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: *16/804,567*
FILING DATE: *February 28, 2020*
PATENT NUMBER: *10,703,809*
ISSUE DATE: *July 7, 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

DocCode – SEQ.TXT

SCORE Placeholder Sheet for IFW Content

Application Number: 16804567 Document Date: 02/28/2020

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- Sequence Listing

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Form Revision Date: March 1, 2019

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/Melissa St Germain
Attorney Docket Number:	AXJ-114BUSCN7/TRACK1

Filed as Large Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	10	100	1000
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**6860**

Electronic Acknowledgement Receipt	
EFS ID:	38721017
Application Number:	16804567
International Application Number:	
Confirmation Number:	7508
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/Melissa St Germain
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN7/TRACK1
Receipt Date:	28-FEB-2020
Filing Date:	
Time Stamp:	14:21:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$6860
RAM confirmation Number	E20202RE22194736
Deposit Account	501196
Authorized User	Melissa St Germain
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

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	2020_01_23_Figures_AXJ-114BUSCN7.pdf	3061707 57c5bcc299fbad5479d07f6748d637514374058d	no	4
Warnings:					
Information:					
2	Oath or Declaration filed	2020_02_28_Declarations_AXJ-114BUSCN7.pdf	2597433 1a6b2a97a740557192de5966734c22fb51040f8a	no	4
Warnings:					
Information:					
3	CRF Statement Paper and CRF are the same	2020_02_28_Sequence_Listing_Statement_AXJ-114BUSCN7.pdf	186122 592daa0a18a5ce621c79746e928ee01017d42636	no	2
Warnings:					
Information:					
4	Power of Attorney	2020_02_28_Power_of_Attorney_--_AXJ-114BUSCN7.pdf	620978 71b241ad8d23529eb0d985c85a81644d9754f988	no	2
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
5	TrackOne Request	2020_02_28_Track_One_Request_--_AXJ-114BUSCN7.pdf	191416 925527dc60003d98f86580080763b7b7151d5b18	no	1
Warnings:					
Information:					
6	Sequence Listing (Text File)	AXJ-114BUSCN7_Sequence_Listing.txt	10452	no	-
Warnings:					

Information:					
7	Specification	2020_02_28_Specification_AXJ-114BUSCN7.pdf	754426 8aa736d80588d5f09b08f8ef2d7bf57abd854b0e	no	56
Warnings:					
Information:					
8	Application Data Sheet	2020_02_28_Application_Data_Sheet_--_AXJ-114BUSCN7.pdf	1350146 60ef949f6f313f963607bfb76bfacce6f8cf2272	no	9
Warnings:					
Information:					
9	Preliminary Amendment	AXJ-114BUSCN7_Prelim_Amendment_with_Exhibit.pdf	17222351 cd532eba331cd032677e1b72a5b9b8b1d66bb5ba	no	15
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	41725 d587db64ee9318ad1ca49197b0fdc2f48cc02e9f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	26036756		

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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.

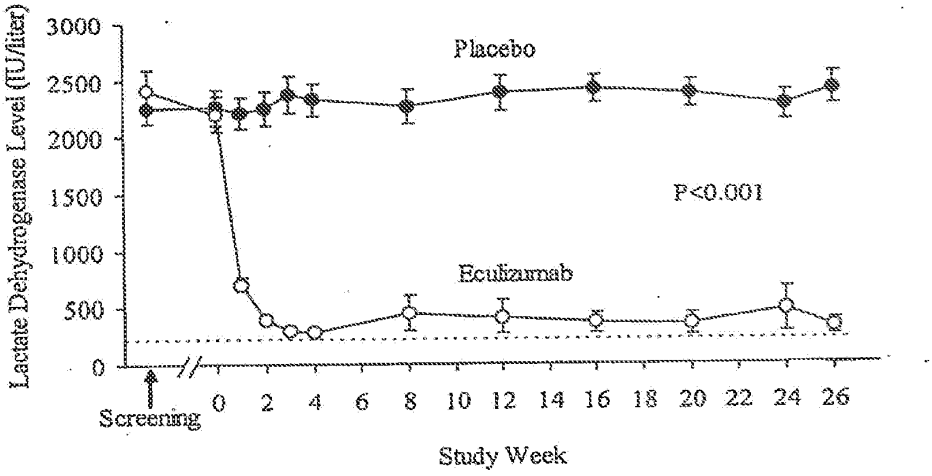

Lactate Dehydrogenase Level (IU/liter)
3000
2500
2000
1500
1000
500
0
Placebo
P<0.001
Eculizumab
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1A

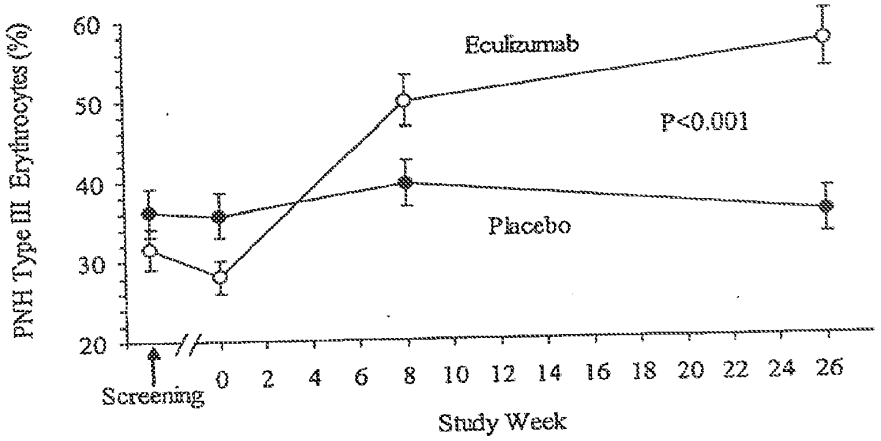

PNH Type III Erythrocytes (%)
60
50
40
30
20
Eculizumab
P<0.001
Placebo
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1B

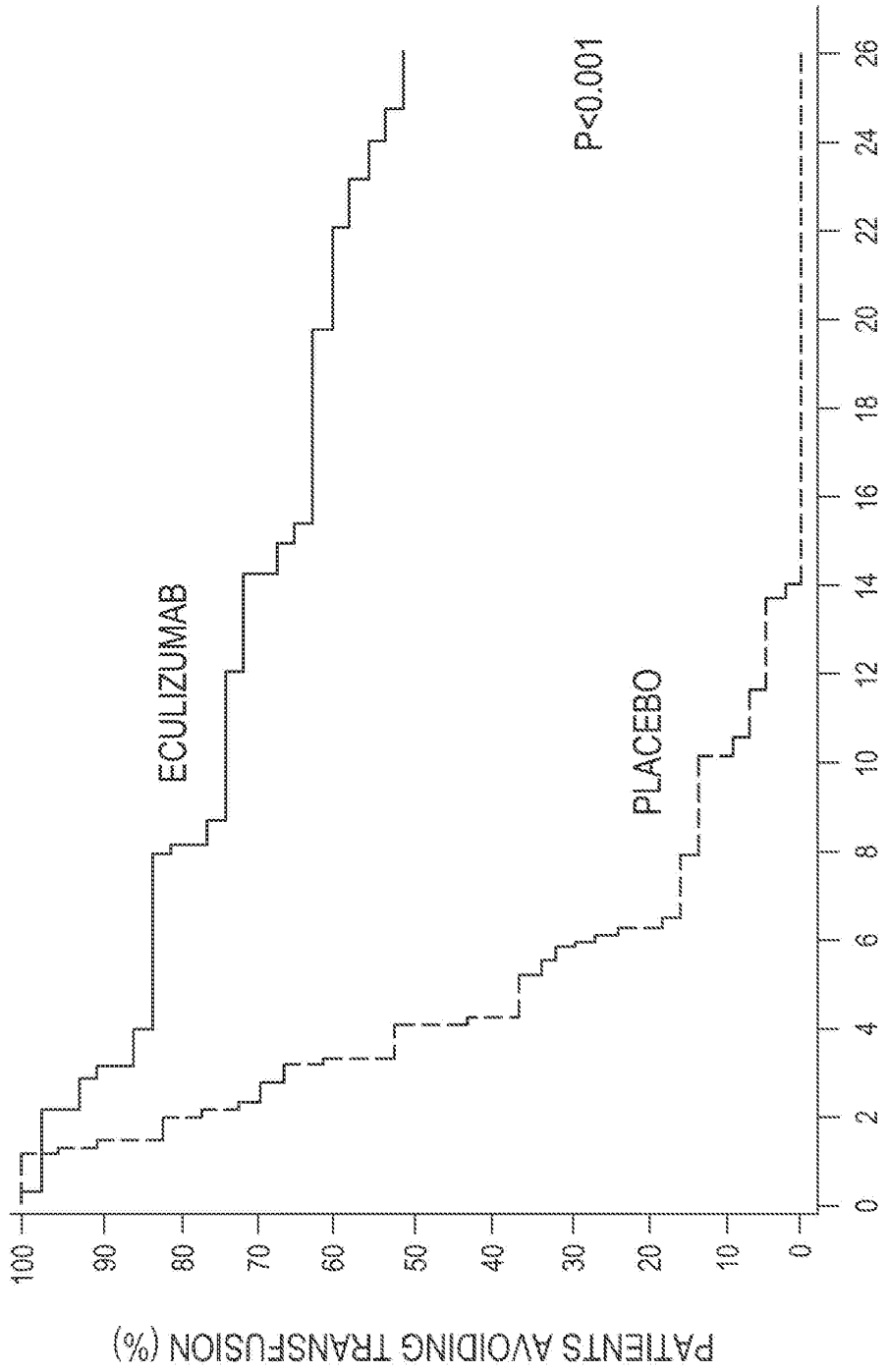

PATIENTS AVOIDING TRANSFUSION (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
STUDY WEEK
ECULIZUMAB
PLACEBO
P<0.001

FIGURE 2

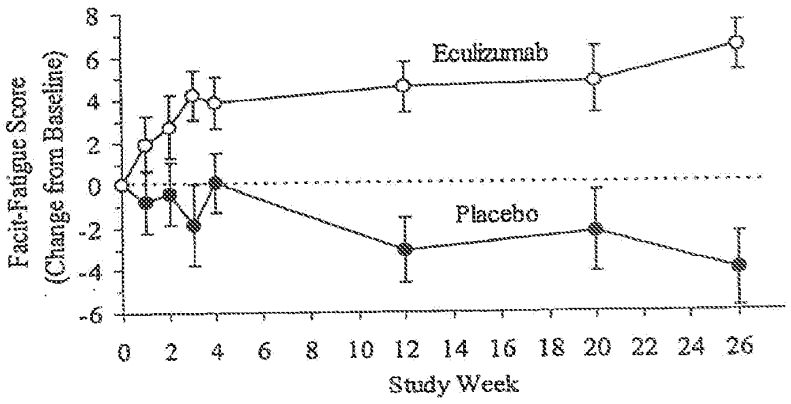

Facit-Fatigue Score
(Change from Baseline)
8
6
4
2
0
-2
-4
-6
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Eculizumab
Placebo

FIGURE 3

PTO/AIA/01 (06-12)
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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.

PTO/SB/AIA02 (07-13)
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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

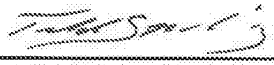
- [ ] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

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.

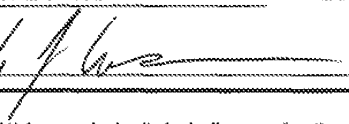
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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.

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: February 28, 2020
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN7
(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.: Not Yet Assigned

Filed: Concurrently Herewith

Art Unit: Not Yet Assigned

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

Examiner: Not Yet Assigned

STATEMENT PURSUANT TO 37 CFR 1.821

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

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: February 28, 2020

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, 30th Floor
Boston, Massachusetts 02109-2127
617-217-4630 (Tel)
617-217-4699 (Fax)
Attorney/Agent For Applicant

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

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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	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	AXJ-114BUSCN7

SIGNATURE of Applicant or Patent Practitioner

Signature	/Jill Gorny Sloper, Esq./	Date (Optional)	February 28, 2020
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 C.F.R. § 1.6(a)(4).

Dated: February 28, 2020 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

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) 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 patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[X] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number:

OR

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)

[X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

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		

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

[ ] Total of 1 forms are submitted.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Leonard BELL	Nonprovisional Application Number (if known):	Not Yet Assigned
Title of Invention:	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. [x] **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. [ ] **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	/Jill Gorny Sloper, Esq./	Date	February 28, 2020
Name (Print/Typed)	Jill Gorny Sloper, Esq.	Practitioner Registration Number	60,760

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

[ ] *Total of 1 forms are submitted.

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

Dated: February 28, 2020 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN7
	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	State/Province	Country of Residence
Woodbridge	CT	US

Mailing Address of Inventor:

Address 1	59 Tumblebrook Road
Address 2	

City	State/Province	Postal Code	Country
Woodbridge	CT	06525	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	State/Province	Country of Residence
Oklahoma City	OK	US

Mailing Address of Inventor:

Address 1	10325 Forest Meadow Drive
Address 2	

City	State/Province	Postal Code	Country
Oklahoma City	OK	73151	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

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN7
	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-114BUSCN7	**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.

PTO/AIA/14 (02-18)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN7
	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	16/750978			2020-01-23
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/750978	Continuation of	15/642096	2017-07-05	10590189	2020-03-17
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/642096	Continuation of	15/284015	2016-10-03	9732149	2017-08-15
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/284015	Continuation of	15/260888	2016-09-09	9725504	2017-08-08
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/260888	Continuation of	15/148839	2016-05-06	9718880	2017-08-01

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN7
	Application Number	
Title of Invention	TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	

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
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.			Add

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.			Add

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.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN7
	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.

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN7
	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 — Remove

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. ☒

Organization Name	Alexion Pharmaceuticals, Inc.		
Mailing Address Information For Applicant:			
Address 1	121 Seaport Boulevard		
Address 2			
City	Boston	**State/Province**	MA
Country	US	Postal Code	02210
Phone Number		Fax Number	
Email Address			

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

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.

