weeks. Patients received premedication prior to infusion and anti-*Pneumocystis carinii* and anti-herpes prophylaxis while on treatment and for at least 2 months after the last dose of Campath.

Two supportive, multicenter, open-label, noncomparative studies of Campath enrolled a total of 56 patients with B-CLL (Studies 2 and 3). These patients had been previously treated with fludarabine or other chemotherapies. In Studies 2 and 3, the maintenance dose of Campath was 30 mg three times per week with treatment cycles of 8 and 6 weeks respectively. A slightly

different dose escalation scheme was used in these trials. Premedication to ameliorate infusional reactions and anti-*Pneumocystis carinii* and anti-herpes prophylaxis were optional.

Objective tumor response rates and duration of response were determined using the NCI Working Group Response Criteria (1996). A comparison of patient characteristics and the results for each of these studies is summarized in Table 1. Time to event parameters, except for duration of response, are calculated from initiation of Campath therapy. Duration of response is calculated from the onset of the response.

Table 1: Summary of Patient Population and Outcomes

	Study 1 (N = 93)	Study 2 (N = 32)	Study 3 (N = 24)
Median Age in Years (Range)	66 (32 □68)	57 (46 - 75)	62 (44 - 77)
Median Number of Prior Regimens (Range)	3 (2 □7)	3 (1 □10)	3 (1 □8)
Prior Therapies:			
Alkylating Agents	100%	100%	92%
Fludarabine	100%	34%	100%
Disease Characteristics:			
Rai Stage III / IV Disease	76%	72%	71%
B-Symptoms	42%	31%	21%
Overall Response Rate	33%	21%	29%
(95% Confidence Interval)	(23%, 43%)	(8%, 33%)	(11%, 47%)
Complete Response	2%	0%	0%
Partial Response	31%	21%	29%
Median Duration of Response (months)	7	7	11
(95% Confidence Interval)	(5, 8)	(5, 23)	(6, 19)
Median Time to Response (months)	2	4	4
(95% Confidence Interval)	(1, 2)	(1, 5)	(2, 4)
Progression-Free Survival (months)	4	5	7
(95% Confidence Interval)	(3, 5)	(3, 7)	(3, 9)

INDICATIONS AND USAGE

Campath is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy. Determination of the effectiveness of Campath is based on overall response rates. (See CLINICAL STUDIES.) Comparative, randomized trials demonstrating increased survival or clinical benefits such as improvement in disease-related symptoms have not yet been conducted.

CONTRAINDICATIONS

Campath is contraindicated in patients who have active systemic infections, underlying immunodeficiency (e.g., seropositive for HIV), or known Type I hypersensitivity or anaphylactic reactions to Campath or to any one of its components.

WARNINGS (See BOXED WARNING.)

Infusion-Related Events:

Campath has been associated with infusion-related events including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash. In order to ameliorate or avoid infusion-related events, patients should be premedicated with an oral antihistamine and acetaminophen prior to dosing and monitored closely for infusion-related adverse events. In addition, Campath should be initiated at a low dose with gradual escalation to the effective dose. Careful monitoring of blood pressure and hypotensive symptoms is recommended especially in patients with ischemic heart disease and in patients on antihypertensive medications. If therapy is interrupted for 7 or more days, Campath should be reinstituted with gradual dose escalation. (See ADVERSE EVENTS and DOSAGE AND ADMINISTRATION.)

Immunosuppression/Opportunistic Infections:

Campath induces profound lymphopenia. A variety of opportunistic infections have been reported in patients receiving Campath therapy (see ADVERSE EVENTS, Infections). If a serious infection occurs, Campath therapy should be interrupted and may be reinitiated following the resolution of the infection.

Anti-infective prophylaxis is recommended upon initiation of therapy and for a minimum of 2 months following the last dose of Campath or until $CD4^+$ counts are $\geq$ 200 cells/μL. The median time to recovery of $CD4^+$ counts to $\geq$ 200/μL was 2 months, however, full recovery (to baseline) of $CD4^+$ and $CD8^+$ counts may take more than 12 months. (See BOXED WARNING and DOSAGE AND ADMINISTRATION.)

Because of the potential for Graft versus Host Disease (GVHD) in severely lymphopenic patients, irradiation of any blood products administered prior to recovery from lymphopenia is recommended.

Hematologic Toxicity:

Severe, prolonged, and in rare instances fatal, myelosuppression has occurred in patients with leukemia and lymphoma receiving Campath. Bone marrow aplasia and hypoplasia were observed in the clinical studies at the recommended dose. The incidence of these complications increased with doses above the recommended dose. In addition, severe and fatal autoimmune anemia and thrombocytopenia were observed in patients with CLL. Campath should be discontinued for severe hematologic toxicity (see Table 3 Dose Modification and Reinitiation of Therapy for Hematologic Toxicity) or in any patient with evidence of autoimmune hematologic toxicity. Following resolution of transient, non-immune myelosuppression, Campath may be reinitiated with caution. (See DOSAGE AND ADMINISTRATION.) There is no information on the safety of resumption of Campath in patients with autoimmune cytopenias or marrow aplasia. (See ADVERSE REACTIONS.)

PRECAUTIONS

Laboratory Monitoring:

Complete blood counts (CBC) and platelet counts should be obtained at weekly intervals during Campath therapy and more frequently if worsening anemia, neutropenia, or thrombocytopenia is observed on therapy. $CD4^+$ counts should be assessed after treatment until recovery to ≥ 200 cells/μL. (See WARNINGS and ADVERSE REACTIONS.)

Drug/Laboratory Interactions:

No formal drug interaction studies have been performed with Campath. An immune response to Campath may interfere with subsequent diagnostic serum tests that utilize antibodies.

Immunization:

Patients who have recently received Campath, should not be immunized with live viral vaccines, due to their immunosuppression. The safety of immunization with live viral vaccines following Campath therapy has not been studied. The ability to generate a primary or anamnestic humoral response to any vaccine following Campath therapy has not been studied.

Immunogenicity:

Four (1.9%) of 211 patients evaluated for development of an immune response were found to have antibodies to Campath. The data reflect the percentage of patients whose test results were considered positive for antibody to Campath in a kinetic enzyme immunoassay, and are highly dependent on the sensitivity and specificity of the assay. The observed incidence of antibody positivity may be influenced by several additional factors including sample handling, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Campath with the incidence of antibodies to other products may be misleading. Patients who develop hypersensitivity to Campath may have allergic or hypersensitivity reactions to other monoclonal antibodies.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No long-term studies in animals have been performed to establish the carcinogenic or mutagenic potential of Campath, or to determine its effects on fertility in males or females. Women of childbearing potential and men of reproductive potential should use effective contraceptive methods during treatment and for a minimum of 6 months following Campath therapy.

Pregnancy Category C:

Animal reproduction studies have not been conducted with Campath. It is not known whether Campath can affect reproductive capacity or cause fetal harm when administered to a pregnant woman. However, human IgG is known to cross the placental barrier and therefore Campath may cross the placental barrier and cause fetal B and T lymphocyte depletion. Campath should be given to a pregnant woman only if clearly needed.

Nursing Mothers:

Excretion of Campath in human breast milk has not been studied. Because many drugs including human IgG are excreted in human milk, breast-feeding should be discontinued during treatment and for at least 3 months following the last dose of Campath.

Pediatric Use:

The safety and effectiveness of Campath in children have not been established.

Geriatric Use:

Of the 149 patients with B-CLL enrolled in the three clinical studies, 66 (44%) were 65 and over, while 15 (10%) were 75 and over. Substantial differences in safety and efficacy related to age were not observed; however the size of the database is not sufficient to exclude important differences.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Safety data, except where indicated, are based on 149 patients with B-CLL enrolled in studies of Campath as a single agent administered at a maintenance dose of 30 mg intravenously three times weekly for 4 to 12 weeks. Table 2 lists adverse events including severe or life threatening (NCI-CTC Grade 3 or 4) adverse events reported in > 5% of the patients. More detailed information and follow-up were available for Study 1 (93 patients), therefore the narrative description of certain events, noted below, is based on this study.

Infusion-Related Adverse Events:

Infusion-related adverse events resulted in discontinuation of Campath therapy in 6% of the patients enrolled in Study 1. The most commonly reported infusion-related adverse events on this study included rigors in 89% of patients, drug-related fever in 83%, nausea in 47%, vomiting in 33%, and hypotension in 15%. Other frequently reported infusion-related events include, rash in 30% of patients, fatigue in 22%, urticaria in 22%, dyspnea in 17%, pruritus in 14%, headache in 13%, and diarrhea in 13%. Similar types of adverse events were reported on the supporting studies (see Table 2). Acute infusion-related events were most common during the first week of therapy. Antihistamines, acetaminophen, antiemetics, meperidine, and corticosteroids as well as incremental dose escalation were used to prevent or ameliorate infusion-related events. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Infections:

On Study 1, all patients were required to receive anti-herpes and anti-PCP prophylaxis (see DOSAGE AND ADMINISTRATION) and were followed for infections for 6 months. Forty (43%) of 93 patients experienced 59 infections (one or more infections per patient) related to

Campath during treatment or within 6 months of the last dose. Of these, 34 (37%) patients experienced 42 infections that were of Grade 3 or 4 severity; 11 (18%) were fatal. Fifty-five percent of the Grade 3 or 4 infections occurred during treatment or within 30 days of last dose. In addition one or more episodes of febrile neutropenia (ANC ≤ 500/μL) were reported in 10% of patients.

The following types of infections were reported in Study 1: Grade 3 or 4 sepsis in 12% of patients with one fatality, Grade 3 or 4 pneumonia in 15% with five fatalities, and opportunistic infections in 17% with four fatalities. Candida infections were reported in 5% of patients; CMV infections in 8% (4% of Grade 3 or 4 severity); Aspergillosis in 2% with fatal Aspergillosis in 1%; fatal Mucormycosis in 2%; fatal Cryptococcal pneumonia in 1%; *Listeria monocytogenes* meningitis in 1%; disseminated *Herpes zoster* in 1%; Grade 3 *Herpes simplex* in 2%; and Torulopsis pneumonia in 1%. PCP pneumonia occurred in one (1%) patient who discontinued PCP prophylaxis.

On Studies 2 and 3 in which anti-herpes and anti-PCP prophylaxis was optional, 37 (66%) patients had 47 infections while or after receiving Campath therapy. In addition to the opportunistic infections reported above, the following types of related events were observed on these studies: interstitial pneumonitis of unknown etiology and progressive multifocal leukoencephalopathy.

Hematologic Adverse Events:

Pancytopenia/Marrow Hypoplasia: Campath therapy was permanently discontinued in six (6%) patients due to pancytopenia/marrow hypoplasia. Two (2%) cases of pancytopenia/ marrow hypoplasia were fatal.

Anemia: Forty-four (47%) patients had one or more episodes of new onset NCI-CTC Grade 3 or 4 anemia. Sixty-two (67%) patients required RBC transfusions. In addition, erythropoietin use was reported in nineteen (20%) patients. Autoimmune hemolytic anemia secondary to Campath therapy was reported in 1% of patients. Positive Coombs test without hemolysis was reported in 2%. (See BOXED WARNING.)

Neutropenia: Sixty-five (70%) patients had one or more episodes of NCI-CTC Grade 3 or 4 neutropenia. Median duration of Grade 3 or 4 neutropenia was 28 days (range: 2 □165 days). (See Infections.)

Thrombocytopenia: Forty-eight (52%) patients had one or more episodes of new onset Grade 3 or 4 thrombocytopenia. Median duration of thrombocytopenia was 21 days (range: 2 □165 days). Thirty-five (38%) patients required platelet transfusions for management of thrombocytopenia. Autoimmune thrombocytopenia was reported in 2% of patients with one fatal case of Campath-related autoimmune thrombocytopenia. (See BOXED WARNING.)

Lymphopenia: The median $CD4^+$ count at 4 weeks after initiation of Campath therapy was 2 (two) /μL, at 2 months after discontinuation of Campath therapy, 207/μL, and 6 months after discontinuation, 470/μL. The pattern of change in median $CD8^+$ lymphocyte counts was similar to that of $CD4^+$ cells. In some patients treated with Campath, $CD4^+$ and $CD8^+$ lymphocyte counts had not returned to baseline levels at longer than 1 year post therapy.

237 **Table 2: Adverse Events in > 5% of the B-CLL Study Population**
238 **During Treatment or Within 30 Days (N = 149)**

	B-CLL STUDIES (N = 149)	
Adverse Event:	**ANY Grade (%)**	**Grade 3 or 4 (%)**
Body As A Whole		
Rigors	**86**	**16**
Fever	**85**	**19**
Fatigue	**34**	**5**
Pain, Skeletal Pain	**24**	**2**
Anorexia	**20**	**3**
Asthenia	**13**	**4**
Edema, Peripheral Edema	**13**	**1**
Back Pain	**10**	**3**
Chest Pain	**10**	**1**
Malaise	**9**	**1**
Temperature Change Sensation	**5**	**--**
Cardiovascular Disorders, General		
Hypotension	**32**	**5**
Hypertension	**11**	**2**
Heart Rate & Rhythm Disorders		
Tachycardia, SVT	**11**	**3**
Central & Peripheral Nervous System Disorders		
Headache	**24**	**1**
Dysthesias	**15**	**--**
Dizziness	**12**	**1**
Tremor	**7**	**--**
Gastrointestinal Disorders		
Nausea	**54**	**2**
Vomiting	**41**	**4**
Diarrhea	**22**	**1**
Stomatitis, Ulcerative Stomatitis, Mucositis	**14**	**1**
Abdominal Pain	**11**	**2**
Dyspepsia	**10**	**--**
Constipation	**9**	**1**
Hematologic Disorders		
WBC Disorders: Neutropenia	**85**	**64**
RBC Disorders: Anemia	**80**	**38**
Pancytopenia	**5**	**3**
Platelet, Bleeding & Clotting Disorders:		
Thrombocytopenia	**72**	**50**
Purpura	**8**	**-**
Epistaxis	**7**	**1**

Adverse Event:	B-CLL STUDIES (N = 149)	
	ANY Grade (%)	Grade 3 or 4 (%)
Musculoskeletal Disorders		
Myalgias	11	--
Psychiatric Disorders		
Insomnia	10	--
Depression	7	1
Somnolence	5	1
Resistance Mechanism Disorders		
Sepsis	15	10
Herpes Simplex	11	1
Moniliasis	8	1
Infection (other viral or unidentified)	7	1
Respiratory System Disorders		
Dyspnea	26	9
Cough	25	2
Bronchitis, Pneumonitis	21	13
Pneumonia	16	10
Pharyngitis	12	--
Bronchospasm	9	2
Rhinitis	7	--
Skin & Appendage Disorders		
Rash, Maculopapular Rash, Erythematous Rash	40	3
Urticaria	30	5
Pruritus	24	1
Sweating increased	19	1

Serious adverse events:

The following serious adverse events, defined as events which result in death, requiring or prolonging hospitalization, requiring medical intervention to prevent hospitalization, or malignancy, were reported in at least one patient treated on studies where Campath was used as a single agent (and are not reported in Table 2). These studies were conducted in patients with lymphocytic leukemia and lymphoma (N = 745) and in patients with non-malignant diseases (N =152) such as rheumatoid arthritis, solid organ transplant, or multiple sclerosis.