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
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.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN7
	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.

Remove

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. Add

Signature:

Remove

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)	2020-02-28
First Name	Jill Gorny	Last Name	Sloper	Registration Number	60,760

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

PTO/AIA/14 (02-18)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	AXJ-114BUSCN7
	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.

```
============================================================
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: Zhang, Yizhu (ASRC)
Timestamp: [year=2020; month=3; day=2; hr=10; min=16; sec=53; ms=350; ]
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Validated By CRFValidator v 1.0.5

Application No: 16804567 Version No: 1.0

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Output Set:

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Finished: 2020-02-28 14:22:29.621
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Total Warnings: 10
Total Errors: 1
No. of SeqIDs Defined: 10
Actual SeqID Count: 10

Error code		Error Description
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SEQUENCE LISTING

<110> ALEXION PHARMACEUTICALS, INC.

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

<130> AXJ-114BUSCN7

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<151> 2016-05-06

<150> 13/426,973
<151> 2012-03-22

<150> 12/225,040
<151> 2009-05-13

<150> PCT/US2007/006606
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Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Gly Glu Ile Leu Pro Gly Ser Gly Ser Thr Glu Tyr Thr Glu Asn Phe
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Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
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Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
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Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
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Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
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Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
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His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
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Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
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Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro
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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
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Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Asn
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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
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            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
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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. 16/750,978, filed January 23, 2020, which is a continuation of U.S. Patent No. 10,590,189, issued March 17, 2020, which is a continuation of U.S. Patent No. 9,732,149, issued August 15, 2017, which is a continuation of U.S. Patent No. 9,725,504, issued August 8, 2017, which is a continuation of U.S. Patent No. 9,718,880, issued August 1, 2017, 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 February 28, 2020, is named AXJ-114BUSCN7_Sequence_Listing.txt and is 10,452 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.

lntravascular 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

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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.

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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

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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

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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 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

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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.

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,

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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.

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

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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- 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

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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

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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.

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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 (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

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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. 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

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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 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

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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

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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 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-CRl , 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

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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 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

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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 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.

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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

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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 "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.,*

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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 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

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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

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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).

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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

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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 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,

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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 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,

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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 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

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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 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

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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

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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.

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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 proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set

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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

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

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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 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

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(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

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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 ($P<0.001$), 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

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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.

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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

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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WHAT IS CLAIMED IS:

1. A method of treating a patient having paroxysmal nocturnal hemoglobinuria (PNH), wherein the method comprises intravenously 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.

2. The method of claim 1, wherein the antibody is formulated in a pharmaceutical composition comprising a single unit dosage form.

3. The method of claim 2, wherein the single unit dosage form is a 300 mg single unit dosage form.

4. The method of claim 3, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.

5. The method of claim 4, wherein the antibody is diluted to a concentration of 5 mg/mL prior to administration.

6. The method of claim 1, wherein the patient is anemic.

7. The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

8. The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7 ± 1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7 ± 1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14 ± 2 days.

9. The method of claim 1, wherein the patient exhibits decreased lactate dehydrogenase levels after treatment with the antibody.

10. The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

11. The method of claim 10, wherein the immediate decrease occurs within one week of administration of the antibody.

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12. The method of claim 1, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

13. The method of claim 1, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

14. The method of claim 12, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

15. The method of claim 1, wherein the patient has about a 51% likelihood of transfusion avoidance after administration of the antibody.

16. The method of claim 1, wherein the patient has less than a 3% likelihood of developing antibodies to the antibody that binds C5 after 26 weeks of treatment.

17. The method of claim 1, wherein the patient exhibits improved quality of life as measured by a FACIT-Fatigue score or an EORTC QLQ-C30 score.

18. The method of claim 5, wherein the patient is treated with the antibody for at least 26 weeks.

19. The method of claim 5, wherein the patient is anemic.

20. The method of claim 5, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

21. The method of claim 5, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7 ± 1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7 ± 1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14 ± 2 days.

22. The method of claim 5, wherein the patient exhibits decreased lactate dehydrogenase levels after treatment with the antibody.

23. The method of claim 5, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

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24. The method of claim 23, wherein the immediate decrease occurs within one week of administration of the antibody.

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

26. The method of claim 5, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

27. The method of claim 5, wherein the patient has about a 51% likelihood of transfusion avoidance after administration of the antibody.

28. The method of claim 5, wherein the patient has less than a 3% likelihood of developing antibodies to the antibody that binds C5 during the 26 weeks.

29. The method of claim 5, wherein the patient exhibits improved quality of life as measured by a FACIT-Fatigue score.

30. The method of claim 5, wherein the patient exhibits improved quality of life as measured by an EORTC QLQ-C30 score.

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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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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: February 28, 2020
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN7
(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.: Not Yet Assigned

Filed: Concurrently Herewith

Art Unit: Not Yet Assigned

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

Examiner: Not Yet Assigned

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

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

Dear Sir:

INTRODUCTORY COMMENTS

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/Arguments begin on page 3 of this paper.

AMENDMENTS TO THE SPECIFICATION

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

REMARKS

Sequence Listing and Amendment to the Specification

It has come to Applicant's attention that the light chain recited in the specification 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, Applicant submits 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. Applicant has also amended the specification to update the "Sequences" summary on page 44 (lines 24-29) of the specification.

Applicant respectfully notes 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 amendment to SEQ ID NO:4 does not constitute new matter. *No new matter has been added.*

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: February 28, 2020

Respectfully submitted,

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EXHIBIT A

Downloaded from http://www.jci.org on January 19, 2017. https://doi.org/10.1172/JCI115649

Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to *Haemophilus influenzae* Type b Capsular Polysaccharide Are Dominated by a Limited Number of V_κ and V_λ Segments and VJ Combinations

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Abstract

The immune repertoire to *Haemophilus influenzae* type b capsular polysaccharide (Hib PS) appears to be dominated by certain light chain variable region genes (IgV_L). In order to examine the molecular basis underlying light chain bias, IgV_L genes have been cloned from a panel of heterohybridomas secreting human anti–Hib PS (antibody) (anti–Hib PS Ab). One hybridoma, representative of the predominant serum clonotype of anti–Hib PS Ab in older children and adults following immunization or Hib infection, uses a V_κII segment identical to the germline gene A2, and a JK3 segment. A second kappa hybridoma uses a member of the V_κI family and a JK4 segment. Four lambda antibodies, all cross-reactive with the structurally related antigen *Escherichia coli* K100 PS, use V_λVII segments which are 96–98% homologous to one another, and may originate from a single germline gene. Two additional lambda antibodies, not K100–cross-reactive, are encoded by members of the V_λII family. All lambda antibodies use highly homologous J_λ2 or J_λ3 segments. The VJ joints of all lambda antibodies and the V_κII–encoded antibody are notable for the presence of an arginine codon, suggesting an important role in antigen binding. Although more complex than heavy chain variable region gene usage, a significant portion of serum anti–Hib PS Ab is likely to be encoded by a limited number of V_κ and V_λ segments and VJ combinations, which may be selectively expressed during development, or following antigen exposure. (*J. Clin. Invest.* 1992: 89:729–738.) Key words: B-cell repertoire • somatic mutation • gene rearrangement • carbohydrate antigen

Introduction

The development of the antibody repertoire involves the recombination of individual members of two or three groups of germline segments, nucleotide insertion or deletion at these junctions, and somatic mutation of rearranged genes (1–4). The individual contributions of these molecular mechanisms to the generation of the immune repertoire against a specific antigen has been extensively studied in murine systems, but it is uncertain whether these findings can be extrapolated to humans. The chromosomal organization of the human heavy and light chain variable region segments within the immunoglobulin loci differ from those of mice (5–7). Furthermore, the response of highly inbred laboratory animal strains, and the use of simple haptens in most studies, may not be comparable with the human response to clinically relevant antigens, such as those presented by microbial pathogens.

The immune response to *Haemophilus influenzae* type b capsular polysaccharide (Hib PS)[1] is an excellent model to examine the immune repertoire to a functionally significant antigen. Hib is a major bacterial pathogen in young children and antibody directed against the capsular polysaccharide, a repetitive polymer of polyribosylribitol phosphate, protects against invasive infection (8). Similar to the response to other polysaccharide antigens, the immune response to Hib PS is age-dependent. Children under 5 yr have lower antibody responses and are at greatest risk of infection. Additionally, there appear to be variations in individual and ethnic susceptibilities to invasive Hib disease (9–11). Analysis of the immune response to Hib PS will contribute to our understanding of the development of the human antibody repertoire, and provide insight into age-related and possible genetic predisposition to infection caused by Hib.