Body As A Whole: allergic reactions, anaphylactoid reaction, ascites, hypovolemia, influenza-like syndrome, mouth edema, neutropenic fever, syncope

Cardiovascular Disorders: cardiac failure, cyanosis, atrial fibrillation, cardiac arrest, ventricular arrhythmia, ventricular tachycardia, angina pectoris, coronary artery disorder, myocardial infarction, pericarditis

Central and Peripheral Nervous System Disorders: abnormal gait, aphasia, coma, grand mal convulsions, paralysis, meningitis

Endocrine Disorders: hyperthyroidism

Gastrointestinal System Disorders: duodenal ulcer, esophagitis, gingivitis, gastroenteritis, GI hemorrhage, hematemesis, hemorrhoids, intestinal obstruction, intestinal perforation, melena, paralytic ileus, peptic ulcer, pseudomembranous colitis, colitis, pancreatitis, peritonitis, hyperbilirubinemia, hepatic failure, hepatocellular damage, hypoalbuminemia, biliary pain

Hearing and Vestibular Disorders: decreased hearing

Metabolic and Nutritional Disorders: acidosis, aggravated diabetes mellitus, dehydration, fluid overload, hyperglycemia, hyperkalemia, hypokalemia, hypoglycemia, hyponatremia, increased alkaline phosphatase, respiratory alkalosis

Musculoskeletal System Disorders: arthritis or worsening arthritis, arthropathy, bone fracture, myositis, muscle atrophy, muscle weakness, osteomyelitis, polymyositis

Neoplasms: malignant lymphoma, malignant testicular neoplasm, prostatic cancer, plasma cell dyscrasia, secondary leukemia, squamous cell carcinoma, transformation to aggressive lymphoma, transformation to prolymphocytic leukemia

Platelet, Bleeding, and Clotting Disorders: coagulation disorder, disseminated intravascular coagulation, hematoma, pulmonary embolism, thrombocythemia

Psychiatric Disorders: confusion, hallucinations, nervousness, abnormal thinking, apathy

White Cell and RES Disorders: agranulocytosis, aplasia, decreased haptoglobin, lymphadenopathy, marrow depression

Red Blood Cell Disorders: hemolysis, hemolytic anemia, splenic infarction, splenomegaly

Reproductive System Disorders: cervical dysplasia

Resistance Mechanism Disorders: abscess, bacterial infection, *Herpes zoster* infection, *Pneumocystis carinii* infection, otitis media, Tuberculosis infection, viral infection

Respiratory System Disorders: asthma, bronchitis, chronic obstructive pulmonary disease, hemoptysis, hypoxia, pleural effusion, pleurisy, pneumothorax, pulmonary edema, pulmonary fibrosis, pulmonary infiltration, respiratory depression, respiratory insufficiency, sinusitis, stridor, throat tightness

Skin and Appendages Disorders: angioedema, bullous eruption, cellulitis, purpuric rash

Special Senses Disorders: taste loss

Urinary System Disorders: abnormal renal function, acute renal failure, anuria, facial edema, hematuria, toxic nephropathy, ureteric obstruction, urinary retention, urinary tract infection

Vascular (Extracardiac) Disorders: cerebral hemorrhage, cerebrovascular disorder, deep vein thrombosis, increased capillary fragility, intracranial hemorrhage, phlebitis, subarachnoid hemorrhage, thrombophlebitis

Vision Disorders: endophthalmitis

OVERDOSAGE

Initial doses of Campath of greater than 3 mg are not well-tolerated. One patient who received 80 mg as an initial dose by IV infusion experienced acute bronchospasm, cough, and shortness of breath, followed by anuria and death. A review of the case suggested that tumor lysis syndrome may have played a role.

Single doses of Campath greater than 30 mg or a cumulative weekly dose greater than 90 mg should not be administered as higher doses have been associated with a higher incidence of pancytopenia. (See BOXED WARNING and DOSAGE AND ADMINISTRATION.)

There is no known specific antidote for Campath overdosage. Treatment consists of drug discontinuation and supportive therapy.

DOSAGE AND ADMINISTRATION

Campath should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Dosing Schedule and Administration:

Campath therapy should be initiated at a dose of 3 mg administered as a 2 hour IV infusion daily. (See ADVERSE EVENTS.) When the Campath 3 mg daily dose is tolerated (e.g., infusion-related toxicities are ≤ Grade 2), the daily dose should be escalated to 10 mg and continued until tolerated. When the 10 mg dose is tolerated, the maintenance dose of Campath 30 mg may be initiated. The maintenance dose of Campath is 30 mg/day administered three times per week on alternate days (i.e., Monday, Wednesday, and Friday) for up to 12 weeks. In most patients, escalation to 30 mg can be accomplished in 3 - 7 days. **Dose escalation to the recommended maintenance dose of 30 mg administered three times per week is required. Single doses of Campath greater than 30 mg or cumulative weekly doses of greater than 90 mg should not be administered since higher doses are associated with an increased incidence of pancytopenia.** (See BOXED WARNING.) Campath should be administered intravenously only. The infusion should be administered over a 2 hour period. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.**

Recommended Concomitant Medications:

Premedication should be given prior to the first dose, at dose escalations, and as clinically indicated. The premedication used in clinical studies was diphenhydramine 50 mg and acetaminophen 650 mg administered 30 minutes prior to Campath infusion. In cases where severe infusion-related events occur, treatment with hydrocortisone 200 mg was used in decreasing the infusion-related events.

Patients should receive anti-infective prophylaxis to minimize the risks of serious opportunistic infections. (See BOXED WARNING.) The anti-infective regimen used on Study 1 consisted of trimethoprim/sulfamethoxazole DS twice daily (BID) three times per week and famciclovir or equivalent 250 mg twice a day (BID) upon initiation of Campath therapy. Prophylaxis should be continued for 2 months after completion of Campath therapy or until the $CD4^+$ count is ≥ 200 cells/μL, whichever occurs later.

Dose Modification and Reinitiation of Therapy:

Campath therapy should be discontinued during serious infection, serious hematologic toxicity, or other serious toxicity until the event resolves. (See WARNINGS.) Campath therapy should be permanently discontinued if evidence of autoimmune anemia or thrombocytopenia appears. Table 3 includes recommendations for dose modification for severe neutropenia or thrombocytopenia.

Table 3: Dose Modification and Reinitiation of Therapy for Hematologic Toxicity

Hematologic Toxicity	Dose Modification and Reinitiation of Therapy
For first occurrence of ANC < 250/μL and/or platelet count ≤ 25,000/μL	Withhold Campath therapy. When ANC ≥ 500/μL and platelet count ≥ 50,000/μL, resume Campath therapy at same dose. If delay between dosing is ≥ 7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then to 30 mg as tolerated.
For second occurrence of ANC < 250/μL and/or platelet count ≤ 25,000/μL	Withhold Campath therapy. When ANC ≥ 500/μL and platelet count ≥ 50, 000/μL, resume Campath therapy at **10 mg**. If delay between dosing is ≥ 7 days, initiate therapy at Campath 3 mg and escalate to **10 mg only**.
For third occurrence of ANC < 250/μL and /or platelet count ≤ 25, 000/μL	Discontinue Campath therapy permanently.
For a decrease of ANC and/or platelet count to ≤ 50% of the baseline value in patients initiating therapy with a baseline ANC ≤ 500/μL and/or a baseline platelet count ≤ 25,000/μL	Withhold Campath therapy. When ANC and/or platelet count return to baseline value(s), resume Campath therapy. If the delay between dosing ≥ 7 days, initiate therapy at Campath 3 mg and escalate to 10 mg and then to 30 mg as tolerated.

Preparation for Administration:

Parenteral drug products should be inspected for visible particulate matter and discoloration prior to administration. If particulate matter is present or the solution is discolored, the vial should not be used. **DO NOT SHAKE AMPOULE PRIOR TO USE.** As with all parenteral drug products, aseptic technique should be used during the preparation and administration of Campath. Withdraw the necessary amount of Campath from the ampoule into a syringe. Filter with a sterile, low-protein binding, non-fiber releasing 5 μm filter prior to dilution.

Inject into 100 mL sterile 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. **Gently invert the bag to mix the solution.** Discard syringe and any unused drug product.

Campath contains no antimicrobial preservative. Campath should be used within 8 hours after dilution. Campath solutions may be stored at room temperature (15-30°C) or refrigerated. Campath solutions should be protected from light.

Incompatibilities:

No incompatibilities between Campath and polyvinylchloride (PVC) bags, PVC or polyethylene-lined PVC administration sets, or low-protein binding filters have been observed. No data are available concerning the incompatibility of Campath with other drug substances. Other drug substances should not be added or simultaneously infused through the same intravenous line.

HOW SUPPLIED

Campath (Alemtuzumab) is supplied in single-use clear glass ampoules containing 30 mg of Alemtuzumab in 3 mL of solution. Each box contains either three Campath ampoules (NDC 50419-355-10) or 12 Campath ampoules (NDC 50419-355-12).

Campath should be stored at 2-8°C (36-46°F). Do not freeze. DISCARD IF AMPOULE HAS BEEN FROZEN. Protect from direct sunlight.

Rx only.

U.S. Patents: 5,545,403; 5,545,405; 5,654,403; 5,846,534

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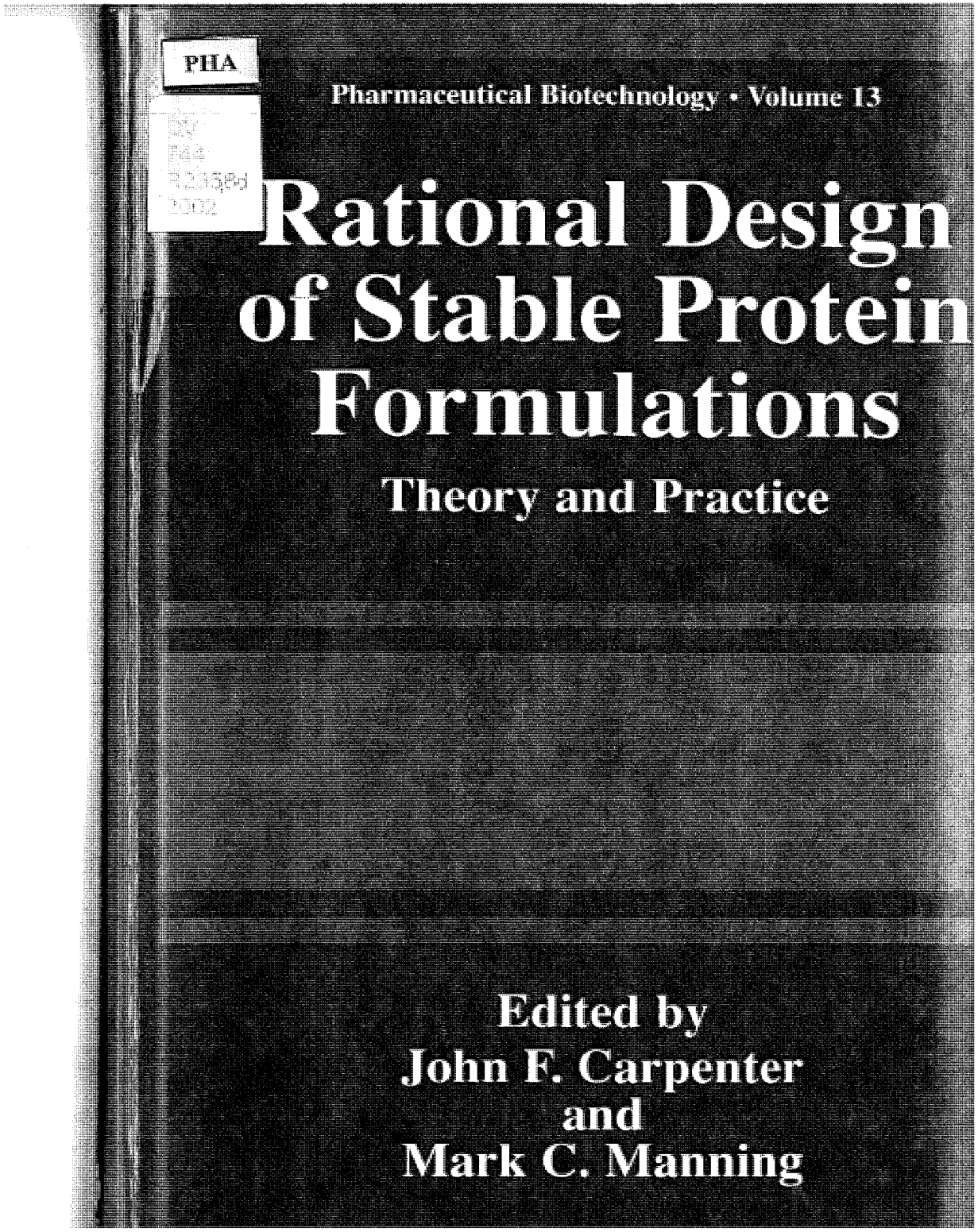

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Rational Design of Stable Protein Formulations

Theory and Practice

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Rational Design of Stable Protein Formulations

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Theory and Practice

Edited by

John F. Carpenter

and

Mark C. Manning

University of Colorado Health Sciences Center
Denver, Colorado

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Contributors

Tsutomu Arakawa • Alliance Protein Laboratories, Thousand Oaks, California 91360

John Carpenter • Center for Pharmaceutical Biotechnology, Department of Pharmaceutical Sciences, School of Pharmacy, University of Colorado Health Sciences Center, Denver, Colorado 80262

Byeong S. Chang • Department of Pharmaceutics and Drug Delivery, Amgen, Inc., Thousand Oaks, California 90132

William Garzon-Rodriguez • Center for Pharmaceutical Biotechnology, Department of Pharmaceutical Sciences, School of Pharmacy, University of Colorado Health Sciences Center, Denver, Colorado 80262

Susan Hershenson • Department of Pharmaceutics and Drug Delivery, Amgen, Inc., Thousand Oaks, California 90132

Bert Ho • Tularik Corporation, S. San Francisco, California 94080

LaToya S. Jones • Center for Pharmaceutical Biotechnology, Department of Pharmaceutical Sciences, School of Pharmacy, University of Colorado Health Sciences Center, Denver, Colorado 80262