Previous studies employing partial amino acid sequencing of anti–Hib PS serum antibody purified to clonality have shown that light chains of anti–Hib PS antibody are encoded by V_λ, and at least three V_κ gene families (12). Although highly informative, these studies have inherent technologic limitations. To obtain sufficient antibody for analysis, only individuals with antibody concentrations much higher than those elicited in young infants could be studied (12). Amino acid sequences were unobtainable on V_λ-encoded antibodies, and certain regions of V_κ-encoded antibodies (12, 13). Obtaining nucleic acid sequences of variable region genes encoding anti–Hib PS Abs would permit precise comparison of variable region genes obtained from different individuals, allowing classification of these genes into germline families and subfamilies, analysis of D- and J-segment usage, and assessment of the role of somatic mutation in the clonal evolution of this immune response. Additionally, this information could be applied to examination of the germline and expressed immune repertoire

Presented in part at the annual meeting of the Society for Pediatric Research, New Orleans, LA, 2 May 1991, and published in abstract form (*Pediatr. Res.* 29:155A).

Address correspondence and reprint requests to Dr. William L. Carroll, Program in Human Molecular Biology and Genetics, University of Utah, Bldg. 533, Salt Lake City, UT 84112.

Received for publication 14 August 1991 and in revised form 5 November 1991.

J. Clin. Invest.
© The American Society for Clinical Investigation, Inc.
0021-9738/92/03/0729/10 $2.00
Volume 89, March 1992, 729–738

1. *Abbreviations used in this paper:* Ars, anti-p-azophenylarsonate; Hib, Haemophilus influenzae type b; Hib PS, Hib capsular polysaccharide; IgV_L, light chain variable region gene; PCR, polymerase chain reaction; SSC, standard saline citrate.

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of individuals of various ages, and populations at high risk for invasive Hib infection.

Our previous work, and that of others, indicated that the heavy chains of anti-Hib PS Abs are encoded by a very restricted number of V_HIII gene segments, in combination with a variety of D and J_H segments (12, 14). We have extended our studies to examine light chain variable region gene (IgV_L) usage in the human anti-Hib PS response. A major component of serum anti-Hib PS Ab expresses a cross-reactive idiotype associated with the use of a V_κII gene (15, 16). Antibodies expressing this light chain account for the majority of anti-Hib PS antibody in older infants and adults following invasive Hib disease or immunization. Most lambda-encoded anti-Hib antibodies and some kappa-encoded (V_κI and V_κIII) anti-Hib PS Abs cross-react with the capsular polysaccharide of *E. coli* K100 (12, 17). Naturally acquired antibody of the majority of children expresses K100 PS cross-reactivity, and thus, colonization with this organism may provide protective immunity before exposure to Hib (18). Our results indicate that two important anti-Hib PS light chains, one associated with V_κII expression and the other with lambda antibodies cross-reactive with K100 PS, are encoded by two germline elements that may be expressed with little or no somatic mutation. Moreover, a nongermline-encoded arginine at the VJ joint is seen in the majority of anti-Hib PS Ab light chains, a result suggesting an essential role in antigen recognition.

Methods

Hybridomas. Heterohybridomas secreting human monoclonal anti-Hib PS antibody were obtained, as previously described (14). Volunteers were immunized with either plain Hib-PS vaccine (Praxis Biologicals, Rochester, NY) or Hib-PS diphtheria toxoid conjugate vaccine (Hib-PS-D) (Connaught Laboratories, Swiftwater, PA). 7 d following immunization, peripheral blood lymphocytes were harvested and fused to the nonsecreting mouse myeloma SP2/O-Ag14. Anti-Hib PS Ab was detected by binding to Hib PS in an ELISA, as previously described (14). Specificity was documented by antibody binding to ^{125}I-labeled antigen (19), and by inhibition of binding by 1.25 μg/ml of soluble Hib PS in an ELISA (20). Cross-reactivity with *E. coli* K100 PS was assayed by inhibition of binding to Hib PS-poly-L-lysine with 100 μg/ml of soluble K100 PS in an ELISA. An antibody concentration was selected that gave half-maximum absorbance in the ELISA. Greater than 15% inhibition was considered positive. The *E. coli* K100 PS was prepared from *E. coli* strain Easter, by the same method used to prepare Hib PS (19). The generation of hybridoma line 16M3C8 was described previously (21).

Cloning and sequencing of IgV_L genes. Total RNA was prepared from 10^6 hybridoma cells using the guanidine isothiocyanate method (22). 2 to 8 μg of total RNA served as template for first-strand cDNA synthesis, as previously described (14). 10 pmol of a consensus antisense primer corresponding to conserved sequences within the human kappa or lambda constant region (23) (C_κ codons 181-172:5'CAGCGTCAAGCTTCTGCTGTGGCTGTAGGT 3', C_λ codons 171-181:5'CAGGCTCAGGAAGCTTCTGGCCGCGTACTTGTT 3') was used to initiate cDNA synthesis by avian myeloblastosis virus (AMV) reverse transcriptase (RT; Life Sciences, St. Petersburg, FL). One half (10 μl) of the cDNA reaction was directly diluted into polymerase chain reactions (PCR), (24).

PCR conditions were as previously described, except that 70 pmol of an internal constant region consensus primer (C_κ codons 125-117:5'CAACGGATCCTCTGATGGCGGGAAGAT 3', C_λ codons 125-117:5'TGGGGATCCAGCTCCTCAGAGGAGGG 3') and 70 pmol of a degenerate 3' kappa or lambda leader sequence primer (kappa:5'GGGAATTCATGGACATG(GA)(GA)(GA)(GAT)(TC)CC-(ACT)(GAC)G(TC)(GT)CA(GC)CTT 3', lambda 5'GGGAATTCATG(GA)CCTG(GC)(AT)C(TC)CCTCTC(TC)T(TC)CT(GC)(AT)-(TC)C 3') were used to amplify rearranged variable region genes (14, 25).

PCR products were isolated from low melting-point agarose gels (FMC Bioproducts, Rockland, ME). Artificial restriction enzymes sites in each primer allowed directional cloning into M13mp18 and M13mp19 phage vectors (Boehringer Mannheim Corp., Indianapolis, IN). Sequencing of V_L genes was performed by the dideoxy technique (26). Two to five positive clones were obtained and sequenced for each hybridoma gene.

The 16M3C8 light chain was generated by amplification of first-strand cDNA, with primers corresponding to amino acid positions −7 of the leader, to position 6 of the lambda light chain (5'CTGCACAGGGTCCTGGGCCGAGCTCGTGGTGACTCA 3'), and the C_λ constant region (antisense, 5'GCATTCTAGACTATTATGAACATTCTGTAGGGGC3'). Blunt-ended PCR products were cloned into SmaI cut M13 mp18 and M13mp19 and sequencing was also performed by the dideoxy method.

Southern blot analysis of genomic DNA. Peripheral blood was obtained from 10 unrelated healthy adult volunteers, from L.S. (the donor of hybridoma LSF2), and from a parent of L.S. Lymphocytes were separated on a Ficoll-Hypaque gradient, and genomic DNA was prepared by Proteinase K digestion (27). 10 μg of each subject's genomic DNA was digested with BamHI (4 U/μg DNA) (Boehringer Mannheim Corp.) at 37°C for 16 h, according to manufacturer's specifications. Digested DNA was separated by electrophoresis in a 0.8% agarose gel using TAE buffer (0.04 M Tris-acetate/0.001 M EDTA), and was transferred to Duralon UV membranes (Stratagene Inc., La Jolla, CA), using a positive pressure blotting apparatus (Posiblotter; Stratagene, Inc.). To examine germline representation of anti-Hib PS Ig genes, genomic DNA was hybridized with a 320-bp EcoRI/SmaI V_λ segment from hybridoma LSF2 that lacked the associated J_λ and C_λ regions. Probe was radiolabeled to high specific activity using T7 DNA polymerase (28). Prehybridization and hybridizations were carried out in 5× standard saline citrate (SSC), 5× Denhardt's solution, and 200 μg/ml sheared and denatured salmon sperm DNA (Boehringer Mannheim Corp.) at 42°C overnight. Filters were washed with 2× SSC, 0.2% SDS at room temperature twice, then with 0.2× SSC, 0.2% SDS at 55 to 60°C twice, and exposed to X-OMAT AR film (Eastman Kodak Co., Rochester, NY) for 2–7 d.

In order to further localize germline candidates within V region families, an oligonucleotide probe corresponding to conserved sequences within the CDR-1 region (sense oligonucleotide: 5'GGCTCCAGCACTGGAGATGTCACCAGT 3', antisense oligonucleotide: 5'GTAGGGATAATGACCACTGGTGACATCTCC 3') was hybridized to genomic DNA using the method described by Hellman (29). 15 μg of BamHI-digested human genomic DNA was separated by electrophoresis in 0.8% agarose gel using TBE buffer (0.09 M Tris-borate/0.002 M EDTA). Agarose gels were dried under vacuum and hybridized in 5× saline/sodium phosphate/EDTA (SSPE), 0.1% SDS, and 10^6 μg/ml of sheared and denatured salmon sperm DNA with 2×10^6 cpm of probe/ml of hybridization solution at 60°C for 16 h (30, 31). Hybridization conditions were previously adjusted to minimize nonspecific binding. Gels were washed with 6× SSC at room temperature for 20 min twice, followed by a 4-h room temperature wash. The gel was finally washed in 6× SSC for 3 min at 64°C, and exposed to X-OMAT AR film for 4 d.

Results

Hybridomas

Eight hybridoma cell lines from seven individuals were initially selected from 20 cell lines. All individuals demonstrated substantial increases in serum anti-Hib PS Ab 1 mo after vaccination (Table I). Hybridomas were selected to exemplify serologic characteristics (kappa or lambda expression, and K100 PS

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*Table I. Summary of Hybridoma Cell Lines**

Hybridoma	Isotype	Age	Vaccine Form	K100 Inh of mAb	Serum Anti-Hib PS Ab: Total Ab Pre	Total Ab Post	ΔK100 Inh Pre	ΔK100 Inh Post
RC3	IgA/k	Adult	PS-D	−	1.1	300	11	11
ED6.1	IgG_2/k	4 yr	PS-D	−	0.8	22	0	0
SB5/D6	IgA_1/λ	Adult	PS-D	+	2.0	688	30	27
RAY4	IgA_2/λ	Adult	PS-D	+	1.9	28	0	42
LSF2	IgA_1/λ	Adult	PS	+	ND	138	ND	29
JB32	IgA_1/λ	11 yr	PS	+	0.3	125	19	33
JB21	IgG_2/λ	11 yr	PS	−	0.3	125	19	33
16M3C8	IgG_2/λ	Adult‡	PS	−	ND	ND	ND	ND

* Columns show name of hybridoma cell line, isotype of anti-Hib PS Ab secreted, age of subject at immunization, type of vaccine (PS is plain polysaccharide, PS-D is Hib PS covalently linked to diphtheria toxoid), presence (+) or absence (−) of inhibition of binding of anti-Hib PS Ab by *E. coli* K100 PS, concentration of total serum anti-Hib PS AB pre- and 1 mo post-immunization, and percent inhibition of binding of serum lambda antibodies to Hib PS by *E. coli* K100 PS in pre- and 1 mo post-immunization sera. ‡ Pool of 3 adult donors. ND, not done.

cross-reactivity) and to represent the response to "T-independent" plain polysaccharide, or "T-dependent" polysaccharide-protein conjugate forms of antigen. (Table I).

Four lambda-expressing anti-Hib PS Ab, obtained from four different subjects, cross-reacted with K100 PS. One of these individuals, RAY4, had no detectable serum cross-reactivity before immunization. The Abs JB32 and JB21 were obtained from the same individual, and differed in heavy chain isotype and K100 cross-reactivity.

IgV_L genes. IgV_L nucleic acid sequences were obtained from two kappa and six lambda hybridomas. Candidate germline IgV_L sequences were sought by comparing hybridoma sequences to those registered with EMBL and GenBank (32).

Four lambda-expressing hybridomas, derived from four unrelated subjects, use V_λ segments which are 96–98% homologous to one another, and are members of the germline V_λVII family of which a single member, 4A, has been previously described (33) (Fig. 1). Notably, each of these four V_λVII-encoded hybridomas cross-reacts with K100 PS. The high degree of homology between these segments suggests that these genes may be encoded by a single, or group of, closely related germline elements. The four hybridoma genes share a number of nucleic acid differences (maximum nucleic acid sequence homology 89%) from the only previously sequenced V_λVII germline gene 4A, implying that these genes may be derived from another, as yet undescribed, V_λVII germline element.

The homology of the translated amino acid sequences of these 4 V_λVII sequences parallels the nucleic acid homology. The hybridoma V_λVII genes are 90 to 97% homologous at the amino acid level (Fig. 2). Framework regions are 94 to 100% homologous, whereas CDR regions are 72 to 96% homologous. Whether these minor differences reflect genetic polymorphisms, or somatic mutation, cannot be resolved from these data.

JB21 and 16M3C8, the lambda-expressing hybridomas which do not cross-react with K100 PS, are encoded by a V_λII gene family member (34), (Fig. 3). JB21 is 91% homologous to the germline V_λ2.1 gene (99% homologous in framework regions and 74% homologous in CDRs). 16M3C8 is 89% homologous to V_λ2.1 (95% in framework regions and 77% in CDRs). JB21 shares 87% amino acid homology with the translated V_λ2.1 germline sequence (99% in framework regions and 60% in CDR regions), and 16M3C8 shares 82% amino acid homology (92% in framework regions and 60% in CDRs) (Fig. 4).

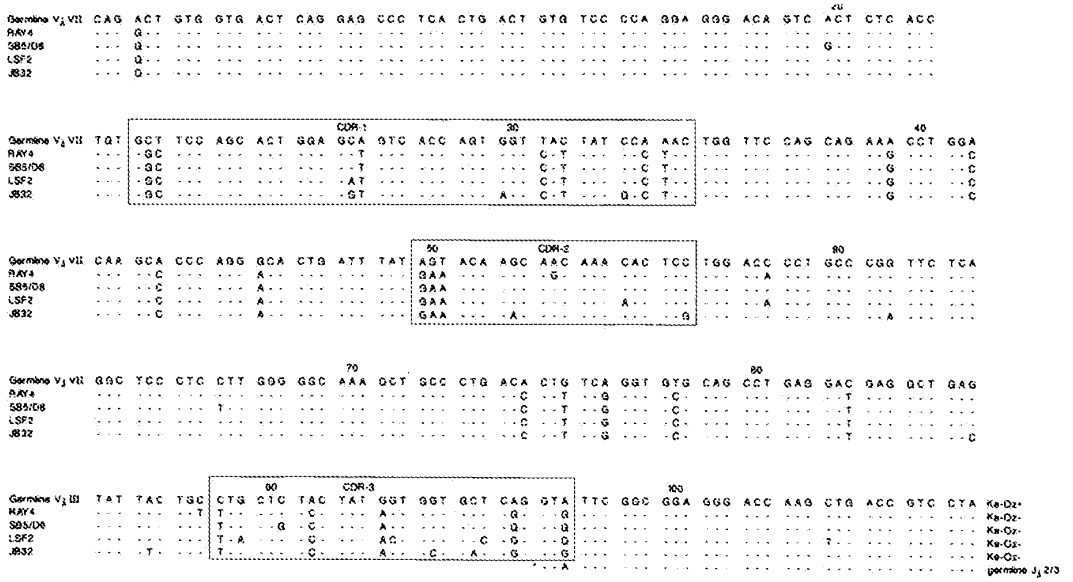


Figure 1. Nucleotide sequences of the V_λ and J_λ genes from four hybridoma cell lines (RAY4, SB5/D6, LSF2, JB32), and from the V_λVII germline gene, 4A (33). Numbering is according to Kabat (23). These sequence data are available from EMBL/GenBank Data Libraries under accession numbers M80917 (RAY4), M80918 (SB5/D6), M80915 (LSF2), and M80919 (JB32).

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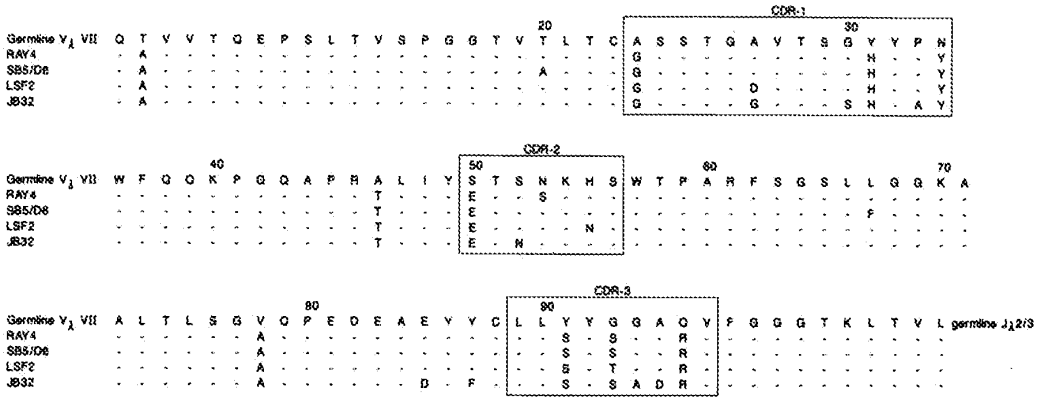


Figure 2. Translated amino acid sequences of V_λ and J_λ from four hybridoma cell lines (RAY4, SB5/D6, LSF2, JB32), and from the V_λVII germline gene, 4A (33). (See Fig. 1.)

These two V_λII-encoded gene segments are 91% homologous to one another, and have in common a number of nucleic acid differences from the V_λ2.1 germline gene (especially in CDRs). Whether they derive from another germline gene, or whether these differences reflect mutation, is unknown.

All four of the V_λVII-encoded antibodies are also encoded by V_HIII segments closely homologous to the germline gene 9.1 (5). Similar V_H segments also encode Ab utilizing other V_λ and V_κ gene segments (Table II) (manuscript in preparation). It is uncertain whether pairing of 9.1-like V_H and V_λVII-encoded heavy and light chains contributes to binding specificity or avidity. JB21 and RC3, also encoded by 9.1-like V_H gene segments, but paired with V_λII- and V_κII-encoded light chains, respectively, do not cross-react with K.100 PS.

All six of the lambda light chains are encoded by a common J_λ segment closely homologous to both J_λ2 and J_λ3 germline genes (Fig. 1) (23). J_λ2 is associated with the use of the (Kern$^-$Oz$^-$)C_λ segment 2, and J_λ3 with the (Kern$^-$Oz$^+$)Cλ segment 3 (37). Each of these J_λ segments substitutes the codon GTG for the reported germline sequence GTA at amino acid position 97. Interestingly, this change does not result in an amino acid replacement, and is therefore not of importance in antigen binding. This minor sequence difference may reflect a shared genetic polymorphism, rather than somatic mutation.

The hybridoma RC3 uses a V_κII segment identical to the germline V_κII gene A2, and a J_κ3 segment closely homologous to the germline sequence (Fig. 5) (13). The second kappa hybridoma, ED6.1, is encoded by a member of the V_κI family

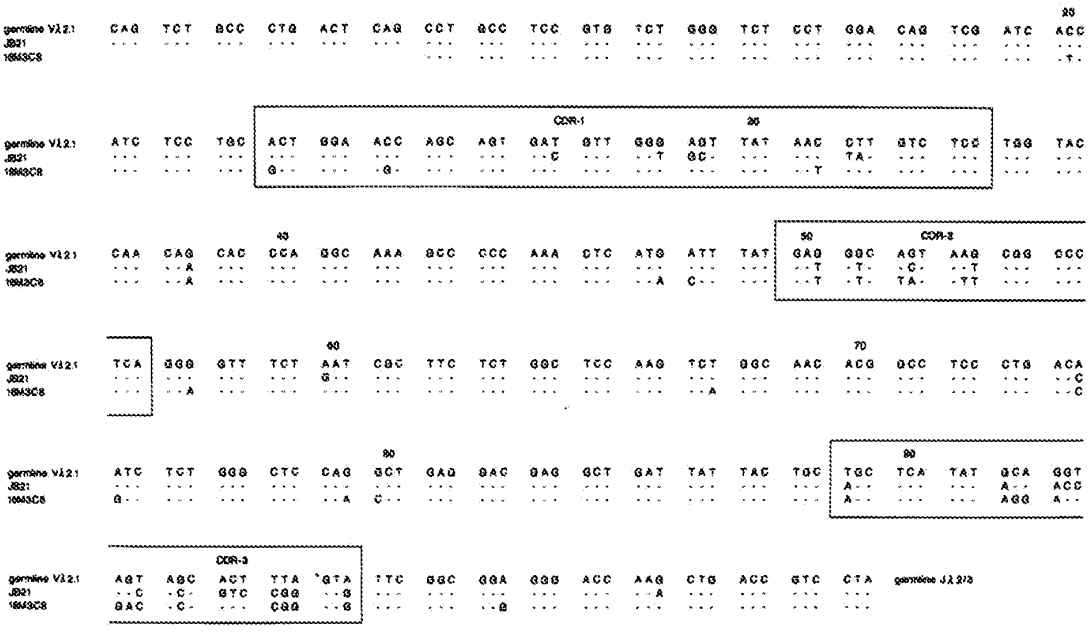


Figure 3. Nucleotide sequences of V_λ and J_λ genes from two hybridoma cell lines (JB21 and 16M3C8). Also shown is a germline gene V2.1 (34), and germline J_λ2/3 gene (23). An asterisk denotes the beginning of the J_λ segment. Numbering is according to Kabat (23). These sequence data are available from EMBL/GenBank Data Libraries under accession numbers M80916 (JB21) and M80921 (16M3C8).

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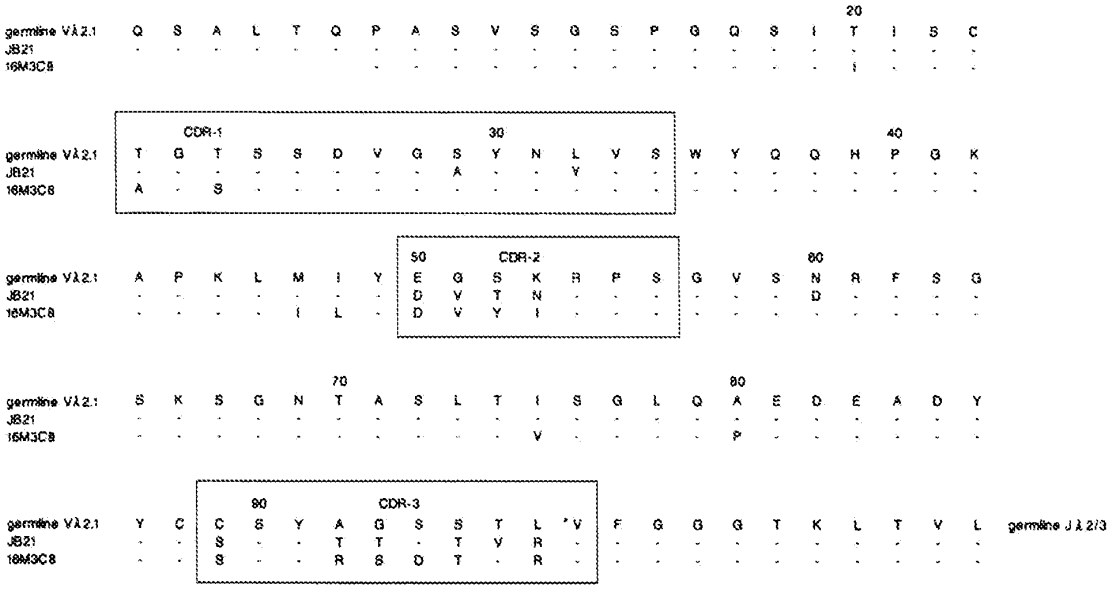


Figure 4. Translated amino acid sequences of V_λ and J_λ genes from two hybridoma cell lines (JB21 and 16M3C8). Shown for comparison is the translated sequence of the V_λ germline gene V_λ2.1, and J_λ2/3 germline gene. An asterisk denotes the beginning of the J_λ segment. (See Fig. 3.)

(36), and uses a J_κ4 segment differing from the germline sequence by a single base (Fig. 6). The ED6.1 sequence is identical to the partial amino acid sequence reported previously for 2 kappa antibodies purified from serum (12).

VJ joints of seven of these eight hybridoma V_L genes are notable for the presence of an arginine codon (Fig. 7). Comparison of germline sequences indicates that in the RC3 V_L gene, the codon CGA could only have arisen by the addition of a non–germline-encoded G at the $V_\kappa J_\kappa$ joint. In the V_λVII-encoded antibodies, the relevant germline V_λ segment is unknown. The arginine codon may be germline-encoded, or result from either mutation or N sequence addition. The VJ splice junction in all lambda antibodies is identical, implying this V_λ/J_λ combination is a necessary prerequisite for generation of the arginine. Since the CDR-3 region encodes the third hypervariable region, the frequent finding of an arginine residue at this location, and particularly its presence in both kappa and lambda anti–Hib PS Ab clonotypes, implies this residue is of considerable importance in antigen binding.