Brent S. Kendrick • Amgen, Inc., Boulder, Colorado 80301

Geoffrey Lee • Department of Pharmaceutical Technology, Friedrich-Alexander University, Erlangen, Germany

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Tiansheng Li • Amgen, Inc., Thousand Oaks, California 90132

Mark Manning • Center for Pharmaceutical Biotechnology, Department of Pharmaceutical Sciences, School of Pharmacy, University of Colorado Health Sciences Center, Denver, Colorado 80262

Jeffrey D. Meyer • Center for Pharmaceutical Biotechnology, Department of Pharmaceutical Sciences, School of Pharmacy, University of Colorado Health Sciences Center, Denver, Colorado 80262

Linda O. Narhi • Amgen, Inc., Thousand Oaks, California 90132

Rajiv Nayar • HTD Biosystems, Hercules, California 94547

Theodore W. Randolph • Center for Pharmaceutical Biotechnology, Department of Chemical Engineering, University of Colorado, Boulder, Colorado 80503

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1

Practical Approaches to Protein Formulation Development

Byeong S. Chang and Susan Hershenson

INTRODUCTION

As is the case with other pharmaceuticals, formulation development is one of the critical steps in developing a protein as a therapeutic product. Development of stable protein formulations may require even more resources and effort than conventional small molecule pharmaceuticals. Proteins typically have more stability issues as a result of their complexity and delicate structural stability. Fortunately, a great deal of research regarding protein stability has been conducted and this information is readily available in the literature (reviewed by Manning et al., 1989; Chen, 1992; Ahern and Manning, 1992a, 1992b; Arakawa et al., 1993; Cleland et al., 1993; Wang and Pearlman, 1993; Pearlman and Wang, 1996; Volkin and Middaugh, 1997). Ultimately, it would be ideal to be able to develop a pure pharmaceutical containing only the native protein. However, it is not practical to have only the native form of a protein in the formulation because the protein must be purified from a complex biological mixture containing a pool of other proteins which includes misfolded, denatured, and degraded forms of the same protein. Furthermore, a major challenge is to maintain the integrity of the purified protein during routine pharmaceutical processing, storage, handling, and delivery to the patient. One could envision achieving this goal by developing a formulation with

Byeong S. Chang and Susan Hershenson • Department of Pharmaceutics and Drug Delivery, Amgen, Inc., Thousand Oaks, CA 90132.

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perfect stability, i.e., no physical and chemical change in the protein. Because proteins are complex molecules composed of numerous reactive chemical groups and delicate three-dimensional structures, identifying a set of conditions to keep all components stable is virtually impossible. In general, commercial therapeutic protein formulations are developed under the assumption that some degree of physicochemical changes will occur during storage and handling.

Realizing that it is impossible to develop a perfectly stable formulation, especially while meeting an aggressive product development timeline, the main objective then becomes one of maintaining the appropriate safety and efficacy of the product. In order to achieve this objective, it is imperative to understand the broad spectrum of degradation pathways affecting proteins, and to have available equipment and expertise in an extensive repertoire of analytical methods. Formulation development focuses on determining the potential degradation pathways, assessing the significance of each and optimizing variables to minimize the degradation products that are clinically significant.

Regulatory guidelines also are critical elements for guiding formulation development. They provide information about how to conduct studies and obtain useful results for evaluating formulations. The results obtained allow formulation scientists to write an appropriate developmental pharmaceutics section in regulatory filings. The guidelines also help to evaluate the significance of some inevitable degradation products that are produced during manufacturing, shipping and storage. For example, if the degradation products have properties comparable to those of the desired product with respect to activity, efficacy, and safety, they can be classified as product-related substances. This classification is significantly different from considering the degradation product as an impurity when there is not sufficient supporting evidence to justify classification as a product-related substance (Appendix, Regulatory Document 1). Understanding of these practical issues of regulatory requirements is critical for formulation scientists during design, implementation, evaluation and reporting of their studies.

In addition to insight into the scientific and regulatory issues, developing commercial formulations requires a clear understanding of the potential market. For example, indication, patients, method of delivery, frequency of dosing, typical dose requirement, market distribution and other business-related information will provide directions for the design of a successful formulation. Also, it is important to consider the competitiveness of the formulation as compared to other products available in the market.

In this chapter, an overview of critical factors affecting the design of therapeutic protein formulations and a general guide to developing commercially viable dosage forms for protein pharmaceuticals will be discussed. Since the majority of practical issues are not covered very well in the scientific literature, this chapter also includes information from regulatory guidance documents (see Appendix), labels from marketed products and routine industrial experience.

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PREPARATION FOR FORMULATION DEVELOPMENT

Resource Requirements for Formulation Development

A list of resources that should be available before starting formulation development is summarized in Table 1. Some resources may not be as critical as others, depending on the nature of problems encountered, but it is important to have sufficient resources to discover major formulation issues as early as possible in the product development process. Without the appropriate equipment and personnel, the development of an acceptable formulation can be greatly hampered, potentially to such a degree that the product is never brought to market. Of course, not all of the resources need to be at the company developing the therapeutic protein, but if outside contractors are employed it is essential that timely access to resources is available. In addition, the quality of raw materials should be carefully evaluated because unexpected impurities may introduce unnecessary

Table 1.
Resource Requirements for Initial Protein Formulation Development

Resources	Requirement	Example
Purified protein	Representative of manufacturing process; sufficient quantity to cover dose bracket, formulation variables, and stress conditions; minimum complication by impurity (precipitation of impurity, degradation by impurity like proteolytic cleavage).	Purified bulk, sample from final purification process
Qualified excipients	Pharmaceutically acceptable quality, manufacturers with qualified production procedures and sufficient scale, specifications on critical impurities, quality that can be carried on to clinical studies and commercial distribution.	USP, Ph. Eur, JP
Access to fill finish facility	Capability to sterilize container/closure components; fill/finish under aseptic environment; head-space purge system; drying equipment	Sterile hood, filling machine, lyophilizer
Analytical instruments	Structural analyses; concentration determination, chromatographic analyses; electrophoresis; bioassays; other microcharacterizations.	CD, UV, fluorescence, HPLCs, mass-spectrometry, SDS-PAGE
Facility to accommodate stability studies	Controlled temperature, controlled light exposure, controlled relative humidity, devices to provide controlled agitation.	Freezer, refrigerator, incubator, light chamber, RH incubator, agitator

Table 2.
Examples of Information Useful for Designing Formulation Studies

Information	Examples
Clinical indication	Site of treatment (self-administration, office visit, hospital), methods of delivery, concomitant medication, competition.
Patient population	Age, strength, tolerability, capability to manipulate devices, sensitivity to excipient
Typical routes of delivery	Injectables (IV, SC, IM, IP, ICV, IT, IO), topical, inhalation, nasal, oral, etc.
Dose requirement	PK profile, frequency of dosing, variable vs. fixed dose, single-dose/multidose
Drug interaction	Co-administration with other drug, dilution or reconstitution with other solution; presence of undesirable compounds like reducing sugars, preservatives
Typical dosage forms	Liquid, lyophilized, spray-dried, aerosol by liquid or powder, other novel carrier; stability, physical properties, reconstitution art
Container/closure	Vial/stoppers, prefilled syringes, prefilled cartridges, dual-chamber cartridges, blister packages, product contact material, leacheates, breakage, light sensitivity, moisture penetration
Delivery device	Syringes, prefilled-syringes, pen injectors, auto-injectors, needle-free injectors, inhalation devices, infusion pumps

complications in the stability profile that is determined during formulation development and testing.

Useful Information for Designing Formulations

The configuration of a protein formulation is affected by how the drug will be used as a product. If such information is available when designing formulation studies, it is recommended to consider the limitations and challenges associated with each application. Examples of such information are listed in Table 2.

PREFORMULATION DEVELOPMENT

It is important to understand the critical properties of a protein before starting large studies to design and test the final formulation. Preformulation studies are designed to learn about the protein's susceptibility to a variety of pharmaceutically relevant stresses. The main objectives of preformulation research

Table 3.
Information Obtained from Pre-formulation Studies for Protein Pharmaceuticals

Characterization	Examples
Physical properties	Primary, secondary, tertiary and quaternary structures, solubility, viscosity, self-association, hydrophobicity, molecular weight, extinction coefficient, glycosylation, effects of ionic strength, etc.
Biological properties	Substrate or receptor affinity, in vitro activity model, *in vivo* preclinical model, etc.

include: general characterization of the product; investigation of potential stability issues; development of relevant analytical methods; establishment of a stability profile with stability-indicating assays; and identification of major formulation challenges. A summary of these issues will be presented in this section.

Characterization of Protein Pharmaceuticals

There is available in the literature extensive coverage of analytical methods and their principles for the characterization of proteins (e.g., Jones, 1993; Reubsaet et al., 1998; Herron et al., 1995). General points to consider when characterizing a protein as an active ingredient are listed in Table 3. As a protein's biological activity is dependent on its structure, significant emphasis has been given to structural properties and stability against various stresses.

Accelerated Stability Studies

In order to predict potential stability problems within a short period of time and to develop appropriate analytical methods, proteins are exposed to stronger-than-real stresses and various degradation products induced by the stresses are examined. The results obtained from these so-called "accelerated stability studies" might also be useful to predict the kinetics of the degradation processes under real handling conditions, when there are not sufficient real-time results available because of time and resource constraints. However, the accelerated stability study is not acceptable to determine expiry of the product, so it is best used to rank order the importance of different degradation pathways. Approaches and cautions in the extrapolation of data from accelerated stability testing to real-time stability and normal handling conditions are discussed in detail below.

Table 4.
Various Conditions Used to Accelerate Protein Degradation

Stresses	Routine ranges	Practical applications	Problems to monitor
Temperature	0–50°C	Storage, shipping, handling, delivery	Structural changes (precipitation, aggregation, recovery loss), solubility, increased reaction rates for all degradations
Light	>1.2 million lux hrs illumination, >200 watt hrs/square meter UV energy	Light exposure, container, package	Oxidation, cleavage
Freezing	Multiple freeze-thaw, liquid nitrogen freeze	Frozen storage, accidental freezing, lyophilization	Precipitation, aggregation, pH change, crystallization of excipients
Oxidation	Oxygen purge, peroxide spike	Storage, excipient stability, impurity	Oxidations, inactivation
Humidity	0–100% RH	Storage, container integrity, powder	Moisture content, moisture related degradations
Mechanical stresses	Vortex, agitation, shear-stress ($3000\,s^{-1}$)	Manufacturing, filling, shipping, handling, delivery	Precipitation, aggregation, recovery loss
Other denaturants	—	Impurities, pH, denaturing excipients	Precipitation, aggregation, recovery loss, structural changes

Conditions to accelerate various degradation reactions in protein products and potential problems to monitor are listed in Table 4. Proteins contain numerous amino acid side chains and delicate three-dimensional structures, which can be susceptible to different stresses. Therefore, it is important to test the protein under a variety of physical and chemical stresses in order to provide a good simulation of the degradation products that can be generated.

Development of Analytical Methods

A brief summary of typical analytical methods is presented in Table 5. It is essential to have a wide range of analytical methods available to identify and characterize degradation products. The analytical methods should be further selected and customized to accommodate the specific needs for each protein product.

Table 5.
Typical Methods Used to Characterize Proteins and Degradation Products

Methods	Examples	Applications
Column chromatography	HPLC, FPLC, low pressure LC; size-exclusion, reversed-phase, ion-exchange, hydrophobic, affinity columns; coupled with UV, fluorescence, RI, and other analytical instruments as detectors	Most physical and chemical degradations, excipient impurities, leacheates
Electrophoresis	SDS-PAGE, native PAGE, isoelectric focusing, capillary electrophoresis, etc.	Degradations with changes in size and/or charge
Spectroscopy	CD, fluorescence, FTIR, UV, Raman, NMR, etc.	Structural changes, chemical modifications of side groups
Thermal analysis	Differential scanning calorimetry, thermogravimetric analysis, thermomechanical analysis, etc.	Protein structure, lyophilized cake structure, powder characterizations
Light scattering/turbidity	Dynamic light scattering, other light scattering devices, turbidity, particle size determination, particle counter, etc.	Aggregation, precipitation, molecular weight determination
Other microcharacterization methods	Peptide mapping, peptide sequencing, amino acid analysis, mass spectrometry, other specific analyses for individual reactive groups	Identification of impurities and chemical degradation, analysis of complex proteins, e.g., antibody and glycoprotein

Evaluation of the Significance of Problems

As stated earlier, it would be ideal to have a pure protein in an absolutely stable formulation. In reality, however, scientists have to design formulation based on compromises that deal with several different potential problems. To make matters worse, the formulation needs to be recommended long before it is evaluated fully, because of typical aggressive timelines in the industry. In general, the formulation will have to be optimized based on assumptions and extrapolations of results obtained during a limited time. Therefore, it is important to utilize the given time efficiently, by collecting as much relevant information as possible for evaluating the significance of each problem.

Due to the marginal stability of proteins, it is possible to create rapidly a variety of degradation products during accelerated stability testing. However, not

all the degradation products that are observed will be significant under normal handling, shipping and storage conditions. Furthermore, the rank order of different degradation processes under accelerated stability testing will NOT be the same under practical handling conditions, because each reaction has a different temperature dependency, i.e., reaction order and activation energy. Another important thing to keep in mind when evaluating different degradation processes is the contribution to the pharmaceutical quality of the product. Critical degradation products should be designated not on the quantity obtained during accelerated stability studies, but on a comprehensive understanding of their contributions to the quality of the product.

Quantitative Assessment. Usually, the rate of each degradation reaction during real storage conditions (e.g., at 4–8°C) should be very slow. In order to predict the rate under real storage conditions, reaction rates obtained under accelerated stability conditions can be extrapolated by using the Arrhenius equation.

Predicting the correct reaction rate requires a proper understanding of the reaction order, because the amount of the degradation product does not linearly increase over time unless the reaction follows zero-order kinetics. One way to determine the reaction order is to calculate the linearity between the concentration of residual native protein and time. The reaction order can be calculated from:

$$dC/dt = kC^n \tag{1}$$

where, C is the protein concentration, t is the time, k is the reaction rate constant, n is the reaction order. For a zero order reaction $n = 0$ and $C_0 - C = k \cdot t$. For a first order reaction $n = 1$ and $\log C_0 - \log C = k \cdot t$. For a second order reaction $n = 2$ and $1/C - 1/C_0 = k \cdot t$. For each reaction order a characteristic transformation of concentration will show a linear relationship with time, e.g., log C will show a linear relationship with time for a first order reaction, whereas $1/C_0$ will be linear versus time for second order reactions.

After obtaining the reaction rate constants for different temperatures, the activation energy can be found by using with the Arrhenius equation.

$$k = A \cdot e^{(-Ea/RT)} \tag{2}$$

The activation energy is obtained by plotting (log k) vs (1/T) and determining the slope of the plot. Using the activation energy, the reaction rate constant for real storage condition, e.g., 2–8°C for refrigerated storage, can be estimated by extrapolation.

Care must be taken when extrapolating the rate constants because there are numerous cases when the Arrhenius relationship does not apply. The Arrhenius reaction applies only to irreversible reactions where the product is accumulated as a single quantifiable species. If the degradation product is the result of serial

reactions, the reaction order and rate constant will be determined only by the rate-limiting reaction at the testing condition. If the rate-limiting reaction changes or another significant variable is introduced at the extrapolated condition, then the extrapolated rate constant will be in error. Such complications routinely can be found in various degradation pathways that are affected by temperature-sensitive reactions such as structural changes, pH changes, by physical changes such as the glass transition of an amorphous phase in a lyophilized formulation and by changes in reactants like dissolved oxygen. For example, proteins have relatively high activation energies for structural changes. Thus, many reactions that are dependent on a major perturbation of the native protein structure tend to cause substantial damage under accelerated storage conditions, e.g., higher temperature. However, many of these reactions are not necessarily major problems when the product is stored at 2–8°C where the protein maintains its native conformation. In contrast, degradation reactions with lower activation energies, which might not be coupled to protein conformational changes (e.g., oxidation of surface methionine residues), tend to be much more problematic in the development of protein formulations.

Results from stresses (e.g., agitation) other than heat imposed in accelerated stability studies potentially could be extrapolated in a similar way to storage and actual handing conditions. The major challenge is the ability to assess quantitatively the magnitude of the stress so that the stress-stability relationship can be established. To date there are not published guidelines for such quantitation.

Qualitative Assessment. Not all of the degradation products are equivalent in terms of their contribution to the pharmaceutical quality of the protein product. Therefore, a qualitative assessment of each degradation product is important when weighing their significance. Regardless of their quantity, some degradation products are generally less acceptable than others. If the degradation product comprises the safety of the product, then it should be considered less acceptable. For example, even at levels of a few percent or less of the total protein population, non-native aggregates can cause adverse reactions in patients such as immune responses and even anaphylactic shock. Also, if the degradation reaction results in the inactivation of protein, it needs to be considered more important than other degradation reactions that do not affect the activity. For example, certain chemical changes (e.g., deamidation) may not alter the activity of a given product, whereas other reactions (e.g., oxidation) may render that product inactive. The relative impact of each degradation product on safety and efficacy cannot be predicted and must be determined for each protein therapeutic.

Information useful for the qualitative evaluation of degradation products includes the identity, clinical and preclinical experiences with the degradation product, biological activity, stability and potential side effects. Regulatory documents also provide clear guidance about what assessment is necessary for protein degradation products (Appendix, Regulatory Documents 2,3). The criteria for

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identification, reporting and qualification of degradation products are set up based on the total patient exposure and percentage of the degradation products (Appendix, Regulatory Document 3). When certain degradation products cannot be prevented from forming in the formulation, their inclusion in the product must be qualified, which may require that additional information on safety and efficacy be obtained as recommended in the regulatory guidelines (Appendix, Regulatory Documents 2,3). Obtaining this information requires a significant amount of additional work, which may include clinical studies.

FORMULATION DEVELOPMENT

As discussed above, the critical parameters affecting the pharmaceutical quality of a protein therapeutic are defined during the preformulation studies. In formulation development, the effects of formulation variables on the defined critical parameters are examined to optimize protein stability. Which variables are most important depends of the formulation type chosen. For example, resistance to agitation and/or accidental freezing is a critical property for an aqueous formulation, which would not be a concern for a lyophilized formulation. Similarly, choosing excipients that provide a glassy matrix to stabilize the protein is only a concern for dried formulations.

Formulation Options for Protein Pharmaceuticals

Different types of formulations need to be developed based on clinical needs, patient compliance, delivery method, stability of the drug, storage and distribution, and market competitiveness. Having a clear plan about what type of formulation is desired will allow one to design better formulation studies. Liquid formulations have been generally preferred due to the convenience of manufacturing and use. However, protein drugs may not be stable enough to be handled as a liquid formulation. Dried formulations (e.g., lyophilized) or suspension formulations (e.g., insulin zinc suspension) have been successfully used to overcome stability problems. In addition, specific applications and delivery may demand the appropriate type of formulation, e.g., a spray-dried powder for pulmonary delivery. As details of the stability issues are discussed in other chapters in this book, only practical issues regarding these different types of formulations will be summarized here.

Liquid Formulations. It is important to understand that developing conditions to keep proteins stable in a liquid form for a pharmaceutically relevant

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storage time (e.g., two years) is not a simple task. For most proteins, including relatively stable ones, at least some degradation should be expected even during refrigerated storage. Unless there is strong evidence supporting that the protein remains stable for two years and the evidence is supported by a broad spectrum of analytical methods, one needs to be very careful about the final decision to market a liquid formulation. Physical or chemical changes that have low activation energy should be monitored especially carefully under real storage conditions. If there is a degradation product that can significantly affect the pharmaceutical quality at its minimum concentrations (e.g., formation of particulates) great care must be taken to assure that such a product does reach unacceptable levels during real-time storage. If long-term storage studies are not implemented until late in the product development process, there is a risk that problems due to unacceptable levels of degradation products will not be discovered in time to test alternative formulations. In addition to stability during storage, temporary exposure to temperatures outside the recommended conditions should also be tested because it can affect the quality of the drug. Also, results obtained from multiple freeze-thawing cycles will be useful to determine if the formulation can accommodate unexpected freezing during distribution and storage. Likewise, sensitivity to agitation or surface denaturation needs to be understood to support formulation choices as well as shipping and handling guidelines. For formulations containing low protein concentration, special attention is required to avoid impurity-related stability issues (e.g., oxidation fostered by metal contaminants in excipients).

Solid Dosage Forms. Recent improvements in devices designed for easier use of lyophilized products, e.g., dual chamber syringes, dual chamber cartridges and convenient reconstitution devices, have helped pharmaceutical industries to develop lyophilized products without too many concerns surrounding patient compliance issues. Because lyophilized products have less stability-related issues and have a much greater potential tolerance for room-temperature storage, many biopharmaceutical industries consider the lyophilized formulation as a default option. In fact, lyophilization has been widely utilized to overcome various stability issues of labile proteins. However, it is important to note that lyophilization can present its own challenges, particularly in designing appropriate formulations and economic cycles. Detailed discussion about the rational design of stable lyophilized formulations is available in another chapter in this book.

In addition to the required stability, a successful lyophilized formulation should also have the desired physical properties of the dried powder, e.g., ruggedness of the cake and the maintenance of the physical states for each of the ingredients. For example, crystallization of an initially amorphous excipient during storage can lead to unacceptable degradation of the protein product and loss of cake structure. Furthermore, optimal water content for protein stability should be studied and controlled during storage. It is preferable to define an acceptable

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range of water contents to provide flexibility in the manufacturing process. To assure that the appropriate water content is maintain, the integrity of container/packaging should be monitored in a high relative humidity environment.

The identity and volume of the reconstitution medium should also be clearly defined, because the use of injectable fluids other than the recommended one may compromise the quality of the product (e.g., solution tonicity or protein stability). Reconstitution should be convenient and rapid, and the stability of the reconstituted solution during handling and delivery needs to be demonstrated.

Only recently have spray-dried formulations become commonly used with the advent of novel protein delivery technologies. For example, spray-dried powders have been useful for developing products that require uniform particle size (e.g., pulmonary inhalation for systemic delivery). Similar issues to the lyophilized formulation apply to the spray-dried formulation, and the details of development of spray-dried formulations are presented in another chapter in this book. In addition to protein stability, physical properties pertinent to powder processing and powder stability (e.g., flowablity, hygroscopicity, agglomeration, density and crystallization of excipients) need to be well characterized.

Single Dose and Multidose Forms. Most protein pharmaceuticals are marketed as single dose forms. However, multidose formulations are useful when the dose needs to be split (e.g., dose titration or dose combination). Multidose formulations are distinguished by the presence of preservatives in the formulation, which prevent microbial contamination and/or growth during multiple disruptions of container closure integrity. In general, the addition of preservative(s), regardless of the preservative used, significantly changes the stability profiles of proteins (Maa and Hsu, 1996; Fransson et al., 1997; Lam et al., 1997). In some extreme cases, visible precipitation and aggregation have been reported. Therefore, the effect of various preservatives on the stability of protein should be carefully examined. Other experiments required to qualify a multidose formulations include the preservative effectiveness test and the stopper self-sealing test. Detailed procedures and specification are available from the USP (U.S. Pharmacopeia), the Ph. Eur. (European Pharmacopeia) and the JP (Japan Pharmacopeia).

Desired properties of the ideal preservative include: effectiveness at low concentration against a wide variety of organisms; chemical stability; solubility; compatibility with the protein drug, excipients and auxiliary agents; free from objectionable odor, taste, color and stinging; and non-toxic and non-sensitizing both internally and externally at the required concentration. Also, it must not absorb, penetrate, or interact with containers or closures (Thompson, 1998). For further details on preservatives, readers are referred to Regulatory Document 4 in the Appendix and Thompson (1988). Examples of typical preservatives used for parenteral protein pharmaceuticals are benzyl alcohol, phenol, *m*-cresol and benzalkonium chloride.

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Typical Protein Stability Problems: Causes and Solutions

Table 6 summarizes typical stability problems observed during protein formulation development and potential methods to solve each problem. The list does not represent the complexity of multiple problems that can be experienced with a given protein. Formulation research should be designed to handle each protein based on its unique stability profile.

Optimization of Formulation Variables

Overview of the Process. The optimization of formulation variables for product stability is the most critical part of protein formulation development. Various formulation excipients and buffers (Table 7) can be utilized and must, therefore, be chosen to maximize the pharmaceutical quality of the product (i.e., stability and activity) without introducing significant side effects. Among the listed formulation variables, the most powerful one is pH. Problems associated with the physical properties of a protein, e.g., precipitation due to solubility and/or stability, are generally very difficult to manage by other formulation means. Optimization of pH is a simple but very useful solution for such problems (Kolvenbach et al., 1997). Most chemical reactions also are affected by pH, e.g.,

Table 6.
Typical Stability Problems Observed in Protein Pharmaceuticals

Problems	Potential causes	Possible solutions
Non-covalent aggregation	Solubility, structural changes, heat, shear, surface, denaturants, impurities	pH, ionic additives, amino acids, surfactants, protein concentration, raw material purity
Covalent aggregation	Disulfide scrambling, other unknown mechanisms	pH, inhibit non-covalent aggregation
Deamidation	pH < 5.0 or pH > 6.0	pH optimization
Cyclic imide	pH around 5	pH optimization
Cleavages	Protease impurity, other unknown mechanisms	pH, product purity, inhibitors
Oxidation	Active oxygen species, free radicals, metals, light, impurity	Excipient purity, free-radical scavenger, active oxygen scavengers
Surface denaturation, adsorption	Low protein concentration, specific affinity, protein hydrophobicity	Surfactants, protein concentration, pH

Table 7.
Important Components of Protein Formulations

Formulation Variables	Desired attributes	Examples
pH	Provides good physical properties of protein, minimize degradations	
Stabilizer	Inhibit degradations, effective at low concentrations	Surfactants, sugars, salts, antioxidants
Solubilizer	Improve the solubility, effective at low concentrations	Salts, amino acids, surfactants
Buffer	Good buffering capacity, stable to temperature change, stable to freezing, good safety record	Phosphate, acetate, histidine, glutamate
Tonicity modifier; bulking agent	Inert, good safety record	Sodium chloride, sorbitol, mannitol, glycine

deamidation, cyclic imide formation, disulfide scrambling, peptide bond cleavage, and oxidation (see reviews listed above). Other functional excipients should be also carefully evaluated for the benefit of the product (e.g., use of sucrose to stabilize protein during lyophilization and storage in the dried solid).

In addition to their intended use, excipient candidates should be also qualified as appropriate pharmaceutical ingredients. Generally, it is preferred to select excipients that have been used in marketed products with a relevant route of delivery. Further, it is preferable if these excipients have been used with similar frequency of dosing, history of chronic use and similar patient populations. Otherwise, the approval and safety of the excipients need to be carefully examined. If the excipient is considered safe with a solid scientific basis or has a proven clinical safety record, it can be considered equivalent to approved excipients. The list of excipients used for parenteral pharmaceuticals is available in the literature (Powell et al., 1998; Nema et al., 1997; Appendix Regulatory Document 5). When it is necessary to introduce other excipients with minimum safety records, a significant risk associated with the excipients will be added to the product development and additional pre-clinical and clinical studies may be needed.

Another important requirement in qualifying an excipient is the purity of the raw material. Depending on the historical use as a pharmaceutical ingredient, several different pharmaceutical grades are available, e.g., USP (U.S. Pharmacopeia), Ph. Eur. (European Pharmacopeia) and JP (Japan Pharmacopeia). These pharmaceutical grade materials should be considered as a primary resource, but the quality provided may not be good enough for specific product development. For example, significant stability problems can be found with some impurities

even at concentrations below their specification, e.g., metal ions, peroxides, proteases and reducing sugars. These problems are more prominent in low protein concentration products due to a high impurity-protein ratio, although problems like visible precipitation of the protein may be independent of protein concentration. If adjustment in the existing specification is necessary, it is critical to look into the availability of GMP quality raw materials with modified specifications as early as possible, once the potential problem is identified.

The use of excipients derived from animals (e.g., Tweens) or humans (e.g., human serum albumin) should be avoided if possible due to the risk associated with transmissible diseases like bovine spongiform encephalopathy, Creutzfeldt-Jakob Disease, hepatitis virus and HIV. Numerous regulatory guidelines have been issued to discourage the use of animal/human-derived excipients (Appendix Regulatory Documents 6,7,8). When animal-derived excipients have to be included in the product, the manufacturer will need to demonstrate that their selection is fully justified.

Design of the Study. A design for the formulation optimization study should be in place before commencing the work. A typical study protocol will include the following information:

- Study title
- Study objective
- Source and quality of drug substance and excipients
- Material preparation
- Formulation matrix
  - Formulation variables
  - Protein concentrations or bracket
- Analytical methods
- Storage conditions (temperature, light, humidity)
- Additional sample handling conditions (temporary exposure to stresses, container orientation, etc.)
- Sampling schedule and expected duration of the study
- Plan for data analysis and report

The study can be more efficiently designed by utilizing experimental design software packages, which will help to minimize the resources required for sample preparation, analyses, and data analysis.