*Table II. Summary of V_H and V_L Gene Segments**

Hybridoma	V_H Segment	V_L Segment
SB5/D6	V_HIII 9.1 (5)	V_λVII 4A (33)
RAY4	V_HIII 9.1	V_λVII 4A
JB32	V_HIII 9.1	V_λVII 4A
JB21	V_HIII 9.1	V_λII 2.1 (34)
RC3	V_HIII 9.1	V_κII A2 (13)
LSF2	V_HIII 9.1	V_λVII 4A
16M3C8	V_HIII VH26 (35)	V_λII 2.1
ED6.1	N.K.	V_κI clone KC-1 (36)

* Columns show name of hybridoma cell line and most closely homologous known germline V_H and V_L segments. Reference for germline shown in parentheses. NK, Not known.

Southern blots/analysis of germline V_λVII genes

The available repertoire of V_λVII family members was examined by hybridization of human genomic DNA with the V_λVII probe generated from LSF2. 10 prominent bands, as well as an additional 5 fainter bands, were demonstrated (Fig. 8). Notably, polymorphism such as the presence or absence of a 5.0-kb fragment, and varying intensity of the 3.5-kb fragment, was demonstrated even within this relatively small sample. The human lambda variable region locus is believed to contain about 60 members, of which 10 are members of the V_λVII family (33, 38). The five less prominent bands may represent members of other V_λ families sharing significant homology with the V_λVII family. To determine if the V_λVII-encoded antibodies derive from a single germline gene, an oligonucleotide probe corresponding to conserved V_λVII CDR-1 sequence was used to identify a single 3.7-kb genomic DNA fragment. Although more than one V gene may be present in a single restriction fragment, both the repeated isolation of highly homologous V_λVII genes, and the single prominant band detected with the oligonucleotide probe, suggests that a single V_λ gene may be responsible for the generation of lambda anti–Hib PS Ab that cross-reacts with K100 PS (Fig. 9). Less prominant higher molecular weight bands are also present, but hybridize weakly to the oligomer after subtraction of nonspecific background binding by high molecular weight DNA.

Discussion

To examine the molecular basis of the immune response to Hib PS, a panel of hybridomas secreting human monoclonal anti–Hib PS Ab has been developed. Our previous studies showed exclusive use of members of the V_HIII gene family in this im-

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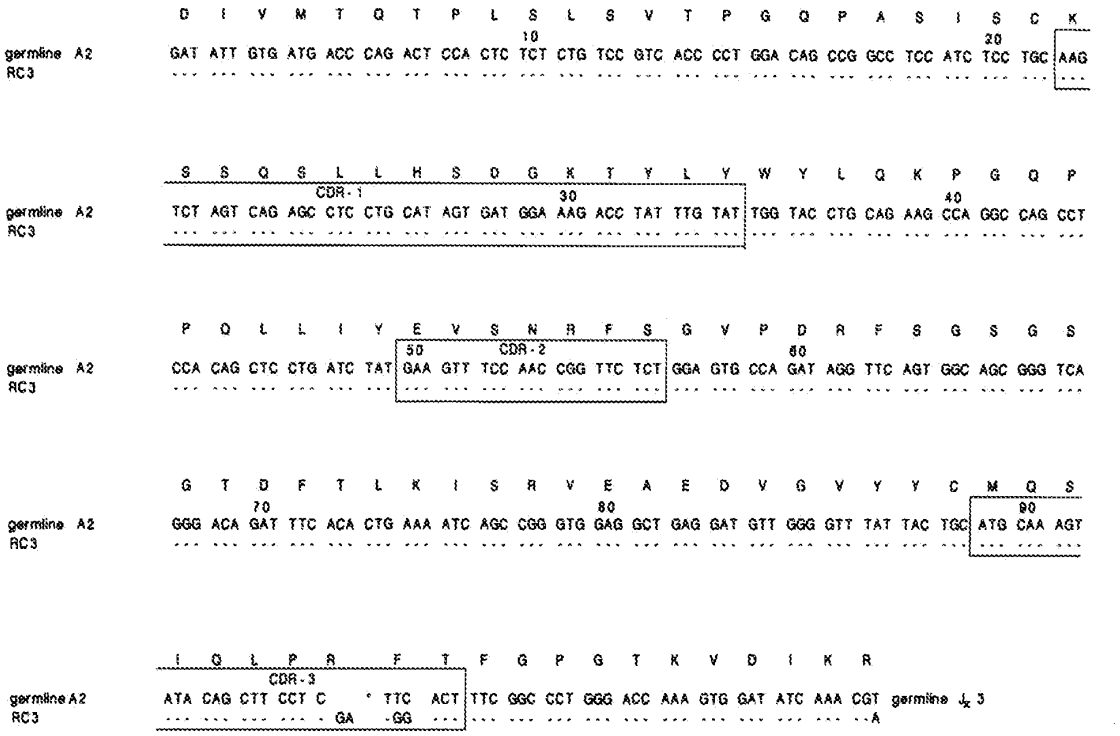


Figure 5. Nucleotide sequences of V_κ and J_κ genes from the hybridoma cell line RC3. Also shown is the translated amino acid sequence of the RC3 V_κ gene. Shown for comparison is the nucleotide sequence of a germline V_κ gene, A2 (13), and germline $J_\kappa 3$ gene. An asterisk denotes the beginning of the J_κ segment. Numbering is according to Kabat (23). This sequence data is available from EMBL/GenBank Data Libraries under accession number M80914 (RC3).

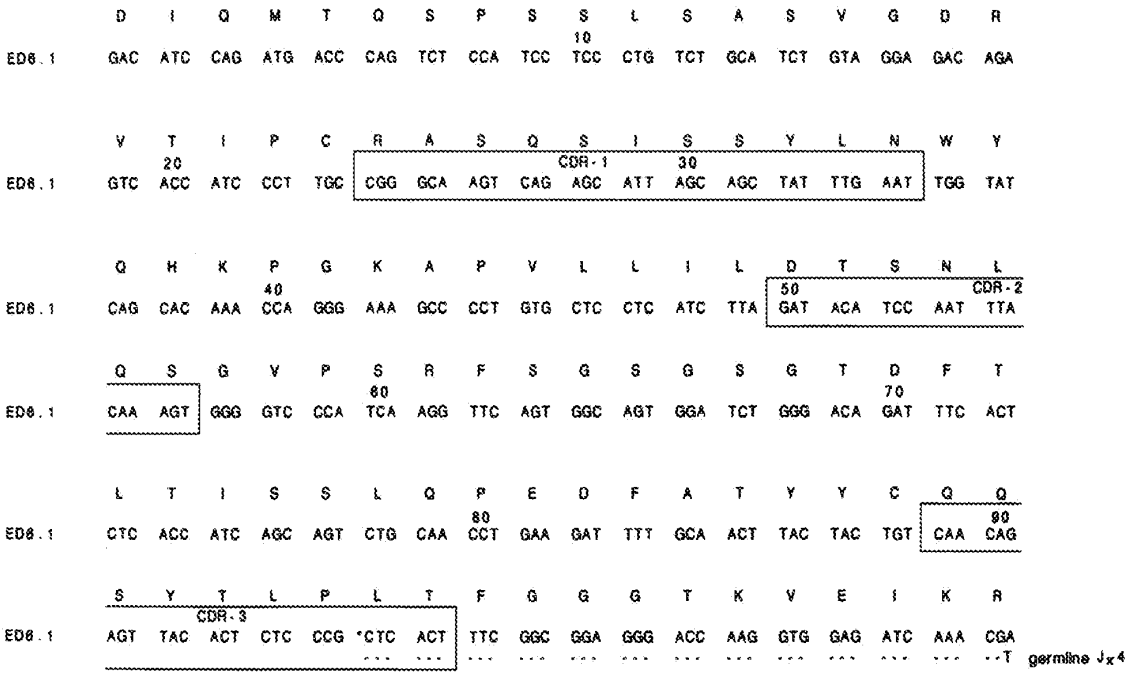


Figure 6. Nucleotide sequence of V_κ and J_κ genes from hybridoma cell line ED6.1. Also shown is the translated amino acid sequence of the ED6.1 V_κ gene. An asterisk denotes the beginning of the J_κ segment. Numbering is according to Kabat (23). This sequence data is available from EMBL/GenBank Data Libraries under accession number M80920 (ED6.1).

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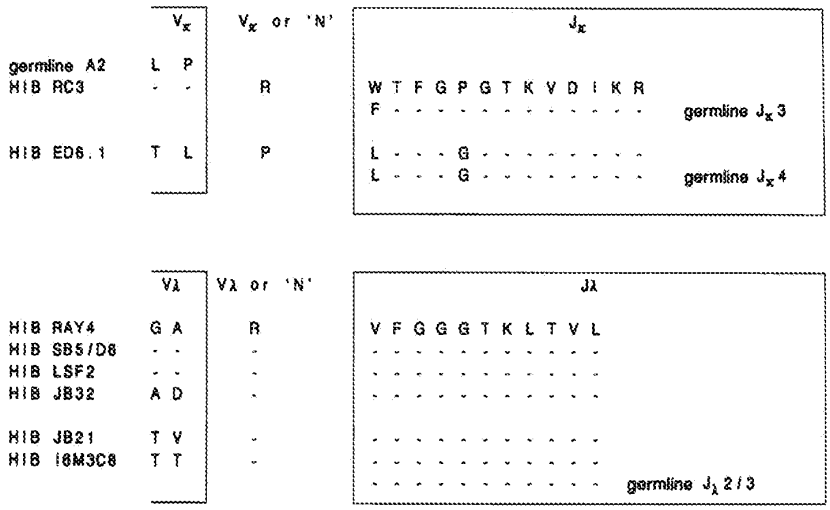


Figure 7. Translated amino acid sequences of VJ joints from seven hybridoma cell lines (RC3, ED6.1, RAY4, SB5/D6, LSF2, JB21, and 16M3C8). Also shown are translated amino acid sequences of the germline V_κ gene A2, and germline $J_\kappa 3$, $J_\kappa 4$, and $J_\lambda 2/3$ genes. (See Figs. 2, 4, and 6.)

mune response, and the apparent restriction to two or three germline V_H genes. In contrast, V_L gene usage is more complex, with antibody encoded by a number of V_λ and V_κ families (12). Analysis of light chain variable region genes obtained from cell lines selected to represent various characteristics of serum antibodies showed that despite diversity in the variety of light chain variable region gene segments utilized, most serum anti-Hib PS Abs may be encoded by a limited number of V_κ and V_λ germline genes.

The light chain distribution of anti-Hib PS Ab is characterized by a predominance of kappa light chains, although some individuals predominantly or exclusively express lambda light chains (39, 40). Scott et al. have shown that V_κII light chains are the most commonly expressed light chains among clonally purified serum anti-Hib PS antibodies from adults with high responses to immunization. Limited amino acid sequences of a number of these serum antibodies showed that greater than 60% of subjects immunized with plain Hib PS produce antibody encoded by a V_κII family member, and further, that a number of these antibodies show identical amino acid homology with the translated amino acid sequence of the germline V_κII gene A2 (12, 13). Lucas et al. have described an anti-idiotypic monoclonal antibody (Hibid-1) that identifies anti-Hib PS antibodies expressing this light chain (16). On average, 60%

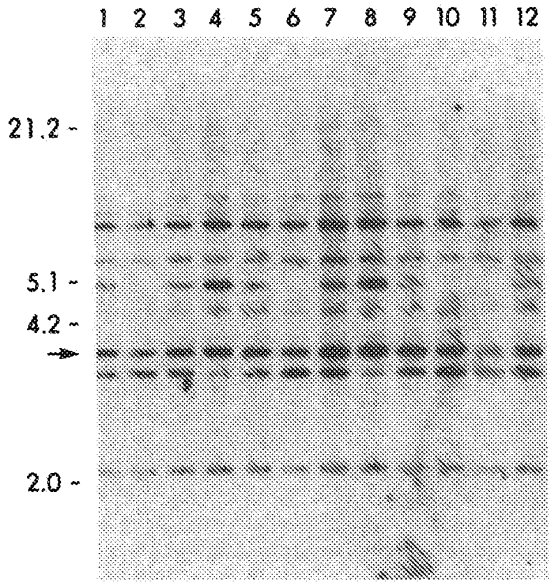


Figure 8. Southern blot analysis for V_λVII family members in BamHI-digested human genomic DNA. Lane *12* contains genomic DNA from the subject from whom hybridoma LSF2 was obtained. Lane *9* contains genomic DNA from a parent of LS. The remaining 10 donors are unrelated. An arrow indicates the 3.7-kb fragment which is identified by the oligonucleotide probe illustrated in Fig. 9.

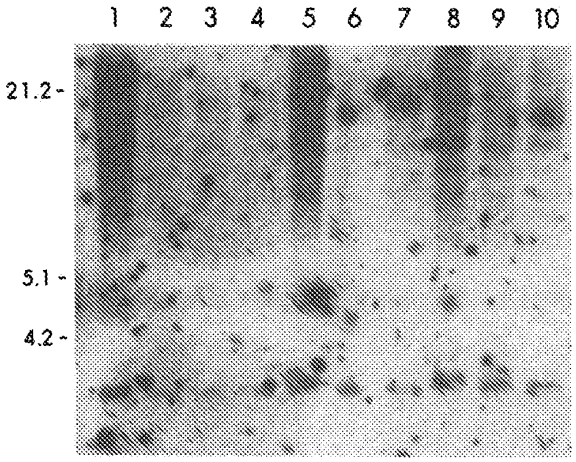


Figure 9. Dried gel hybridization of BamHI-digested human genomic DNA with an oligonucleotide probe corresponding to conserved V_λVII hybridoma CDR-1 sequences. Genomic DNA in lanes *1, 4, 5, 6, 7, 9* and *10* of Fig. 8 corresponds to that in lanes *2, 7, 4, 8, 10, 5* and *9* of Fig. 9, respectively.

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of the total anti–Hib PS antibody of most children and adults immunized with either Hib PS or Hib PS-conjugate vacine expresses this idiotype (15, 16). Taken together, this suggests the most common clonotype of anti–Hib PS Ab is encoded by a single V_κII gene. The V_κ locus contains approximately 50 functional genes, of which 40% are members of the V_κII family (41). The V_κII A2 germline gene is known to be present in a single copy (13). Our findings definitively demonstrate that at least a portion of V_κII-encoded antibodies are encoded by unmutated germline elements. Our subject R.C. was immunized with PS-protein conjugate vaccine, whereas Scott's subjects were immunized with the plain PS vaccine. Thus it is possible that the unmutated V_κII A2 segment is utilized irrespective of antigen presentation in a T-independent or T-dependent form.

Lambda variable region gene usage appears similarly restricted. The majority of lambda-expressing anti–Hib PS Ab in adults with high antibody responses to vaccine cross-reacts with *E. coli* K100 PS (17). The capsular polysaccharides of Hib and *E. coli* K100 are structurally similar and gastrointestinal colonization with *E. coli* K100 induces antibody to Hib PS in humans (42). "Naturally occurring" anti–Hib PS Ab in children commonly cross-reacts with K100 PS, whereas Ab of individuals immunized with Hib PS or responding to Hib infection is less frequently cross-reactive (18). The kappa/lambda ratio of natural anti–Hib PS Ab is lower in infants than in older children, and in the vaccine-induced antibody of adults (39). Further, Hibid-1 (the CRI associated with expression of the V_κII light chain) is expressed less frequently and comprises a smaller proportion of total anti–Hib PS Ab in preimmune compared with postimmunization sera. Expression of Hibid-1 following immunization is similar in adults and children. These results imply that cross-reactive antigens may induce the natural antibody of children. K100 PS-cross-reactive antibody may provide protective immunity in young children upon first exposure to Hib. These cross-reactive antibodies appear to be subsequently replaced or dominated by antibody specific for Hib PS when individuals are exposed to this antigen by immunization, colonization, or infection. We demonstrate that cross reactivity of lambda antibodies may be mediated through a single light chain germline gene. The mechanism for the clonal dominance of the V_κII antibodies is unclear; the avidity for Hib PS of these K100 PS–cross-reactive antibodies from adults is similar to that of Hib specific PS antibodies (P. Shackelford, unpublished observation).

Lambda antibodies expressing the V_λII gene did not cross-react with *E. coli* K100 PS. Whether all noncross-reactive antibodies are encoded by closely related members of the V_λII gene family will require further characterization of additional antibodies.

By the age of about 5 yr most individuals have acquired protective anti–Hib PS Ab. All of the hybridomas in this study were derived from older children or adults, who had detectable preimmunization antibody. The B cells immortalized by fusion, therefore, most likely represent a secondary immune response. Despite this, V_H gene segments obtained from these hybridomas appear to be relatively unmutated (14), and it appears that some V_L genes are similarly conserved. The RC3 V_κ gene segment is identical to the A2 germline gene, and although the pertinent V_λVII germline gene is not known, the paucity of differences in V_λVII segments from four different subjects suggests these gene segments are relatively unmutated. J_κ and J_λ segments are also highly homologous to germline elements. Thus, at least a portion of the anti–Hib PS response represents the use of unmutated germline elements.

VJ joints of the majority of rearranged V_L genes also appear to be an additional source of restriction in the anti–Hib PS immune response. Although there is variability in the use of J_κ segments, V_κII-encoded V_L genes are characterized by the presence of an arginine at amino acid position 95a (13). In the RC3 V_L gene and at least one of the antibodies (B-G2a) described by Scott, this appears to have arisen by N sequence addition. In four other kappa antibodies described by Scott, alternative joining may have generated this invariant arginine (13). All of the lambda V_L genes in the present study are similarly characterized by an invariant arginine-96. The germline V_λVII segment is not known; therefore the mechanism used to generate this codon is uncertain. The invariant presence of this residue in many anti–Hib PS Abs supports the previous suggestion that it may be of great importance in antigen binding (13). This also is supported by studies of the murine anti-*p*-azophenylarsonate (Ars) response. Anti-Ars light chains also contain an invariant arginine at position 96, encoded by intracodonic splicing of a single V_κ (V_κ10-Ars) and a single J_κ (J_κ1) segment (43). This arginine is essential for Ars binding, and the substitution of tyrosine for arginine has been shown to abolish binding (44). The presence of arginine residues clustered within the CDR's of the heavy chains of murine anti–DNA antibodies correlates with increased affinity, and the arginine requirement in the anti–Hib PS response may indicate its participation in the recognition of the similar phosphate–ester linkage of the repeating carbohydrate moiety (45). Thus, although diversity exists in the use of a variety of V and J segments, certain VJ combinations, which produce arginine codons by junctional flexibility or N segment addition, may be strongly selected.

Does the restricted nature of V_H and V_L segment usage in the human anti–Hib PS response explain the age-related acquisition of immunity to this organism? In both mice and humans, preferential use of certain V_H gene segments is observed in early development. In mice, biased usage of J_H-proximal V_H gene segments occurs in fetal and neonatal animals (46, 47). Developmental regulation of V_L gene usage is less extensively studied than V_H genes. Teale and Morris noted preferential expression of certain V_κ families in LPS-stimulated murine fetal B cells compared to adult B cells, with no evidence for position-dependent bias (48). Kaushik et al. also described nonstochastic use of V_κ families in adult mice, suggesting molecular constraints may persist beyond the neonatal period (49). Two or three V_H gene segments, and a single V_κ and a single V_λ gene segments, appear to encode a large proportion of anti–Hib PS Ab in immune subjects. The use of highly conserved V gene segments in human anti–Hib PS response may place considerable restraints on the immune response. The inability to utilize these genes, whether due to chromosomal position or other molecular constraints, may be responsible for the age-related susceptibility to Hib infection. The lack of somatic hypermutation in a portion of these antibodies would also place greater dependence on the germline repertoire, in that it may be impossible to improve antibody affinity by antigen-driven selection of favorable mutations. The absence or polymorphism of these genes also may contribute to individual and ethnic susceptibility to invasive Hib disease. In addition, the repertoire differences detected in some individuals (such as the absence of kappa antibody, or the absence of the V_κII-associated CRI) may be explained by the use of other minor light chains. An individ-

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ual missing the A2 germline gene has been described, although the functional implications of such a deletion are not known (13).

Expression of certain V_H gene family members in mice is correlated with B cell subpopulations (50). An alternative explanation for the poor response to plain Hib PS may be a maturational delay in recruitment of a critical B cell population that selectively expresses important variable region gene segments. We and others note that an arginine is expressed at the VJ joint in the great majority of anti-Hib PS light chains. In some circumstances N segment addition is required to generate this codon. The addition of these extra nucleotides is infrequent in light chain recombination, suggesting that these B cell precursors may be relatively infrequent (51). Moreover, N segment addition also appears to be developmentally regulated. Neonatal murine B cells lack N sequences, and their presence in heavy chain recombination increases with time (52). In addition, N sequence addition may also correlate with certain B cell subsets. N segments appear to be rare in Ly1-B cell-derived populations (53).

In contrast to plain polysaccharide vaccines, most young infants respond well to the newer Hib-PS protein conjugate vaccines (54). It is presently unknown if this antigen formulation recruits an alternative antibody repertoire, or if, by an uncertain mechanism, developmental restriction of a "dormant" B cell subset is overcome. To address this question, V gene expression in infants must be examined.

Acknowledgments

The authors thank Drs. Moon H. Nahm, Dan M. Granoff, Alan L. Schwartz, and Harvey R. Colten for helpful discussion and review of this manuscript, and Mrs. Darlene Bradley for preparation of the manuscript.

This work was supported by the Lattner Foundation, the Allison Hope Hollenbeck Fund, grant 61 from the March of Dimes, the Markey Center in Molecular Biology of Human Diseases at Washington University, grant R01 AI19350 and AI17217 from the National Institutes of Allergy and Infectious Diseases, grant RR-36 from the General Clinical Research Center, National Institutes of Health, and a Pediatric Fellowship Award (E. E. Adderson) from Connaught Laboratories, Inc.

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	19	Alexion Form 10-Q for Q3 of FY 2019 (Excerpts) 3 pages.	

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	20	Alexion Form 10K for FY 2012 (Excerpts) 3 pages.	
	21	Alexion Form 10K for FY 2013 (Excerpts) 3 pages.	
	22	Alexion Form 10K for FY 2014 (Excerpts) 3 pages.	
	23	Alexion Form 10K for FY 2015 (Excerpts) 3 pages.	
	24	Alexion Form 8-K for FY 2019 (Excerpts) 3 pages.	
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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).

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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)	2020-03-05
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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	2	Alexion Reports Presentation of Membranous Nephritis Clinical Trails" [online] Alexion Pharmaceuticals: News [Retrieved on 2003-06-17]. Retrieved from the world wide web at alexionpharm.com/news/sub press.cfm?prid=241 &selectyear=2002.	
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	7	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen's Inc.'s Objections to Evidence," Case IPR2019-00739, filed December 2, 2019, 9 pages.	
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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2020-03-05
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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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.

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	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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	12	Declaration of Bernhardt L. Trout, Ph.D. and Curriculum Vitae, dated November 22, 2019, 95 pages.	
	13	Declaration of Daniel Bazarko, dated November 22, 2019, 7 pages.	
	14	Declaration of Dr. Alexander Klibanov, dated November 24, 2018, 45 pages.	