Necessary Studies for Formulation Development

Storage Stability Study. Documenting that the formulation will keep the protein stable until the desired expiry can be the most time-consuming part of

formulation development. The expiry requirements are determined by distribution not regulatory requirements. One year is probably too short for effective manufacturing and distribution through normal channels. In general, a shelf life of 18 month is considered acceptable for commercialization. Results obtained from accelerated stability studies are useful for predicting potential degradation products and appropriate analytical methods, but whatever the actual shelf life, it must be supported by sufficient real-time storage data to obtain regulatory approval. Thus, it is important to establish a final formulation and start the real-time storage studies as early as possible during product development.

Process Development. Formulations that can be prepared on a small scale without experiencing any problems may encounter significant problems during the scale-up of the process. For example, mixing solutions in a large stainless steel tank, pumping solutions through stainless steel tubing, filtration and filling through a high-speed filling machine can introduce unexpected stresses to the protein. An increase in the formation of particulates, along with a loss of proteins due to surface adsorption and aggregation, has routinely been observed. It is important to expose the formulation to equivalent stresses and make sure that no formulation adjustment is necessary to accommodate the manufacturing processes. Again, this testing should be done as early in the development process as possible.

Transportation, Handling and Delivery Study. Unexpected environmental changes can be encountered during the distribution and handling of products (e.g., accidental freezing, exposure to temperatures different from the recommended conditions, vigorous agitation, etc). It is critical to develop the formulation with these stresses in mind because they can compromise the quality of the product.

Also, during administration to the patient, proteins can be exposed to different types of stresses introduced by the device and the routes of delivery. Examples include incompatibility with the delivery device (e.g., protein aggregation induced by exposure to tubing surfaces) and/or concomitant medication (e.g., protein aggregation induced by co-administered antibiotics).

Preclinical and Clinical Studies. Results documenting the maintenance of the biophysical and biochemical properties of the protein are essential for a final formulation decision. Before finalizing the formulation, it is also important to confirm that it does not affect critical *in vivo* biological properties of the protein (e.g., activity, pharmacokinetic profile, and toxicity profile). Maintenance of a protein's biophysical properties can be examined using various structural analyses (e.g., circular dichroism, fluorescence and infrared spectroscopies, etc.). It is possible to determine the biochemical equivalence of the protein pharmaceutical by *in vitro* activity and/or preclinical *in vivo* bioassays. Results supporting the toxicity profile of the formulation can be generated by both preclinical and clinical studies.

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Strategies to Overcome Difficult Formulation Problems

Occasionally, problems are encountered that are difficult to overcome with conventional formulation approaches. It is possible to conduct additional studies to confirm that the problem is pharmaceutically acceptable. On the other hand, unique formulation approaches can be introduced to address specific problems. Examples of this approach are provided below.

Qualification of Degradation Products. If decreasing the amount of degradation product below the specified threshold is not feasible, then the degradation product can be defined as a drug substance by demonstrating that it does not affect the pharmaceutical quality of the drug product, i.e., safety and efficacy (Appendix, Regulatory Document 1). If there is not sufficient information available, additional qualification studies recommended in the regulatory guidance can be carried out (see the discussion above). The experience of having these degradation products in the materials used for clinical studies can sometimes be very useful because the results obtained can provide useful insight into the clinical implication of the degradation products.

Site-directed Mutagenesis to Improve Properties. Some problems related to the intrinsic properties of a protein cannot be overcome unless a change in the sequence is introduced. After careful research is carried out to identify the problematic region or residue, the protein can be engineered for better physical and/or chemical properties. For serious problems like precipitation due to insolubility or poor stability, changes in protein sequence have been proven effective for improving physical properties (Murby et al., 1995; Roig and Kennedy, 1995).

Chemical Modifications. The physical properties of proteins can be improved by modifying problematic amino acid side chains with small compounds or large polymers (e.g., attachment of polyethylene glycol) (Fagain, 1995; Guerra et al., 1998; Francis et al., 1998). In addition, there are other desirable improvements that can be achieved by the conjugation chemistry (e.g., enhanced pharmacokinetic profiles, reduced immunogenecity, enhanced adsorption, etc.).

Unconventional Dosage Forms. Some protein stability problems can be resolved by introducing novel approaches in the formulation. Examples include suspension formulations (Defelippis et al., 1998), microencapsulation with cyclodextrin (Brewster et al., 1991), suspension of dry-powder in non-aqueous vehicle (Knepp et al., 1998), and use of non-aqueous vehicles with hydrophobic ion-pairing (Manning et al., 1995).

FORMULATION IN COMMERCIAL PRODUCT DEVELOPMENT

Critical Formulation Decisions During Pharmaceutical Development

A brief summary of the important phases of a commercial product development is shown in Figure 1. Ideally, a stable formulation would be available during the early discovery research period to ensure that the protein is in its active and stable form during critical feasibility studies. However, development of a stable formulation for each drug candidate is not practically possible because such an approach would take too much time and too many resources. Generally, formulation development starts after the decision is made to start clinical trials. A

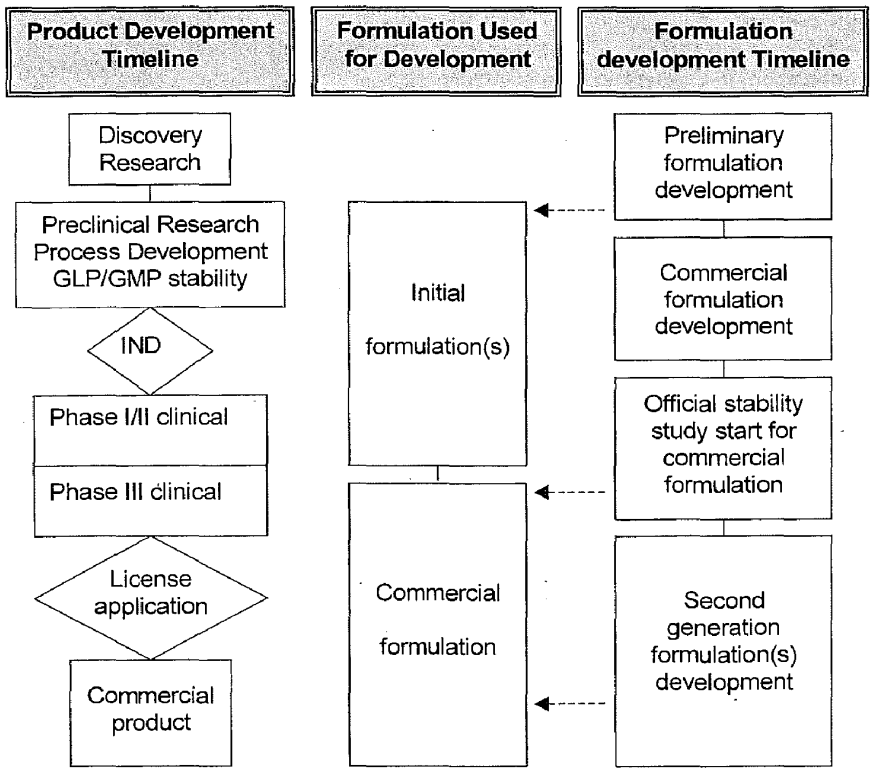

Figure 1. Diagram showing commercial formulation development process.

reliable formulation is required to support various preclinical and clinical studies. The formulation can be further improved later to satisfy the clinical, marketing, and regulatory needs. Although formulation development does not necessarily appear rate-limiting during this improvement period, it is important to understand that changing a formulation may require much more supporting work, including additional clinical trials, which can take years.

Formulation for Early Preclinical and Clinical Studies

When a promising protein drug candidate is identified from preliminary feasibility studies, a decision will be made to introduce the drug to clinical studies. In order to obtain regulatory approval to initiate the clinical trials, it is required to demonstrate safety, manufacturing capability, stability of the drug and reproducibility in studying the drug. A sufficiently stable formulation is necessary at this stage because it is important to maintain the quantity and quality of the protein for all research studies from which results will be used for registration of the product with regulatory agencies. Therefore, formulation development becomes a rate-limiting process at this early stage. Formulations can be stored frozen or lyophilized for this purpose. At this stage in product development, the shelf-life requirement is determined by the logistics of supplying drug for clinical trials.

Commercial Formulation

Commercially viable and market competitive formulations have some common features. Most of all, the formulation should maintain the safety and efficacy profile of the protein drug during all the handling and uses specified on the label. Since commercial distribution channels are not equipped for frozen products, shipping and storage at refrigerated temperature or higher are required. Sufficient shelf life needs to be determined under conditions to which the product will be exposed in the commercial distribution system. Various systematic studies need to be carried out to comply with regulatory requirements for registration. It takes 1–2 years to collect all of these results, so the commercial formulation is developed while preclinical studies or early clinical trials (with the preliminary formulation) are in progress. If possible, the commercial formulation should be introduced before the pivotal clinical trial because clinical experience is the most effective way to confirm the safety and efficacy aspects of the formulation. In addition, formulation changes after this point may introduce formidable challenges to the clinical program and to obtaining regulatory approval.

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Regulatory Issues in Formulation Development

Incorporating regulatory guidelines into the formulation development is not only useful to develop high quality pharmaceutical formulations for maximum benefit to the patients, but also critical to prepare complete documents necessary for regulatory approval for commercialization of the drug. Readers who wish to obtain a comprehensive understanding of the guidelines are referred to the relevant documents published by regulatory agencies. In this section, a brief summary of the guidelines related to the formulation issues is provided.

Guidelines for Stability Studies. Comprehensive guidelines can be obtained from regulatory agencies (Appendix, Regulatory Documents 9–12) and review articles in the literature (Grimm, 1998; Kommanaboyina and Rhodes, 1999; Matthews, 1999). These guidelines generally cover the formal stability studies for bulk drug material, in-process samples and final formulated product. Although some issues may not be relevant for the earlier formulation development work, these guidelines provide key elements for designing stability studies. The guidelines provide information such as what types of experiments should be included in the study protocol, how to propose a stability-indicating profile, and what analytical results are needed to define the purity of the product and the molecular characteristics of degradation products. Another important piece of information provided in the guidelines is the definition of proper experimental conditions, e.g., definition of storage temperature, humidity, light strength, and accelerated and stressed conditions. The guidelines also provide the official protocols to evaluate the results obtained from stability studies.

Results Required to Apply for Regulatory License for a Drug Product. Detailed information regarding the formulation is presented at the Development Pharmaceutics section in the CMC section of regulatory applications (Appendix, Regulatory Docoments 13–16). All of the essential information required to apply for regulatory approval of protein formulations can be found in Note for Guidance on Development Pharmaceutics (Appendix Regulatory Document 17) and Development of Pharmaceutics for Biotechnological and Biological Products (Appendix, Regulatory Document 8). It is important to note that this is currently a European requirement although the international harmonization process may eventually introduce it to U.S. regulatory requirements. A brief summary of the important formulation information is shown in Table 8.

Results Required to File Formulation Amendments. A formulation change can introduce substantial potential adverse effects on the identity, strength, quality, purity or potency of the product as related to the safety or effectiveness of the product. For this reason, it is required that a supplement to the approved license application be submitted. This supplement should include a detailed description of the proposed change. It should also include methods and results for the studies performed to evaluate the effect of the change on the

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Table 8.
Summary of Information Included in Regulatory Applications

	General information	Comments specific to proteins
Active substance (protein)	Compatibility with excipients and other combined products, and physicochemical characteristics	Structural elements responsible for the biological activity; good coverage of degradations occurring during storage, manufacturing, and delivery.
Excipients	Function of each excipients, justification for their inclusion, and compatibility with other excipients, choice of quality	
Formulated products	Overage, physicochemical parameters, components with appropriate results supporting intended purpose; compatibility with diluent, device, and other drugs in contact before delivery; critical physical properties	Stability of structure in terms of biological activity; formulation optimization for both manufacturing process and stability
Packaging material	Integrity of container and closure during storage, reconstitution, admixture, dilution; sorption to container, leaching, and dose reproducibility	Adsorption, denaturation at the interface, and aggregation of the surface-denatured protein; reconstitution of dry-powder formulation
Manufacturing process	Manufacturing process for the preparation of formulation and its justification, appropriate method of sterilization and justification	Results to support the quality and stability of the protein during the manufacturing process; membrane filtration under aseptic conditions sufficient

product's identity, strength, quality, purity, and potency of the product, as related to the product's safety or effectiveness (Appendix, Regulatory Documents 18–20). When the degradation profile is changed qualitatively or quantitatively, it is recommended to follow the impurity-related guidelines discussed above (Appendix, Regulatory Documents 2,3). The manufacturer must obtain approval of the supplement by FDA prior to distribution of the product made using the change. In general, the following studies (Table 9) can be carried out to confirm

Table 9.
Studies Needed to Support Change in Formulation

Research requirements	Supporting results
Purity	Stability, compatibility, Structural analyses
Potency	*In vitro*/*in vivo* bioassays, preclinical and/or clinical pharmacokinetic comparability , clinical efficacy
Safety	Preclinical safety, clinical safety

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that the change in the formulation will not affect the safety and effectiveness c the product. It is recommended to consult the regulatory representative to fin out how much additional information may be needed for the approval of th changed formulation.