	15	Declaration of Dr. Bruce Andrien with Exhibits, dated May 23, 2017, 36 pages.	
	16	Declaration of Dr. Bruce Andrien, dated August 15, 2018, 2 pages.	
	17	Declaration of Dr. Miano, dated March 22, 2018, 27 pages.	
	18	Declaration of Ivan Hofmann, 41 pages, February 14, 2020.	
	19	Declaration of Joseph P. Balthasar, Ph.D. and Curriculum Vitae, dated February 27, 2019, 129 pages.	
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	45	European Application No. 11001632.6, Summons to Attend Oral Proceedings, dated July 5, 2018, 10 pages.	
	46	European Application No. 11001632.6, Urgent Oral Proceedings of the Patentee, dated January 14, 2019, 2 pages.	
	47	European Application No. 11001632.6, Written Submission in Preparation of Oral Proceedings of the Patentee, dated November 24, 2018, 7 pages.	
	48	European Application No. 16172335.8 Alexion Pharmaceuticals, Inc. Written Submission in Response to Summons to Attend Oral Proceedings, dated July 5, 2019, 23 pages.	
	49	European Application No. 16172335.8 Decision of the Examining Division, dated January 20, 2020, 27 pages.	
	50	European Application No. 16172335.8 Decision to Refuse a European Patent, dated January 28, 2020, 27 pages.	

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

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A certification statement is not 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)	2020-03-05
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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	1	European Application No. 16172335.8 Minutes to Oral Proceedings, dated September 5, 2019, 7 pages.	
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	7	European Application No. 16172335.8, Summons to Attend Oral Proceedings, dated March 27, 2019, 13 pages.	
	8	European Application No. 16172335.9, Reply To Written Opinion, dated October 30, 2017, 7 pages.	
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	11	European Application No. 16195355.9 Alexion Pharmaceuticals, Inc. Written Submission in Response to Summons to Attend Oral Proceedings, dated July 5, 2019, 18 pages.	

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	49	Genentech, Inc., Herceptin 1998 Package Insert, 2 pages.	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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).

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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.

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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)	2020-03-05
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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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)	2020-03-05
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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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.

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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.

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

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

	1	US Pharmacopeia (USP29-NF24), p. 2989, retrieved from http://www.pharmacopeia.cn/v29240/usp29nf24s0 c1136.html on May 17, 2017, 4 pages.	
	2	VAKEVA, et al., "Myocardial infarction and apoptosis after myocardial ischemia and reperfusion," Circulation 97:2259-2267 (1998).	
	3	WANG, W. et al., "Antibody Structure, Instability, and Formulation" Journal of Pharmaceuticals, vol. 96(1): 26 pages (2007).	
	4	Wang, W., "Instability, stabilization, and formulation of liquid protein pharmaceuticals," International Journal of Pharmaceutics, vol. 185:129-188 (1999).	
	5	Welt, S. et al., "Phase I Study of Anticolon Cancer Humanized Antibody A33," Clinical Cancer Research, vol. 9:1338-1346 (1997).	
	6	Winter, G. and Harris, W., "Humanized Antibodies," TiPS, vol. 14:139-143 (1993).	
	7	Xiang, J. et al., "Framework Residues 71 and 93 of the Chimeric B72.3 Antibody are Major Determinants of the Conformation of Heavy-chain Hypervariable Loops," J. Mol. Biol., vol. 253:385-390 (1995).	
	8	Young, N., et al., "Safety and Efficacy of the Terminal Complement Inhibitor Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria: Interim Shepherd Phase III Clinical Study," Blood, vol. 108: Abstract 971: 4 pages (2006).	

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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)		
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	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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).

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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2020-03-05
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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Electronic Acknowledgement Receipt

EFS ID:	38760118
Application Number:	16804567
International Application Number:	
Confirmation Number:	7508
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-114BUSCN7
Receipt Date:	05-MAR-2020
Filing Date:	
Time Stamp:	14:23:01
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	AXJ-114BUSCN7_-_10771552.pdf	1114546 a23606e7e66aa910baf63f4c3ca2b56f1bbfa40b	no	26

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2	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_11050543.pdf	1247825 7837b49a9ad0a9a9a71bee8509656534a32ee811	no	27
Warnings:					
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3	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_11595118.pdf	1023802 3980100742 8a69541cf9589fcc8eb861849d1b0a	no	22
Warnings:					
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4	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_12225040.pdf	792607 24cdff8c44fa196353023d743ae388be403647c9	no	17
Warnings:					
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5	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_12621792.pdf	76485 4149e619363035ab731a019da947a633a06b2499	no	2
Warnings:					
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6	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_12902617.pdf	987288 aa047c1a1d8fb0e467ec6a7c86d7b88052ab52f5	no	19
Warnings:					
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7	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_13335518.pdf	2969578 913a0073fd37b27b941c80f367cf6331a494f7e2	no	54
Warnings:					
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8	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_13426973.pdf	1458729 1f755fdca4620693b3c9b9e617ff0be92212cb83	no	27
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9	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_15148839.pdf	1551393 1641048cc4f5db924c1f4c3275695b83fb3a0f50	no	28
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10	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_15260888.pdf	1811728 ae7d46cae0c2dc67f5e18cae127220283dff9ca4	no	34
Warnings:					
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11	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_15284015.pdf	1288087 16cc0152db81100b0cc59144c65f2a0c53bac4a	no	24
Warnings:					
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12	Other Reference-Patent/App/Search documents	AXJ-114BUSCN7_-_15642096_5_1.pdf	2057392 f4aba92d875d6021747ee73451e2dd8285c00a97	no	35
Warnings:					
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13	Transmittal Letter	IDSTRANS.pdf	45743 c8d16ca409e9af21523f810eaf4ee7668ab0403c	no	4
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14	Information Disclosure Statement (IDS) Form (SB08)	SB1.pdf	1038846 3f855e6c4ada36f5a266ac2d99a7b52f52d64f9f	no	15
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15	Information Disclosure Statement (IDS) Form (SB08)	SB2.pdf	1037212 21358d46c84675f2cf3254ddf6557a4e01d1b757	no	8
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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

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
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.

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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

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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).

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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

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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
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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	

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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)).

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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.

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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
Address: COMMISSIONER FOR PATENTS
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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

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
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	

-- 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 *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

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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

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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

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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 _____.

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

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 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	

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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.

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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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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

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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

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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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GAMBEL, PHILLIP	

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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 *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).

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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:

1.☐ Certified copies of the priority documents have been 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	

MAIL DATE	DELIVERY MODE
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.

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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

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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.

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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)	
	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

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EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/01/2011	ELECTRONIC

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

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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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12/225,040	05/13/2009	Leonard Bell	ALXN-P04-114	5538

28120 7590 04/11/2011

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EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/11/2011	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.

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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 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 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.
12/621,792	11/19/2009	Leonard Bell	ALXN-P05-114	3142

28120 7590 09/30/2010

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
09/30/2010	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)	
	12/621,792	BELL ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

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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.
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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 *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: _____.

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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

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/23/2011	ELECTRONIC

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Office Action Summary	Application No.	Applicant(s)
	12/902,617	BELL ET AL.
	Examiner	Art Unit
	PHILLIP GAMBEL	1644

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Period for Reply

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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.

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 *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
United States Patent and Trademark Office
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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

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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
United States Patent and Trademark Office
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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
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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

UNITED STATES PATENT AND TRADEMARK OFFICE

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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

959 7590 09/12/2014

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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

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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
United States Patent and Trademark Office
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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

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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
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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

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EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
01/27/2014	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):

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

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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

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EXAMINER	
ROGERS, JAMES L	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
08/20/2012	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)	
	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

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 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.

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have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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

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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)".

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.

Samsung Bioepis Exhibit No. 1002
Page 377

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 06/07/2017
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.
15/148,839	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.
- ❑ "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 378

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 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

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

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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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 08/16/2016

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
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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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 406

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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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 06/28/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
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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

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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 04/11/2017

Nelson Mullins Riley & Scarborough LLP/Alexion
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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

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):

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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 *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.

* 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, 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.

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December 5, 2016 /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 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):

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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
```

SEQ ID NO: 4 alignment

```
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
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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 440

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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.

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. 15/284,015	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.

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

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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

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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.
- 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 *2/1/2017*.

☐ 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.

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 *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.

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

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 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

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.
- 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 *10/3/2016*.

☐ 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.

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 *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
```

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 ¶). 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.

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October 26, 2016

/JAMES ROGERS/
Patent Examiner, AU 1644

/SHARON WEN/
Primary Examiner, Art Unit 1644

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NOTICE OF ALLOWANCE AND FEE(S) DUE

133485 7590 01/22/2020

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: 01/22/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

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	$1000	$0.00	$0.00	$1000	04/22/2020

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: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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 01/22/2020
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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

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	$1000	$0.00	$0.00	$1000	04/22/2020

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 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

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.
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.
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. _____

Samsung Bioepis Exhibit No. 1002
Page 464

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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One Post Office Square
30th Floor
Boston, MA 02109-2127

EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/22/2020

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 30 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. 15/642,096	Applicant(s) BELL et al.	
	Examiner JAMES L ROGERS	Art Unit 1644	AIA (FITF) 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 12/11/2019.
   ☐ 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 52-59 . 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 L ROGERS/ Examiner, Art Unit 1644	/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

1. Claims 52-59 are pending.

2. Applicant's IDSs, submitted on 12/11/2019 are acknowledged and have been considered.

REASONS FOR ALLOWANCE

3. The following is an Examiner's Statement of Reasons for Allowance:

Applicant's arguments/Response filed 12/11/2019, was considered persuasive and has overcome the obviousness rejections or the prior OA.

The closest prior art was considered to be Evans (US 6,355,245) which was discussed in the prior OA. Evans teaches the antibody 5G1.1, eculizumab. However and as previously noted, Evans does not teach an antibody that binds C5 which have a H and L chain with SEQ ID Nos: 2 and 4, respectively. One of ordinary skill in the art would according need to search for secondary references which provide the missing parts of the currently claimed sequences.

The secondary reference Bowdish (US 2003/232972) which was also discussed in the prior OA teaches an antibody that includes a region where amino acid residues corresponding to at least a portion of two CDRs are replaced with a TPO mimec (see for example claim 1). As was also discussed previously at p. 4 of the prior OA, Bowdish at ¶191 exemplifies this scheme by using an antibody framework, 5G1.1 and refers back to Evans above for this framework. The TPO mimetic peptide was cloned into 5G1.1 so as to replace the native CDR3.

However, and as noted by applicant at p. 12 of applicant's Response, Bowdish is directed to increasing the biological activity of antibody scaffolds rather than to using antibodies against C5 such as the one currently claimed in a method to treating PNH. (see ¶5 of Bowdish).

Even assuming that one of skill in the art would find Bowdish, the fact remains that one of skill in the art would still not end up with the currently claimed antibody. As noted by applicant at pp. 13-14 of the Response, Evan's scaffold 5G1.1 mouse antibody variable regions or the whole 5G1.1 mouse antibody with the sequences for Bowdish's TPO

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

It is noted that at least some of the secondary considerations are evidence of non-obviousness, particularly that the invention as claimed satisfies a long felt need and that there is objective evidence of copying. The argument as to commercial success as no evidence has been presented that the commercial success is due to the claimed invention as opposed to other efforts undertaken by the seller, such as marketing; see MPEP 716.03, in particular subsection (b).

Accordingly, claims 52-59 are deemed allowable.

4. 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."

5. 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).

December 27, 2019

/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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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 06/11/2019

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
06/11/2019	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

Office Action Summary	Application No. 15/642,096	Applicant(s) BELL et al.	
	Examiner JAMES L ROGERS	Art Unit 1644	AIA (FITF) 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 8/24/2019.

☐ 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) 52-59 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) 52-59 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: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

This Office Action vacates the Office Action mailed on 5/31/2019 and resets the time to respond. The Office Action is identical to the correspondence mailed on 5/31/2019 except that the Office Action includes a TC Director's signature.

DETAILED ACTION

1. Claims 52-59 pending and under consideration in the instant examination.

2. Applicant's IDSs filed on 8/22/2017, 3/28/2018, 4/27/2018, and 4/29/2019 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. 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 52 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 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019).

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patent 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 differs from the claimed invention 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. Instead, Hillmen teaches that patients received infusion of 600 mg of eculizumab (treatment schedule at p. 554).

Evans teaches the antibody 5G1.1, eculizumab, 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 PNH 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.