APPENDIX: LIST OF REGULATORY DOCUMENTS

1. International Conference on Harmonization: Guidance on specifications: Te procedures and acceptance criteria for Biotechnological/Biological Produc Federal Register: August 18, Volume 64, Number 159, pp. 44928–449 (1999).
2. International Conference on Harmonization: Impurities in New Drug Prc ucts. FDA Q3B (11/97).
3. Guidance for Industry. ANDAs: Impurities in Drug Products. Draft guidan FDA (12/98).
4. Note for Guidance on Inclusion of Antioxidants and Antimicrobial Pres vatives in Medicinal Products (CPMP/CVMP/QWP/115/95) EMEA (7/9
5. Inactive ingredient guide: inactive ingredients for currently marketed dı products. (1996) FOI Services, Inc. Rockville, MD.
6. Note for guidance on minimizing the risk of transmitting animal spongifc encephalopathy agents via medicinal products. EMEA (4/99).
7. Note for guidance on plasma-derived medicinal products. EMEA (7/98).
8. Development Pharmaceutics for Biotechnological and Biological Produ Annex to Note for Guidance on Development Pharmaceutics (CPM QWP/155/96). EMEA (10/1999).
9. International Conference on Harmonization: Stability testing of new d substances and products. Federal Register, Sept. 22, Volume 59, Number 1 pp. 48754–48759 (1994).
10. International Conference on Harmonization: Final guideline on stab testing of biotechnological/biological products. Federal Register, July Volume 61, Number133, pp. 36466–36469 (1996).
11. Guideline for Industry: Stability testing for drug substances and drug p ucts: draft guidances. FDA, (6/98).
12. International Conference on Harmonization: Guidelines for the photost ity testing of new drug substances and products. Federal Register, May Volume 62, Number. 95, pp. 27115–2712 (1997).
13. Guideline for Submitting Documentation for the Stability of Human D and Biologics FDA. (2/87).
14. Guidance for Industry. For the Submission of Chemistry, Manufacturing Controls and Establishment Description Information for Human Pla

Derived Biological Products, Animal Plasma or Serum-Derived Products. FDA (2/99).
15. Guidance for Industry. INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products Chemistry, Manufacturing, and Controls Content and Format (Draft guidance) FDA (2/99).
16. Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products, FDA (11/95).
17. Note for Guidance on Development of Pharmaceutics (CPMP/BWP/328/99). EMEA (01/1998).
18. Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, April, 1996.
19. Guidance for Industry: Changes to an Approved Application. For Specified Biotechnology and Specified Synthetic Biological Products, 21 CFR 601.12, 314.70; July 24, 1997, Vol 62. No. 142.
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5

Rational Design of Stable Lyophilized Protein Formulations: Theory and Practice

John F. Carpenter[1,2], *Beyong S. Chang*[3], *William Garzon-Rodriguez*[1,2], *and Theodore W. Randolph*[1,4]

INTRODUCTION

For ease of preparation and cost containment by the manufacturer, and ease of handling by the end user, an aqueous therapeutic protein formulation usually is preferred. However, with many proteins it is not possible—especially considering the time constraints for product development—to develop sufficiently stable aqueous formulations. Unacceptable denaturation and aggregation can be induced readily by the numerous stresses to which a protein in aqueous solution is sensitive; e.g., heating, agitation, freezing, pH changes, and exposure to interfaces or denaturants (Arakawa et al., 1993; Cleland et al., 1993; Brange, 2000; Bummer

John F. Carpenter, William Garzon-Rodriguez, and Theodore W. Randdph • Center for Pharmaceutical Biotechnology. *John F. Carpenter, William Garzon-Rodriguez, and Theodore W. Randolph* • Department of Pharmaceutical Sciences, School of Pharmacy, University of Colorado Health Sciences Center, Denver, CO 80262. *Beyong S. Chang* • Amgen, Inc., Thousand Oaks, CA 91320. *Theodore W. Randolph* • Department of Chemical Engineering, University of Colorado, Boulder, CO 80309.

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and Koppenol, 2000). Furthermore, even under conditions that thermodynamically greatly favor the native state of proteins, aggregation can arise during months of storage in aqueous solution (e.g., Gu et al., 1991; Arakawa et al., 1993; Chen et al., 1994; Volkin and Middaugh, 1996; Chang et al., 1996a). In addition, several chemical degradation pathways (e.g., hydrolysis and deamidation) are mediated by water. In aqueous formulations, the rates of these and other (e.g., oxidation) chemical degradation reactions can be unacceptably rapid on the time scale of storage (e.g., 18–24 months) for pharmaceutical products (Manning et al., 1989; Cleland et al., 1993; Goolcharran et al., 2000; Bummer and Koppenol 2000).

In contrast, a properly lyophilized formulation can maintain adequate physical and chemical stability of the protein during shipping and long-term storage even at ambient temperatures. As will be outlined in this chapter, developing stable lyophilized protein formulations should be a rational, straightforward process, which for most proteins should be rapid. With liquid formulation development, it may only be possible to obtain adequate protein stability after lengthy studies. Furthermore, sometimes there are conflicting conditions (e.g., pH) needed to slow sufficiently multiple degradation pathways in aqueous solution. Considering these issues plus the fact that formulation scientists now have to deal with numerous proteins and/or variants of a given protein, lyophilization should be considered as a primary mode for product development. Only if a parallel effort to develop an aqueous formulation is successful, will a final lyophilized product not be needed.

Rapid formulation development has important financial ramifications. A drug product has a finite patent life, during which time the company has an exclusive market. Considering that even a moderately successful drug product has annual sales of hundreds of millions of dollars, potentially millions of dollars in sales are lost for each day of delay in bringing a product to market. Unfortunately there are often delays because the formulations designed during early stage development and clinical trials (e.g., frozen) were not adequate for the final product. With a rational approach to formulation development, pharmaceutical scientists and process engineers can minimize the risk of this problem and the time needed to obtain a successful, final formulation. The success of such efforts depends on frank, open communication between the groups involved. For example, it is critical that the formulation scientists learn from the process engineers the issues for large-scale lyophilization runs, which are usually conducted in units that do not have the capacity to match processing parameters obtained in a small-scale research lyophilizers.

Despite the best efforts of the scientists and engineers, all too often delays in formulation development arise because sufficient resources are not invested in product development. For example, sometimes, purchase of essential equipmen

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(e.g., a differential scanning calorimeter), which costs a minute fraction of a day's sale of product, is not allowed. To avoid unnecessary delays in product launch, which can have disastrous consequences for the company and for patients, it is essential that companies appreciate that product development is ultimately a key limiting factor in getting a therapeutic to market. Hence, development efforts need to be as well funded as the usually much more visible drug discovery research programs. If a product is not stable, it will not be marketed, no matter how dramatic an impact it can have on human health and the financial status of the company.

MINIMAL CRITERIA FOR A SUCCESSFUL LYOPHILIZED FORMULATION

Research over the past several years has demonstrated that five criteria define the minimal conditions necessary for a successful lyophilized protein formulation (Table 1).

The first four criteria can be met with use of the appropriate excipients and lyophilization cycle design. For information on the proper design of lyophilization cycles, the reader is directed to the numerous previous reviews in this area (Franks, 1990; Pikal, 1990; Nail and Gatlin, 1993; Gatlin and Nail, 1994; Carpenter and Chang, 1996; Rey and May, 1999; Cappola, 2000). For the current chapter we will only consider cycle design in terms of the interplay between formulation physical properties (e.g., collapse temperature) and process parameters (see below). The last criterion listed in Table 1 requires insight into the unique physicochemical properties of each therapeutic protein, which will be explained in more detail below. We will discuss in turn why each of these criteria is important. Then we will present an explanation of how to design rationally a formulation to meet these criteria.

Table 1.
Minimal Criteria for a Successful Lyophilized Protein Formulation

1. Protein unfolding during freezing and drying is inhibited.
2. The glass transition temperature of the product exceeds the planned storage temperature (e.g., $T_g > 30°C$).
3. The water content is relatively low (e.g., 1% by mass).
4. A strong, elegant cake structure is obtained (i.e., collapse and meltback are avoided).
5. Steps are taken to minimize specific routes of protein chemical degradation (e.g., product vials are sealed under nitrogen to reduce the rate of methionine oxidation).

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Inhibition of Lyophilization-Induced Protein Unfolding

The stresses of freezing and drying cause protein unfolding, and the formulation must be designed to inhibit unfolding at each step (Prestrelski et al., 1993a,b; Carpenter et al., 1993; Prestrelski et al., 1995; Constantino et al., 1995, 1998; Griebenow and Klibanov, 1995; Allison et al., 1996, 1998, 1999, 2000; Chang et al., 1996b; Krielgaard et al., 1998a, 1999; Chen et al., 1999; Bell, 1999; Carrasquillo et al., 2000). Even if the formulation excipients and/or intrinsic thermodynamic stability of the protein prevent denaturation during freezing, unfolding can arise during subsequent drying (Carpenter et al., 1993; Prestrelski et al., 1993b; Allison et al., 1998; Carrasquillo et al., 2000). Conversely, once a protein unfolds during freezing, it will not regain native structure during dehydration.

For many proteins, unfolding during lyophilization leads to clinically unacceptable, non-native aggregates, even when samples are rehydrated immediately after lyophilization (Prestrelski et al., 1993a, 1995; Allison et al., 1996; Krielgaard et al., 1998a, 1999; Costantino et al., 1998). Aggregates are not necessarily formed during freezing and drying. Rather, during rehydration refolding of structurally perturbed protein molecules competes with formation of non-native protein aggregates (Prestrelski et al., 1993a). Aggregation can be minimized by including stabilizing excipients (e.g., sucrose or trehalose) in the formulation to inhibit lyophilization-induced unfolding (Prestrelski et al., 1993a, 1995; Allison et al., 1996; Krielgaard et al., 1998a, 1999; Costantino et al., 1998). Furthermore, fostering refolding during rehydration (e.g., with surfactants) can reduce aggregation (Chang et al., 1996c; Zhang et al., 1995, 1996).

In addition to minimizing protein aggregation during lyophilization/rehydration, maximizing retention of native protein structure in the dried solid is essential for optimizing long-term storage stability (Prestrelski et al., 1995; Chang et al., 1996b; Krielgaard et al., 1998a, 1999; Allison et al., 2000; Cleland et al., 2001). Both chemical and physical degradation in the dried solid can be accelerated if protein unfolding is not inhibited during lyophilization. With chemical degradation, a non-native structure may provide an environment conducive to covalent modification of one or more residues. For example, exposure of a methionine, which is normally buried deep in the interior of the native protein, on the surface of an unfolded dried protein may foster oxidation. Increased levels of aggregates noted after storage and rehydration of unfolded proteins could be due to formation of non-native intermolecular contacts within the dried solid, perturbation of refolding during rehydration because of chemical degradation, and/or other undefined processes.

Infrared spectroscopy has been used routinely to compare the secondary structures of a protein in lyophilized formulations to that of the native protein in aqueous solution (Prestrelski et al., 1993a,b; Prestrelski et al., 1995; Dong et al.,

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1995; Constantino et al., 1995, 1998; Griebenow and Klibanov, 1995; Allison et al., 1996, 1998, 1999, 2000; Chang et al., 1996b; Krielgaard et al., 1998a, 1999; Carpenter et al., 1998; Chen et al., 1999; Carrasquillo et al., 2000). This method should be considered essential in the development of stable lyophilized formulations, because it allows one to assess rapidly the effectiveness of formulations at inhibiting protein unfolding. Technical details about how to employ infrared spectroscopy to design stable lyophilized protein formulations can be found in the papers cited above.

Storage at Temperatures Below Formulation Glass Transition Temperature

In the dried powder, the protein is a component of an amorphous phase that includes amorphous excipients and water. If this glassy matrix is held below its characteristic glass transition temperature (T_g), the rate of diffusion-controlled reactions, including protein unfolding/aggregation and chemical degradation, are greatly reduced, relative to rates noted at temperatures $>T_g$ (Roy et al., 1991; Franks, 1990; Franks et al., 1991; Pikal, 1994, 1999). T_g can be determined with differential scanning calorimetry (DSC) or other thermal scanning methods (Nail and Gatlin, 1993; Chang and Randall, 1992; Craig and Royall, 1998; Verdonck et al., 1999).

Obtaining a formulation T_g in excess of the planned storage temperature (e.g., room temperature) is absolutely essential for optimal protein stability (e.g., Franks et al., 1991; Pikal, 1994, 1999; Carpenter and Chang, 1996; Duddu and Dal Monte, 1997). The T_g of a given amorphous phase is dependent on the T_g and mass percent of each component, including water (Angell, 1995; Franks et al., 1991; Levine and Slade, 1988, 1992; Pikal, 1994, 1999). Compared to excipients, dried proteins have relatively high T_g's (e.g., >150°C; Angell, 1995). Thus, with all other factors being held constant, the formulation T_g varies directly with the mass fraction of protein. However, care must be taken that the mass fraction of protein is not so high that there are not adequate levels of stabilizing excipients to prevent protein unfolding during lyophilization (Cleland et al., 2001; and see below).

Fortunately, sucrose and trehalose, which are the preferred excipients for inhibiting lyophilization-induced protein unfolding (see below), also provide a glassy matrix with acceptably high T_g values. For example, with water contents of 1% the T_g for pure sucrose and trehalose are about 100 and 65°C, respectively (Crowe et al., 1998).

It has now been documented with several proteins, that simply storing the formulation at temperature below T_g alone does not assure optimal stability. A

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native protein structure is also required. For example, proteins lyophilized in dextran alone are usually unfolded, but in a glassy matrix with a relatively high T_g (e.g., > 75° C). Yet they still degrade at relatively rapid rates compared to those for native protein molecules lyophilized with either sucrose or trehalose (Kriel-gaard et al., 1998a, 1999; Lueckel et al., 1998; Allison et al., 2000; Yoshioka et al., 2000). On pharmaceutical time scales of several months of storage many degradative reactions are not coupled to the glass transition of a formulation. This is because on these times scales there is still significant molecular mobility, even at temperatures well below (e.g., more than 30° C) the T_g (Hancock et al., 1995; Duddu et al., 1997; Pikal, 1999; Yoshioka et al., 1999).

The Water Content is Relatively Low

Because of its very low T_g (−135°C), water is a potent plasticizer for glasses; increasing water content in the dried formulation will greatly reduce T_g. For example, increasing the water content of pure sucrose from 1 to about 3–4% (g H_20/100 g dried powder) is sufficient to reduce the T_g to below room temperature (Crowe et al., 1998). It is critical to achieve a sufficiently low water level for a given formulation such that T_g exceeds the planned storage temperature. The lyophilization cycle dictates the initial water content (see reviews listed above). The most important parameter is the temperature for secondary drying, when the unfrozen water is desorbed (Pikal et al., 1990).

Water can also be transferred to the product from the vial stoppers during storage (Pikal and Shah, 1992; DeGrazio and Flynn, 1992; Hora and Wolfe, 1999). This effect can be dramatic. For example, let's consider a formulation containing 10 mg of dried protein, 40 mg of sucrose and initial water content of 1% by weight. The total amorphous fraction containing protein and sucrose has 0.50 mg of water. If 1.0 mg of water was transferred from the stopper to the product, the water content of this fraction would increase from 1% to 3.0%. This increase would be sufficient to lower the formulation T_g to below room temperature (Crowe et al., 1998). The risk of transfer of moisture from stoppers can be minimized by drying the stoppers before use, and, if acceptable for a given product, using stoppers coated with a material such as Teflon (see Hora and Wolfe, 1999).