The combined references still do not precisely teach that the antibody that binds C5 has a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently claimed.

Bowdish teaches construction of a 5G1.1+peptide antibody (see ¶191 which references Figs. 13A and 13B) having a humanized antibody H chain with an amino acid sequence (SEQ ID NO: 67) which has 96% sequence identity to the currently claimed heavy chain SEQ ID NO: 2. (see sequence alignment below)

```
Query Match             96.0%;  Score 2300.5;  DB 1;  Length 472;\par
  Best Local Similarity   95.4%;  \par
  Matches  437;  Conservative    2;  Mismatches    4;  Indels   15;  Gaps    2;\par
\par
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db         20 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 79\par
\par
Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR----------YFFGSSPNWYFD 110\par
              |||||||||||||||||||||||||||||||||||||||          :    :|     \par
Db         80 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAP----- 134\par
\par
Qy        111 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 170\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        135 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 194\par
\par
Qy        171 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 230\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        195 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 254\par
\par
Qy        231 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 290\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        255 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 314\par
\par
Qy        291 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 350\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        315 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 374\par
\par
Qy        351 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 410\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        375 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 434\par
\par
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Qy        411 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448\par
              ||||||||||||||||||||||||||||||||||||||\par
Db        435 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 472\par
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Bowdish also teaches that the 5G1.1+ peptide has a humanized antibody L chain with an amino acid sequence (SEQ ID NO: 69) which has 100% sequence identity to the currently claimed light chain SEQ ID NO: 4 (see sequence alignment below).

```
Query Match             100.0%;  Score 1110;  DB 4;  Length 236;
  Best Local Similarity   100.0%;
  Matches  214;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 82

Qy         61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 142

Qy        121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        143 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 202

Qy        181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
              |||||||||||||||||||||||||||||||||
Db        203 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

Bowdish further teaches that the sequence of the above **humanized antibody H chain** SEQ ID NO: 67, which as noted supra has 96% sequence identity to the currently claimed H chain SEQ ID NO: 2, is based on Evan's eculizumab 5G1.1 antibody framework from U.S. Application Ser. No. 06/487,263, which is the USD 6,355,245 Evans Patent supra, with the exception that the CD3 region was replaced with a TPO mimetic peptide sequence (¶191). (see Fig. 13A of Bowdish which depicts the TPO H chain sequence where the CDR3 region that has been substituted with the TPO mimetic is highlighted in bold).

(SEQ ID NO: 67)

5G1.1 – TPO Heavy Chain (Bold denotes TPO mimetic) Amino acid sequence:

*MKHVSHVILFLLSVTAGVHS*QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQW
VRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSED
TAVYYCARLPIEGPTLRQWLAARAPVWGQGTLVTVSSASTKGPSVFPLAPCSR
STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
PSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL
TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK.

However, Evan's '245 Patent in Fig. 19 provides the missing CD3 sequence for the5G1.1 eculizumab antibody (see Fig. 19 from Evans, which shows framework 5G1.1

antibody with the CDR3 sequence underlined).

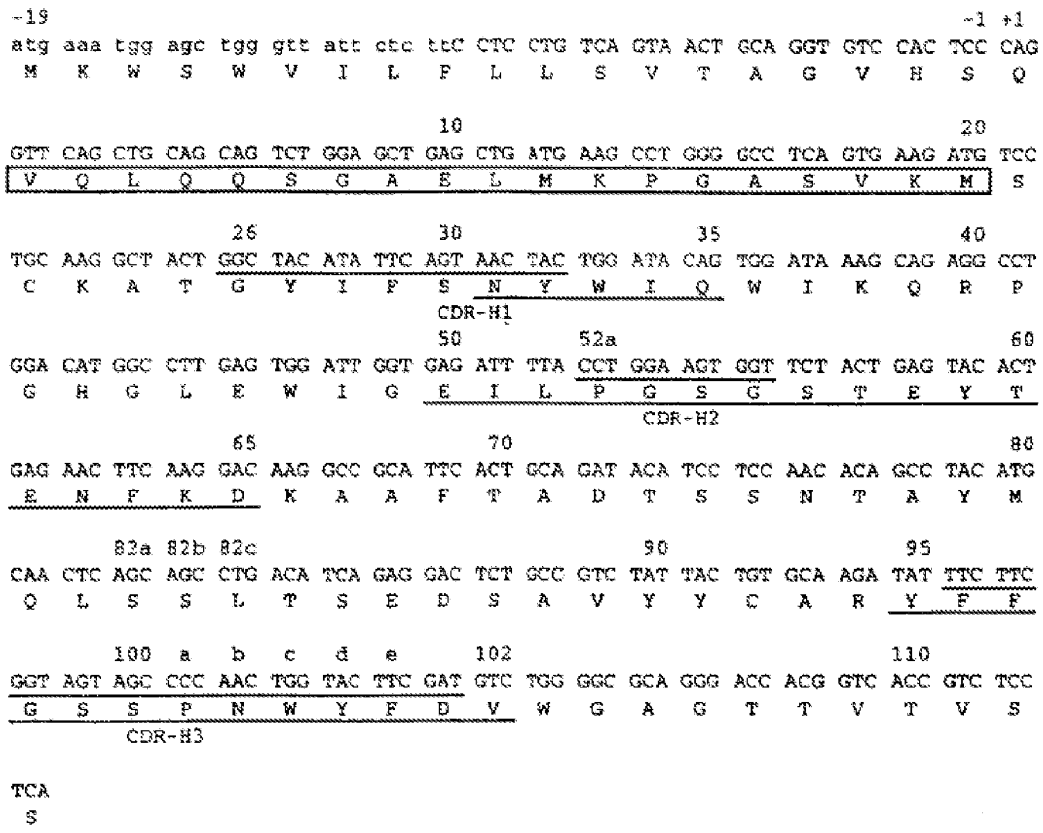


FIG.19

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Bowdish's TPO mimic amino acid sequence in Bowdish's H chain published SEQ ID NO: 67 which is 96% identical with currently claimed H chain SEQ ID NO: 2 with Evan's CDR3 5G1.1 eculizumab amino acid sequence, thereby arriving at a H chain sequence having 100% sequence identity to currently claimed H chain SEQ ID NO: 2 and to have combined that H chain sequence with Bowdish's L chain SEQ ID NO 69 that has 100% sequence identity to currently claimed L chain SEQ ID NO: 4.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Bowdish teaches that the 5G1.1+peptide antibody H chain is based on the 5G1.1 antibody framework taught by Evans, with the exception that the

CDR3 was replaced with a TPO mimic sequence. But the substituted CDR3 was taught by Evans. One of skill in the art would accordingly look to the '245 Evans Patent for the native CDR3. Evans Fig. 19 shows the heavy chain variable region as residues 95-102. Substituting the CDR3 from Evans into the heavy chain 5G1.1+ taught by Bowdish would result in a sequence having 100% sequence identity to currently claimed SEQ ID No: 2. Bowdish also teaches that the light chain of 5G1.1" (published SEQ ID NO: 69), which as shown supra has 100% amino acid sequence identity to currently claimed L chain SEQ ID NO:4.

Thus upon reading Bowdish, one of ordinary skill in the art would have found it obvious to substitute CDRH3 from the 5G1.1 of Evans into the H chain SEQ ID NO: 67 which is only 96% identical in sequence identity due to the missing CDR3 region as taught by Bowdish to arrive at 100% sequence identity for the H chain of currently claimed SEQ ID NO: 2 and to pair it with the L chain SEQ ID NO: 69 from Bowdish, thereby producing an antibody identical to currently claimed SEQ ID NO: 2 and 4. The motivation to do so comes directly form the two references, as Bowdish indicates that the 5G1.1 sequence is that of Evans, albeit with an altered CDR3 in the heavy chain.

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. Claims 52-59 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 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019), as applied to claim 52 above, and further in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

The prior art teachings of Hillmen, Evans, Wang, and Bowdish are discussed supra.

The teachings differs with respect to the characteristics of the patient population. For example, the references differ in the recitation that the patient has received at least four transfusion in the twelve months prior to administration of the antibody (claims 53 and 57), has a platelet count greater than or equal to 100k per microliter prior to administration of the antibody (claims 54 and 58).

The teachings also differ in the recitation that the patient exhibits decreased lactate dehydrogenase levels (claim 56).

The teachings also differ in the recitation that the patient is treated with the antibody for at least 26 weeks as in claims 55 and 59.

However, Hillmen further teaches that the patients in its study had received at least four red-cell transfusions in the preceding 12 months (p. 553, last 2 lines).

Bell also teaches treating PNH using an anti-C5 antibody such as h5G1.1 mAb eculizumab (¶52). Bells teaches that PNH patients were transfusion dependent and hemolytic with a history of four or more transfusion within 12 months (¶81).

Bell further teaches that the patient for treatment has a platelet count preferably in excess of 150k per microliter (¶67).

Bell further teaches that that patients received weekly intravenous infusion of anti-C5 antibody for 64 weeks (¶82).

Bell also teaches that lactate dehydrogenase levels (LDH) are used as an objective indicator of hemolysis and that LDH levels were decreased as a result of the treatment (¶85).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have continued eculizumab treatment for PNH for a period of at least 26 weeks to a patient population having received at least four transfusion in the twelve months prior to administration of eculizumab and having a platelet count in excess of 100k per microliter prior to administration of the antibody as well as to have also used a decreased LDH as a measure of clinical outcome in a method of treating PNH as taught by Hillmen. Those of skill in the art would have had reason to do so because Hillmen itself teaches that patients for treatment of PNH by administration of eculizumab had received at least 4 transfusion in the preceding 12 months, most preferably having a platelet count in excess of 150k, and Bell teaches that in the treatment of PNH with eculizumab, LDH is a known indicator of efficacy and that treatment can continue for 64 weeks, which is a period of greater than 26 weeks. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

From the 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.

Double Patenting

7. 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 time wise 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.

8. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of **US Patent 9,732,149,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 149 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4.

While the ‘149 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the ‘149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the

appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '149 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would have been obvious in view of Bell as is discussed supra.

9. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of **US Patent 9,718,880,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 880 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution..

While the '880 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '880 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would be obvious in view of Bell as is discussed supra.

10. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of **US Patent 9,725,504,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 504 Patent claim the same method of treating PNH using an antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution. See in particular claims 1, and 4-6 of the '504 patent.

The '504 also claims a decreased in mean levels of LDH after administration (claim 9).

11. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of **US Patent 9,409,980,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 980 Patent appear to claim the same anti-C5 antibody (see claim 1 of the '980). In addition, the '980 claim using the antibody to treat PNH (see claim 17).

While the '980 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

12. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of **US Patent 9,415,102,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 102 Patent appear to claim the same anti-C5 antibody (see claims 1-2 of the '102). In addition, the '102 claims using the antibody to treat PNH (see claim 17).

While the '102 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '102 that the intended use for the antibody is PNH (see methods of treatment in the specification) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '102 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

13. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of **US Patent 9,556,263,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 256 Patent appear to claim the same eculizumab antibody (see claim 1 of the '263). In addition, the '263 claim using the antibody to treat PNH (see claim 3).

While the '263 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

14. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-12 of **US Patent 9,352,035,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 035 Patent appear to claim the same eculizumab antibody (see claim 1 of the '035).

While the '035 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '035 that the intended use for the antibody is PNH (see ¶129 of the '35 which lists PNH as one of the complement associated disorders that can be treated by the composition) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '035 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

15. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of **US Patent 9,925,262,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 262 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 4 of the '262 patent.

While the '262 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

16. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-33 of **US Patent 10,239,937,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 937 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 11 of the '937 patent.

While the '937 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

17. No claim is allowed.

18. 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).

June 6, 2019

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 05/31/2019

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EXAMINER	
ROGERS, JAMES L	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
05/31/2019	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

Office Action Summary	**Application No.** 15/642,096	**Applicant(s)** BELL et al.	
	Examiner JAMES L ROGERS	**Art Unit** 1644	**AIA (FITF) 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 8/24/2017.

☐ 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) 52-59 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) 52-59 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: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

1. Claims 52-59 pending and under consideration in the instant examination.

2. Applicant's IDSs filed on 8/22/2017, 3/28/2018, 4/27/2018, and 4/29/2019 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. 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 52 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 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019).

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patent 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 differs from the claimed invention 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. Instead, Hillmen teaches that patients received infusion of 600 mg of eculizumab (treatment schedule at p. 554).

Evans teaches the antibody 5G1.1, eculizumab, 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 PNH 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.

The combined references still do not precisely teach that the antibody that binds C5 has a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently claimed.