A Strong, Elegant Cake Structure is Obtained

Often the most desired cake has strong, porous structure, without macroscopic collapse or meltback. This structure has a high surface area to volume

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ratio, which aids in the rapid dissolution of product upon addition of water. A detailed account of how to obtain such a cake structure is beyond the scope of the current chapter, but is available in several previous reviews (see above). For the current purposes it is sufficient to focus on the impact of formulation composition on avoiding collapse or meltback. When a product is frozen, the protein and amorphous excipients (e.g., sucrose) are dispersed between ice crystals and any excipient used as a crystalline bulking agent (e.g., glycine). To obtain an appropriate cake structure during lyophilization, the product temperature during primary drying, when the water in ice is sublimed, must be below the characteristic collapse and eutectic melting temperatures of amorphous and crystalline solutes, respectively. Above the eutectic temperature, the melting of crystalline solutes leads to massive loss of porous structure and macroscopic dissolution of the frozen matrix into a "puddle". Above the collapse temperature, which closely coincides with the glass transition temperature (T_g') of the maximally freeze-concentrated amorphous phase, the amorphous phase cannot support its own weight. The result is also a loss of pore structure and a macroscopic shrinkage or collapse of the cake.

It should be noted that the T_g' thermal event, which can be measured with differential scanning calorimetry, is also referred to as a softening event (T_s), rather than the actual glass transition temperature of the freeze-concentrated amorphous phase (Shalaev and Franks, 1995). Whatever the exact nature of the thermal event, it can be detected with differential scanning calorimetry as a second order increase in the baseline of the thermogram, which usually occurs just prior to the onset of the endotherm for the melting of ice (e.g., Her and Nail, 1994). The transition can also be measured with electrothermal methods (Her et al., 1994).

Another powerful method, which is essential for rational development of lyophilized formulations, for determining collapse and eutectic melting temperatures is freeze-drying microscopy (e.g., Nail et al., 1994). With this approach, the formulation of interest is directly examined visually for its performance during a simulated freezing, annealing and drying cycle. All of the critical phase changes, including ice formation, solute crystallization, eutectic melting and collapse, can be detected easily, and the temperature of their occurrence can be measured accurately.

Formulation composition dictates collapse temperature. Each pure amorphous excipient has a characteristic T_g' and collapse temperature; the collapse temperature for the formulation is the mass averaged temperatures of all of the components in the amorphous phase. It is important to design a formulation with maximum collapse temperature, because the rate of drying is directly proportional to the sample temperature during lyophilization. To allow for a reasonable drying time the T_g' should not be lower than –40° C. The T_g' values for pure sucrose is –32° C, while that of pure trehalose is –30° C (Skrabanja et al., 1994; Chang and

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Randall, 1992). In contrast, glucose, which should also be avoided because it is a reducing sugar, has a T_g' of −43° C. The collapse temperature of pure protein is about −10° C, which means increasing the protein:sugar mass ratio will increase collapse temperature. Finally, collapse temperature will be decreased if salts and excipients are not maximally crystallized. For example, glycine has a T_g' of −37° C, and its contribution to the amorphous phase can reduce collapse temperature to impractically low values (Carpenter and Chang, 1996). This problem can be avoided by using the appropriate annealing (see Carpenter and Chang, 1996) of the frozen product to maximize crystallization.

Meltback can be avoided by using crystalline solutes with relatively high eutectic melting temperatures. For example, eutectic melting temperatures for mannitol and glycine are −1 and −4° C, respectively. In contrast, additives such as calcium chloride have very low eutectic melting temperatures (e.g., −51° C for calcium chloride). If mannitol or glycine is used as a crystalline bulking agent, the T_g' of the amorphous excipient phase, which is lower that the eutectic melting temperatures of these excipients, will be the value that dictates the temperature of primary drying.

Collapse can also occur during secondary drying, when unfrozen water is desorbed, if the temperature is increased too rapidly. As water is removed from the amorphous phase the T_g of this phase increases. Thus, product temperature can be raised gradually and collapse can be avoided if product temperature at a given time point does not exceed the T_g. Directions for optimizing secondary drying can be found in previous reviews mentioned above.

Steps Taken to Minimize Specific Routes of Protein Chemical Degradation

It is essential that the major routes of chemical, as well as physical, degradation be characterized carefully for each protein, because all of the criteria listed above can be met and a protein might still be damaged during long term storage in the dried solid. For example, methionine oxidation is a common degradation pathway for therapeutic proteins (Manning et al., 1989; Ahern and Manning, 1992; Cleland et al., 1993; Goolcharran et al., 2000). Even in a formulation that prevents protein unfolding and has a T_g exceeding the storage temperature methionine oxidation can proceed at an unacceptably rapid rate. If a methionine residue is on the surface of the protein, maintaining native structure would not prevent this residue's exposure to reactive oxygen species in the dried solid. But why would the glassy matrix not sufficiently retard the mobility of the reactive species to prevent the reaction from occurring? On pharmaceutical time scales (i.e., of many months) relevant motion in a glass is not arrested unless the storage

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temperature is about 50° C below the T_g (e.g., Hancock et al., 1995; Pikal, 1994; Pikal, 1999). Therefore, the mobility of a relatively small reactive oxygen species and the oxidation of methionine residues are probably not coupled to the glass transition of the formulation. An intriguing alternative, but not mutually exclusive, explanation has been suggested by Steve Prestrelski (personal communication). He proposes that reactive oxygen species accumulating during long-term storage might not be causing damage just in the dried solid. Rather upon rehydration oxygen radicals rapidly react with the protein. This is an important area for future research.

Fortunately, despite the rather complicated and poorly understood theoretical aspects of unacceptable methionine oxidation rates in dried protein formulations, from a practical viewpoint dealing with the problem is relatively straightforward. Methionine oxidation can be minimized by sealing vials under nitrogen and/or using formulation additives (e.g., free methionine) to compete with protein residues for reactive oxygen species. These approaches should be effective whether the oxidation of residues occurs in the dried solid, during rehydration or at both times.

RATIONAL DESIGN OF STABLE LYOPHILIZED FORMULATIONS

Two critical practical issues need to be considered when choosing excipients for a therapeutic protein formulation. 1) From a financial standpoint, scientists should focus on using excipients and processing approaches that do not need to be licensed from a patent holder. Acceptable protein stability can be achieved readily using excipients and processing methods that are well known to someone, to use the legal term, "skilled in the art of protein formulation." Clearly, however, the specific applications of such compounds and processes to a given protein drug product and/or a class of proteins often can be patented. Such patents may be critical to the company developing that product.

2) From a regulatory standpoint (and financial perspective, also), the formulation scientist should choose from among excipients that are already used in approved parenteral products. For protein stabilizers, the best choices are the disaccharides, sucrose and trehalose. For bulking agents, the best choices are glycine, mannitol and hydroxyethyl starch. For surfactants, usually the Tweens (20, 40 or 80) are preferred.

Based on these practical concerns and the criteria for a successful lyophilized protein product (Table 1), prototypic rational formulations are presented in Table 2. If the formulations suggested are employed, and the criteria in Table 1 are met, then most likely the product will have acceptable stability.

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Table 2.
Example of Rational Lyophilized Protein Formulation

1. Buffer that does not acidify during freezing (e.g., Tris, histidine, citrate)
2. Specific ligands/pH that optimizes thermodynamic stability of protein
3. Trehalose or sucrose to inhibit protein unfolding and provide glassy matrix
4. Bulking agent (e.g., mannitol, glycine or hydroxyethyl starch)
5. Nonionic surfactant to reduce protein aggregation

It is important to emphasize that not all components listed in Table 2 may be needed for a given protein product. For example, it may not be necessary to include a nonionic surfactant to aid in reducing protein aggregation. If there is not clear evidence that a given component is beneficial for a formulation, then that component should not be included in the formulation. Also, some components that are used because of "tradition" and/or for purposes such as final formulation tonicity can cause great difficulties in lyophilization. The most common example is the use of NaCl as a tonicity modifier. During lyophilization, NaCl can greatly reduce the collapse temperature of a formulation, if a fraction of the salt does not crystallize (Her et al., 1994). Crystallization of NaCl during freezing and annealing can be inhibited by other excipients (e.g., bulking agents and stabilizing sugars). Because of the low collapse temperature, a low temperature cycle must be used, which increases production time and costs. Also, even if formulations with NaCl can be lyophilized successfully in small research lyophilizers, there is great risk that a large fraction of vials will collapse during large scale manufacturing runs. Thus, if at all possible, NaCl should not be used in lyophilized formulations. Alternative tonicity modifiers include mannitol and glycine, which can also serve as crystalline bulking agents.

Every protein and product has unique characteristics, some of which may cause difficulty in designing stable formulations. Thus, the suggestions in Table 1 should be considered only as a good starting point in formulation development. For the remainder of this chapter we will discuss the rationale for the choice of each of the formulation components, their mechanisms of action and other practical approaches that can be used to increase protein stability.

Choice of Buffer

In terms of protein stability, the main concern with choice of buffer is the potential of certain buffer salts to precipitate during freezing and cause large changes in pH. For example, crystallization of the dibasic form of sodium

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phosphate results can result in a pH < 4 (van den Burg, 1959; van den Burg and Rose, 1959; Anchordoquy and Carpenter, 1996). Thus, whenever possible, sodium phosphate buffer should be avoided. Although somewhat obvious, it is important to realize that a sodium phosphate system will be present if one starts with potassium phosphate buffer salts and NaCl, as is the case with phosphate buffered saline. Alternative buffers that do not appear to have major pH changes during freezing include Tris and histidine (Anchordoquy and Carpenter, 1996).

A clear example of the detrimental effects of buffer acidification on the stability of a lyophilized protein formulation has been reported by Lam et al. (1996). These researchers documented that a succinate buffer with an initial pH of 5 exhibited a pH drop of 1–2 units during lyophilization. The result was a reduced stability of interferon-γ during storage of the lyophilized formulation, relative to that noted for formulations prepared with glycolate buffer, which does not undergo freezing-induced acidification.

Specific Ligands/pH that Optimizes Thermodynamic Stability of Protein

Often experience gained during purification, intermediate storage protocols and preformulation studies can provide great insight into specific solution conditions (e.g., pH, ionic strength, buffer type) that confer the greatest stability to a given protein. Before choosing the appropriate "general" stabilizers, which are effective at protecting most proteins, it is absolutely essential that the formulation be optimized for the specific factors that increase the physical and chemical stability of a given protein. For example, simply avoiding extremes in pH can drastically reduce the rate of deamidation (Manning et al., 1989; Goolcharran et al., 2000). Also, specific ligands that increase protein physical stability (e.g., by increasing the free energy of unfolding) should be investigated. The stabilizing effects of heparin and other polyanions on growth factors (e.g., Chen et al., 1994; Volkin and Middaugh, 1996) and calcium on DNase (Chen et al., 1999) provide good examples. As will be described below, increasing the free energy of unfolding directly correlates with increased resistance of proteins to denaturation during freezing. In addition, at least in the case of DNase, there was also dramatic increases in storage stability of the lyophilized protein in formulation containing calcium, which were not due to increased structural stabilization during lyophilization (Chen et al., 1999). The mechanism for this effect is unknown.

Moreover, sometimes protein unfolding during freeze-drying can be minimized by optimizing initial solution pH (e.g., Prestrelski et al., 1995). However, in other cases it has been found that initial solution pH does not impact the degree of unfolding arising during lyophilization (Costantino et al., 1995; Carrasquillo et al., 2000). For each protein it is necessary to investigate the effect of initial pH

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(and potential pH changes during freezing) on structural retention during lyophilization. Infrared spectroscopy can be used to monitor secondary structure in the dried solid, and the resulting data can be used to choose the initial pH that results in the most native-like secondary structure in the dried solid.

Trehalose or Sucrose to Inhibit Protein Unfolding and Provide Glassy Matrix

In this section we will discuss the rationale for choice of stabilizing excipients. Then we will describe the mechanisms for protection of proteins by additives during freezing and drying. Mechanistic insight is important for a clear understanding of protein stabilization during lyophilization and for guiding critical practical choices, such as determining the level of disaccharide needed for optimal protein protection. Finally, we will address this and other practical issues in the use of stabilizing excipients to inhibit protein unfolding during freezing and drying.

Rationale for Choice of Stabilizing Sugar. Among the numerous compounds tested, it appears that the most effective stabilizers of proteins during lyophilization are disaccharides (reviewed in Carpenter et al., 1999). Trehalose and sucrose are the best choices for a stabilizing disaccharide for therapeutic proteins. Both sugars: 1) protect proteins during both freezing and dehydration; 2) are nonreducing; 3) tend to remain amorphous during lyophilization; and 4) have been used in approved parenteral therapeutic products. There are, however, some important differences in the physicochemical properties of these sugars. 1) Trehalose has a higher T_g at a given moisture content than sucrose and, thus, for formulations containing trehalose it may be easier to obtain an appropriate cake structure with an economical lyophilization cycle (Crowe et al., 1998). However, a skilled process engineer should be able to design economical, effective cycles for formulations containing either sugar. In addition, the condition of having a T_g greater than the product storage temperature will hold at higher residual water contents for trehalose. In products with a relatively high protein concentration, the protein could contribute to an increased T_g, which serves to minimize the advantages of trehalose. 2) Trehalose is more resistant than sucrose to acid hydrolysis. Hydrolysis of these disaccharides produces reducing sugars, which must be avoided. Usually this is not a problem, unless very low pH's (ca. < 4) are employed. It should be noted that acid catalyzed hydrolysis of sucrose can occur even in lyophilized solids (Shalaev et al., 2000), suggesting that buffer acidification during freezing (see below) could ultimately result in formation of reducing sugars and resulting damage to proteins in a lyophilized formulation. 3)

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Sucrose appears to be somewhat more effective at inhibiting unfolding during lyophilization (Allison et al., 1999). This difference has been most obvious when there is a relatively high protein concentration and a need to employ a relatively high initial concentration of sugar. Evidence to date indicates that less effective stabilization by trehalose is due to the greater propensity of this sugar to phase separate from polymers (Isutzu et al., 1996) and proteins (S.D. Allison, T.W. Randolph, B.S. Chang and J.F. Carpenter, unpublished observation) during freezing and drying. Whether or not this is a problem with a given formulation cannot be predicted. Hence, the relative capacities of sucrose versus trehalose to inhibit lyophilization-induced unfolding of must be examined for each protein. The final choice of sugar for a given protein product should be based on a direct comparison of sucrose and trehalose as stabilizers during the lyophilization cycle and storage in the dried solid.

Reducing sugars, such as maltose or lactose, should not be used. These compounds may effectively inhibit protein unfolding during the lyophilization cycle, but during storage in the dried solid they can degrade proteins via the Maillard reaction between carbonyls of the sugar and free amino groups on the protein (Hageman, 1992; Li et al., 1996).

Mechanism for Freezing Protection. Many different compounds, such as sugars, polyols, certain amino acids, methylamines and salting-out salts, nonspecifically stabilize proteins during freezing or freeze-thawing ("cryoprotection"). The same compounds have also been shown in nonfrozen aqueous systems to increase protein thermodynamic stability (e.g., increase resistance to temperature- or chaotrope-induced unfolding). Protection of proteins by these compounds during freezing and freeze-thawing is due to the same universal thermodynamic mechanism that Timasheff and colleagues have defined for solute-induced protein stabilization in nonfrozen aqueous solution (reviewed in Carpenter and Crowe, 1988; Carpenter and Chang, 1996; Carpenter et al., 1999; Timasheff, 1998).

Usually relatively high concentrations (ca. > 0.3 M) of solute are needed to stabilize proteins because the interactions of the solute with the protein are relatively weak. Stabilizing solutes are excluded preferentially from the surface of the protein. This statement does not mean that no solute molecules bind to the surface of the protein, but rather that there is a lower concentration of solute in the immediate vicinity of the protein than in the bulk solution. The chemical potential of the protein is increased in the presence of a preferentially excluded solute, which is the basis for the effect of solute of protein thermodynamic stability. Considering a two-state model for protein folding (N $\leftarrow \rightarrow$ D), the native state is favored thermodynamically (e.g., under physiological conditions) because it has a lower free energy than the denatured state. The key to increasing the thermodynamic stability of the native state is to increase the free energy barrier

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between the native and denatured states. So how can increasing the chemical potential of the native state result in stabilization? The degree of preferential exclusion and concomitant increase in protein chemical potential correlates directly with the protein surface area. The denatured state has a much greater surface area than the native state. Thus, in the presence of a preferentially excluded solute, the magnitude for the increase in protein chemical potential will be much greater for the denatured than that for the native state; the native state will be stabilized.

This same mechanism applies to the inhibition of smaller scale structural expansions of the native state, which may be sufficient to promote irreversible protein aggregation, by compounds such as sucrose (e.g., Chang et al., 1996a; Kendrick et al., 1997, 1998; Kim et al., 2000). Many proteins are known to form non-native aggregates from species with conformations that are not greatly different from the most compact native state. One example is the molten globule that has perturbed tertiary structure, but native secondary structure. However, even expanded species within that native state ensemble can participate in intermolecular interactions leading to non-native protein aggregates (e.g., Chang et al., 1996a; Kendrick et al., 1997, 1998; Kim et al., 2000). Preferentially excluded solutes shift the equilibrium between protein species towards that with the lowest surface area, i.e., the most compact species in the native state ensemble. As a result aggregation is inhibited.

Timasheff's preferential interaction mechanism also explains the influence of solutes on the degree of assembly of multimeric proteins. Preferentially excluded solutes tend to induce polymerization and stabilize native oligomers since the formation of contact sites between constituent monomers serves to reduce the surface area of the protein exposed to the solvent. Polymerization reduces the thermodynamically unfavorable effect of preferential solute exclusion. In this case, the assembled protein is much more stable than the constituent monomer because of the direct solute effects, but also because of the increase in oligomer stability gained by intersubunit contacts (e.g., Neet and Timm, 1994). In one example of this effect during lyophilization, maintenance of the native tetramer during freezing has been shown to increase the resistance of lactate dehydrogenase to dissociation and inactivation during subsequent drying (Anchordoquy and Carpenter, 1996; Anchordoquy et al., 2001).

How do we know that the preferential exclusion mechanism is actually operative in the frozen state? It is not possible to measure directly the protein-solute interaction in the frozen state. However, the effects of solutes on protein chemical potential and the resulting protein stabilization can be inferred from a freezing study with hemoglobin, in which the protein was partitioned into separate polyethylene glycol-rich and dextran-rich solution phases (Heller et al., 1996). In a phase separated system, thermodynamic equilibrium requires that chemical potential of each component be equal in both phases. Hence, there should be

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equivalent effects of the different solute conditions in the two phases on the increase in free energy of protein unfolding. In other words, the impact of preferentially excluded solutes on protein stability is equal in the two phases. As predicted from the preferential exclusion mechanism, the degree of structural protection of hemoglobin during freezing (as observed directly in the frozen state with infrared spectroscopy) was equivalent in both phases (Heller et al., 1996).

Mechanism for Inhibition of Dehydration-Induced Unfolding. The interaction of a protein's residues with water are intimately involved with the formation of the native, globular protein structure, and if the protein is dehydrated it will unfold. It has been documented by numerous studies that sucrose and trehalose prevent dehydration-induced unfolding by hydrogen bonding to the dried protein in place of the lost water (e.g., Carpenter and Crowe, 1989; Prestrelski et al., 1993a; Allison et al., 1999; Costantino et al., 1998; Wolkers et al., 1998; Tzannis and Prestrelski, 1999). This so called "water replacement mechanism" is supported by several different observations.

For example, with infrared spectroscopy, it has been found that the band at 1583 cm^{-1} in the spectrum for lysozyme, which is due to hydrogen bonding of water to carboxylate groups, is not present in the spectrum for the dried protein (Carpenter and Crowe, 1989; Remmele et al., 1997; Allison et al., 1999). When lysozyme is dried in the presence of trehalose or sucrose, the carboxylate band is retained in the dried sample, indicating that the sugar is hydrogen bonding in the place of water. Similar results have been obtained with α-lactalbumin and sucrose (Prestrelski et al., 1993a). The magnitude of the retention of the carboxylate band correlates directly with the level of trehalose or sucrose in the lyophilized formulation, as well as with the degree of inhibition of unfolding (Allison et al., 1999). These effects of sugars on proteins in the dried solid are not due to the presence of increased amounts of water in the formulations dried with sugars (Allison et al., 1999; Tzannis and Prestrelski, 1999). The level of water in formulations dried with the sugars is as low as that for the protein lyophilized from just buffer or water, and is so low that the hydration shell of the protein is essentially completely removed (Prestrelski et al., 1993a; Krielgaard et al., 1998a, 1999; Allison et al., 1999).

Furthermore, Farhat et al., (1998) used infrared spectroscopy to study dried gelatin-sugar mixtures and the hydration behaviors of the mixtures, and concluded that the sugars hydrogen bond to the dried protein. Costantino et al. (1997) studied water sorption of proteins lyophilized with sucrose or trehalose and found that the solid-state interactions between protein and sugar reduced the availability of water binding sites. Tzannis and Prestrelski (1999) found that water sorption behavior of spray-dried protein formulations containing stabilizing levels of sucrose indicated hydrogen bonding between dried protein and the sugar. However, if an excessively high sucrose: protein ratio was employed, due to

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formation of protein- and sugar-rich phases, hydrogen bonding of sucrose to protein and resulting protein stabilization were reduced. Also, Suzuki et al. (1998; 1999) found that there was a high degree of stabilization of lactate dehydrogenase when sucrose remained amorphous and hydrogen bonded to the dried protein. Crystallization of sucrose abolished hydrogen bonding between the sugar and dried protein, as well as protein stabilization.

Further support for the water replacement mechanisms comes from two studies that compared the relative effectiveness of saccharides of increasing molecular weight for inhibiting lyophilization-induced unfolding. Tanaka and colleagues (1991) found that the capacity to protect catalase during freeze-drying was inversely related to saccharide size. They suggested that as the size of the saccharide increases, steric hindrance interferes with hydrogen bonding between the saccharide and the dried protein. In support of this contention, the carboxylate band is only minimally detectable in the infrared spectrum of lysozyme freeze-dried in the presence of glassy dextran and the protein is unfolded (Allison et al., 1999). With infrared spectroscopy, Prestrelski et al. (1995) found that as the molecular weight of a carbohydrate additive was increased the capacity to inhibit unfolding of interleukin-2 during lyophilization decreased, and the level of protein aggregation after rehydration increased. Also, it was clear that protection of the protein did not correlate directly with the formation of a glass (all samples were found to be amorphous) or with the glass transition temperature of the sample (the T_g increased as carbohydrate molecular weight increased). Rather, there was a negative correlation between stabilization and molecular weight, which is to be expected if protection during drying is due to the water replacement mechanism.

An alternative mechanism for stabilization of proteins during dehydration states that proteins are simply mechanically immobilized in a glassy, solid matrix during dehydration (e.g., Franks, 1991). The restriction of translational and relaxation processes is thought to inhibit protein unfolding, and spatial separation between protein molecules (i.e., "dilution" of protein molecules within the glassy matrix) is proposed to prevent aggregation. It is clear that protective additives must partition with the protein into the amorphous phase of the dried sample. If the compound crystallizes during lyophilization it does not inhibit protein unfolding (Carpenter et al., 1993; Izutsu et al., 1993; Krielgaard et al., 1999). Also, spatially separating protein molecules can help favor refolding over aggregation during rehydration (Allison et al., 1998, 2000). However, as evidenced by the failure of glassy dextran matrices to prevent unfolding (Prestrelski et al., 1995; Krielgaard et al., 1999; Allison et al., 1998, 1999, 2000), simply forming a glassy solid is not sufficient for inhibiting dehydration-induced unfolding.

Practical Considerations. The protein mass in a unit dose (or multidose) vial of therapeutic protein is dictated by the amount to be given to the patient.

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With a lyophilized product, which can be reconstituted to a volume different from the prelyophilization volume, the initial protein concentration can be varied without changing the total protein mass. Changes in initial protein concentration can affect relative loss of protein due to interaction with vial surfaces (e.g., Page et al., 2000), protein stability during processing, the collapse temperature of the formulation, the T_g of the final dried formulation and the lyophilization process itself. Thus, protein concentration can be an important variable to investigate during formulation development.

Increasing initial protein concentration leads to apparent increased resistance to denaturation during freezing (Strambini and Gabellieri, 1996; Chang et al., 1996c; Krielgaard et al., 1998b). This phenomenon can be demonstrated by determining the percentage protein aggregated after freeze-thawing, which varies inversely with protein concentration. Increasing protein concentration can directly reduce freezing-induced protein unfolding because one component of protein damage during freezing appears to involve protein denaturation during formation of the ice-water interface (Strambini and Gabellieri, 1996; Chang et al., 1996c; Krielgaard et al., 1998b). Assuming that only a finite number of protein molecules can be unfolded per unit area at this interface (Krielgaard et al., 1998b), increasing the initial protein concentration will lead to a smaller percentage of damaged molecules. Of course, other factors such as direct cold denaturation and freeze concentration of salts may predominate over surface denaturation during freezing. For practical purposes, it is not necessary to sort out the relative contribution of the various stresses to freezing-induced damage. Rather, is important to include realative high protein concentrations during early formulation development in order to increase the "intrinsic" resistance of the protein to denaturation. The greater the intrinsic stability of the protein, the lower the concentration of excipient that will be needed.

Another advantage of employing a relatively high initial protein concentration is that increasing protein : disaccharide mass ratio increases both formulation collapse temperature and T_g' of the final dried product. In addition, the formulation volume will be reduced, which will reduce the duration and costs of lyophilization.

Of course, if the ratio of excipient to protein is not sufficiently high, there will not be adequate stabilization of the protein during freezing and dehydration. Freezing protection depends on the initial bulk concentration of the sugar, and if the given protein is freeze-labile sometimes concentrations exceeding 5% (wt/vol) are needed to maximize stabilization. However, often the stability of the protein is sufficient during freezing that the level of sugar needed for optimal protection during lyophilization is dictated by that required for inhibition of unfolding during dehydration. Protection during drying depends on the final mass ratio between the sugar and the protein (Pikal, 1994; Carpenter and Chang, 1996;

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Cleland et al., 2001). Recently it has been demonstrated that the sugar:protein mass ratio predicts not only degree of native structural retention during lyophilization, but also the long-term storage stability of a lyophilized protein (Cleland et al., 2001). Generally, a weight ratio of sugar to protein of at least 1:1 is required for inhibiting lyophilization-induced unfolding, with optimal stability being reached at around 3–5:1. In practice, with the protein concentration held constant, a range of sugar concentrations can be tested during formulation screening to discern the optimal concentration needed for retention of native protein in the dried solid. In general, the optimal sugar concentration for stabilizing the protein during lyophilization will also provide storage stability, if the final dried powder has a T_g well above the storage temperature. Finally, it should be stressed that the minimal effective level of sugar should be employed, because of the effect of changing protein:excipient ratio on glass transition temperatures. Also, if excess levels of sugar are employed there is an increased risk of sugar crystallization if a product should happen to be held at temperatures near or above the formulation T_g (e.g., Krielgaard et al., 1999).

Bulking Agent (e.g., Mannitol, Glycine or Hydroxyethyl Starch)

If the product has a relatively low mass of protein per vial, often it will necessary to have a bulking agent in the formulation to prevent the protein from being lost from the vial during drying and to form the product cake. Mannitol and glycine are examples of bulking agents, which can also serve as tonicity modifiers, that usually crystallize to a substantial degree during lyophilization (Pikal, 1994; Carpenter and Chang, 1996). A disaccharide protein stabilizer will need to be used in combination with these bulking agents. One drawback of mannitol and glycine is that often an annealing step is required to assure maximum crystallization. If a fraction of the bulking agent remains amorphous during lyophilization, there may be problems with obtaining a suitable cake structure, as well as a risk of excipient crystallization during subsequent storage in the dried solid (e.g., Carpenter and Chang, 1996; Carpenter et al., 1997). An alternative, amophous bulking agent is the polymer hydroxyethyl starch, which is used clinically as a plasma volume expander. Its main advantages in lyophilization are that it has a high collapse temperature (ca. −10°C), it forms strong cakes and it has a relatively high T_g for a given moisture content (e.g., >200°C at 2% residual moisture). However, as is the case with dextran, the large polymer hydroxyethyl starch does not inhibit protein unfolding during dehydration, and may actually foster additional protein unfolding due to phase separation from the protein during freezing and drying. Again, stabilizing disaccharides must be used with hydroxyethyl starch to inhibit lyophilization-induced protein unfolding.

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Nonionic Surfactant to Inhibit Aggregation

Surfactants are often included in protein formulations to minimize interfacial denaturation and aggregation, e.g., at vial surfaces, due to bubble entrainment during filling or because of agitation (Chang et al., 1996c; Krielgaard et al., 1998b; Page et al., 2000). For a lyophilized product, a surfactant can be beneficial to minimize protein aggregation during vial filling, freezing and rehydration. Generally, a surfactant will not inhibit protein unfolding during dehydration (Krielgaard et al., 1998a). The mechanisms by which surfactants inhibit protein aggregation will be described in a separate chapter in this volume. For the current discussion it is sufficient to stress that a surfactant should not be included in a lyophilized product, unless there is direct evidence that increases recovery of native protein in the rehydrated sample. Surfactants can decrease the free energy of unfolding of some proteins, which may cause the compound to actually foster aggregation. Also, they have been shown to inhibit the assembly of small soluble aggregates into higher order soluble oligomers and insoluble aggregates (e.g., Krielgaard et al., 1998b). This effect can manifest itself during lyophilization and rehydration. As a result, the presence of a surfactant can cause an undesirable increase in the level of soluble aggregates.

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