Bowdish teaches construction of a 5G1.1+peptide antibody (see ¶191 which references Figs. 13A and 13B) having a humanized antibody H chain with an amino acid sequence (SEQ ID NO: 67) which has 96% sequence identity to the currently claimed heavy chain SEQ ID NO: 2. (see sequence alignment below)

```
Query Match             96.0%;  Score 2300.5;  DB 1;  Length 472;\par
  Best Local Similarity   95.4%;  \par
  Matches  437;  Conservative    2;  Mismatches    4;  Indels   15;  Gaps    2;\par
\par
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db         20 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 79\par
\par
Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR----------YFFGSSPNWYFD 110\par
              |||||||||||||||||||||||||||||||||||||||          :    :|     \par
Db         80 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAP----- 134\par
\par
Qy        111 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 170\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        135 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 194\par
\par
Qy        171 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 230\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        195 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 254\par
\par
Qy        231 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 290\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        255 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 314\par
\par
Qy        291 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 350\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        315 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 374\par
\par
Qy        351 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 410\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        375 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 434\par
\par
Qy        411 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448\par
              |||||||||||||||||||||||||||||||||||||\par
Db        435 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 472\par
```

Bowdish also teaches that the 5G1.1+ peptide has a humanized antibody L chain with an amino acid sequence (SEQ ID NO: 69) which has 100% sequence identity to the currently claimed light chain SEQ ID NO: 4 (see sequence alignment below).

```
Query Match             100.0%;  Score 1110;  DB 4;  Length 236;
  Best Local Similarity   100.0%;
  Matches  214;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

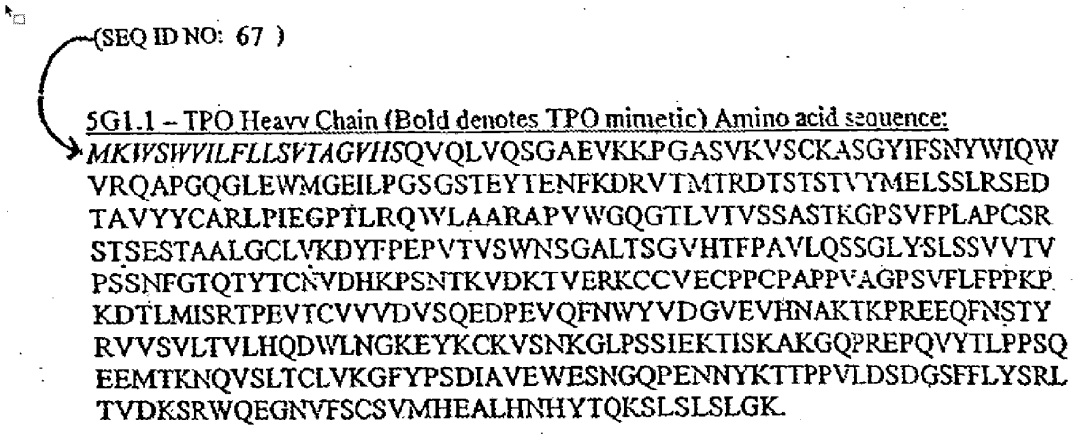
Qy          1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 82

Qy         61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 142

Qy        121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        143 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 202

Qy        181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
              |||||||||||||||||||||||||||||||||
Db        203 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

Bowdish further teaches that the sequence of the above **humanized antibody H chain** SEQ ID NO: 67, which as noted supra has 96% sequence identity to the currently claimed H chain SEQ ID NO: 2, is based on Evan's eculizumab 5G1.1 antibody framework from U.S. Application Ser. No. 06/487,263, which is the USD 6,355,245 Evans Patent supra, with the exception that the CD3 region was replaced with a TPO mimetic peptide sequence (¶191). (see Fig. 13A of Bowdish which depicts the TPO H chain sequence where the CDR3 region that has been substituted with the TPO mimetic is highlighted in bold).



However, Evan's '245 Patent in Fig. 19 provides the missing CD3 sequence for the5G1.1 eculizumab antibody (see Fig. 19 from Evans, which shows framework 5G1.1

antibody with the CDR3 sequence underlined).

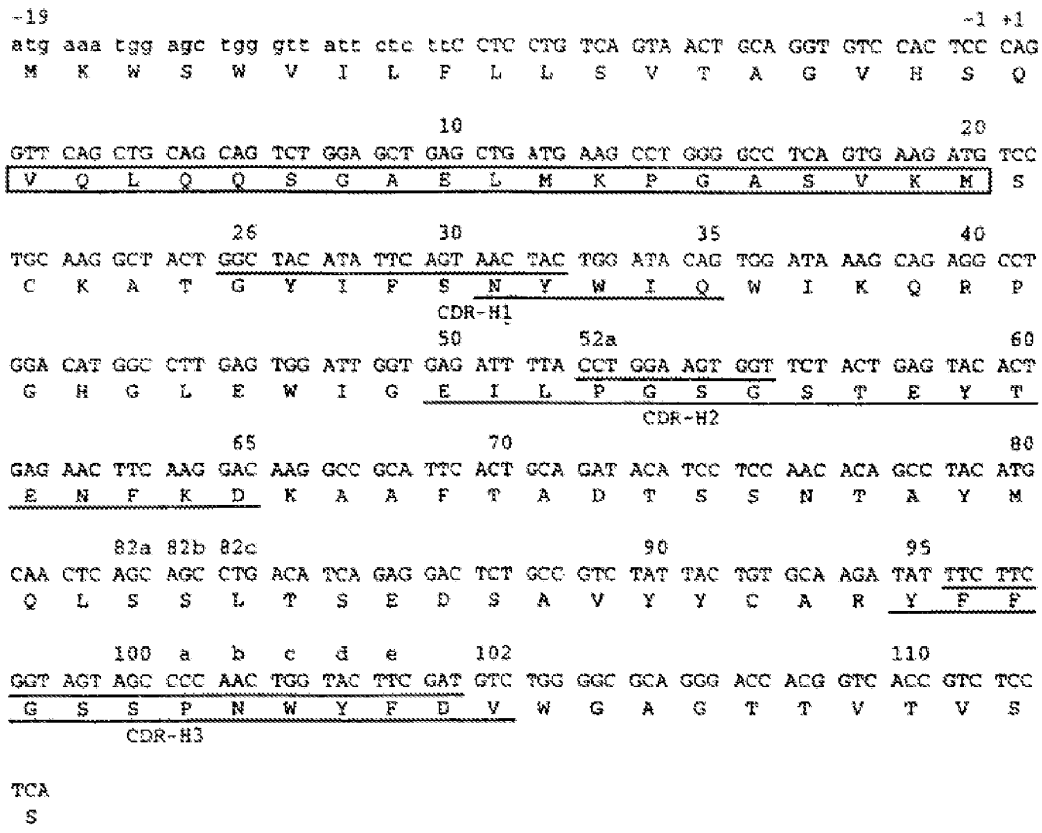


FIG.19

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Bowdish's TPO mimic amino acid sequence in Bowdish's H chain published SEQ ID NO: 67 which is 96% identical with currently claimed H chain SEQ ID NO: 2 with Evan's CDR3 5G1.1 eculizumab amino acid sequence, thereby arriving at a H chain sequence having 100% sequence identity to currently claimed H chain SEQ ID NO: 2 and to have combined that H chain sequence with Bowdish's L chain SEQ ID NO 69 that has 100% sequence identity to currently claimed L chain SEQ ID NO: 4.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Bowdish teaches that the 5G1.1+peptide antibody H chain is based on the 5G1.1 antibody framework taught by Evans, with the exception that the

CDR3 was replaced with a TPO mimic sequence. But the substituted CDR3 was taught by Evans. One of skill in the art would accordingly look to the '245 Evans Patent for the native CDR3. Evans Fig. 19 shows the heavy chain variable region as residues 95-102. Substituting the CDR3 from Evans into the heavy chain 5G1.1+ taught by Bowdish would result in a sequence having 100% sequence identity to currently claimed SEQ ID No: 2. Bowdish also teaches that the light chain of 5G1.1" (published SEQ ID NO: 69), which as shown supra has 100% amino acid sequence identity to currently claimed L chain SEQ ID NO:4.

Thus upon reading Bowdish, one of ordinary skill in the art would have found it obvious to substitute CDRH3 from the 5G1.1 of Evans into the H chain SEQ ID NO: 67 which is only 96% identical in sequence identity due to the missing CDR3 region as taught by Bowdish to arrive at 100% sequence identity for the H chain of currently claimed SEQ ID NO: 2 and to pair it with the L chain SEQ ID NO: 69 from Bowdish, thereby producing an antibody identical to currently claimed SEQ ID NO: 2 and 4. The motivation to do so comes directly form the two references, as Bowdish indicates that the 5G1.1 sequence is that of Evans, albeit with an altered CDR3 in the heavy chain.

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. Claims 52-59 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 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019), as applied to claim 52 above, and further in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

The prior art teachings of Hillmen, Evans, Wang, and Bowdish are discussed supra.

The teachings differs with respect to the characteristics of the patient population. For example, the references differ in the recitation that the patient has received at least four transfusion in the twelve months prior to administration of the antibody (claims 53 and 57), has a platelet count greater than or equal to 100k per microliter prior to administration of the antibody (claims 54 and 58).

The teachings also differ in the recitation that the patient exhibits decreased lactate dehydrogenase levels (claim 56).

The teachings also differ in the recitation that the patient is treated with the antibody for at least 26 weeks as in claims 55 and 59.

However, Hillmen further teaches that the patients in its study had received at least four red-cell transfusions in the preceding 12 months (p. 553, last 2 lines).

Bell also teaches treating PNH using an anti-C5 antibody such as h5G1.1 mAb eculizumab (¶52). Bells teaches that PNH patients were transfusion dependent and hemolytic with a history of four or more transfusion within 12 months (¶81).

Bell further teaches that the patient for treatment has a platelet count preferably in excess of 150k per microliter (¶67).

Bell further teaches that that patients received weekly intravenous infusion of anti-C5 antibody for 64 weeks (¶82).

Bell also teaches that lactate dehydrogenase levels (LDH) are used as an objective indicator of hemolysis and that LDH levels were decreased as a result of the treatment (¶85).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have continued eculizumab treatment for PNH for a period of at least 26 weeks to a patient population having received at least four transfusion in the twelve months prior to administration of eculizumab and having a platelet count in excess of 100k per microliter prior to administration of the antibody as well as to have also used a decreased LDH as a measure of clinical outcome in a method of treating PNH as taught by Hillmen. Those of skill in the art would have had reason to do so because Hillmen itself teaches that patients for treatment of PNH by administration of eculizumab had received at least 4 transfusion in the preceding 12 months, most preferably having a platelet count in excess of 150k, and Bell teaches that in the treatment of PNH with eculizumab, LDH is a known indicator of efficacy and that treatment can continue for 64 weeks, which is a period of greater than 26 weeks. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

From the 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.

Double Patenting

7. 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 time wise 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.

8. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of **US Patent 9,732,149,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 149 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4.

While the ‘149 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the ‘149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the

appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '149 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would have been obvious in view of Bell as is discussed supra.

9. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of **US Patent 9,718,880,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 880 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution..

While the '880 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '880 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would be obvious in view of Bell as is discussed supra.

10. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of **US Patent 9,725,504,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 504 Patent claim the same method of treating PNH using an antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution. See in particular claims 1, and 4-6 of the '504 patent.

The '504 also claims a decreased in mean levels of LDH after administration (claim 9).

11. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of **US Patent 9,409,980,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 980 Patent appear to claim the same anti-C5 antibody (see claim 1 of the '980). In addition, the '980 claim using the antibody to treat PNH (see claim 17).

While the '980 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

12. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of **US Patent 9,415,102,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 102 Patent appear to claim the same anti-C5 antibody (see claims 1-2 of the '102). In addition, the '102 claims using the antibody to treat PNH (see claim 17).

While the '102 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '102 that the intended use for the antibody is PNH (see methods of treatment in the specification) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '102 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

13. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of **US Patent 9,556,263,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 256 Patent appear to claim the same eculizumab antibody (see claim 1 of the '263). In addition, the '263 claim using the antibody to treat PNH (see claim 3).

While the '263 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

14. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-12 of **US Patent 9,352,035,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 035 Patent appear to claim the same eculizumab antibody (see claim 1 of the '035).

While the '035 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '035 that the intended use for the antibody is PNH (see ¶129 of the '35 which lists PNH as one of the complement associated disorders that can be treated by the composition) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '035 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

15. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of **US Patent 9,925,262,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 262 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 4 of the '262 patent.

While the '262 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

16. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-33 of **US Patent 10,239,937,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 937 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 11 of the '937 patent.

While the '937 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

17. No claim is allowed.

18. 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).

May 14, 2019

/JAMES ROGERS/
Art Unit 1644

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644

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 5, 2020
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN7
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 16/804,567

Confirmation No.: 7508

Filed: February 28, 2020

Art Unit: Not Yet Assigned

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.

For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO/SB/08, listing all references cited during the prosecution of the parent applications. The present application is a continuation of U.S. Application No. 16/750,978, filed January 23, 2020 (Atty. Docket No. AXJ-114BUSCN6). 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.

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

Applications			
Serial No.	*Filing Date*	*First Named Inventor*	*Docket No.*
16/750,978	01-23-2020	Leonard Bell	AXJ-114BUSCN6
15/642,096	07-05-2017	Leonard Bell	AXJ-114BUSCN5
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
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Serial No.	Date Mailed from USPTO	Examiner
15/642,096	01-22-2020	J. Rogers
15/642,096	06-11-2019	J. Rogers
15/642,096	05-31-2019	J. Rogers
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11/595,118	07-07-2010	P. Gambel
11/595,118	04-03-2009	F. Vandervegt
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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.

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)). Applicant believes no fee is due with this statement. Applicant believes no fee is due with this statement.

Dated: March 5, 2020

Respectfully submitted,

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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
16/804,567	02/28/2020		2720	AXJ-114BUSCN7	30	1

CONFIRMATION NO. 7508

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

FILING RECEIPT

OC000000115399105

Date Mailed: 03/13/2020

Receipt is acknowledged of this non-provisional utility 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 FIRST INVENTOR, 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 corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction 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 provided that the request is grantable.

Inventor(s)

Leonard BELL, Woodbridge, CT;
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Applicant(s)

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

Domestic Priority data as claimed by applicant

This application is a CON of 16/750,978 01/23/2020
which is a CON of 15/642,096 07/05/2017 PAT 10590189
which 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: 03/12/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/804,567**

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

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.

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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.

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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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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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Page 505

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/804,567

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	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 460 =	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	2720

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	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7

CONFIRMATION NO. 7508

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

FORMALITIES LETTER

OC00000015399106

Date Mailed: 03/13/2020

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 40 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**.

/afessehaye/

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. 16/750,978, filed January 23, 2020, which is a continuation of U.S. Patent No. 10,590,189, issued March 17, 2020, which is a continuation of U.S. Patent No. 9,732,149, issued August 15, 2017, which is a continuation of U.S. Patent No. 9,725,504, issued August 8, 2017, which is a continuation of U.S. Patent No. 9,718,880, issued August 1, 2017, 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 February 28, 2020, is named AXJ-114BUSCN7_Sequence_Listing.txt and is 10,452 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.

lntravascular 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

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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.

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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

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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

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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 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

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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.

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.

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

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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- 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

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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.

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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 (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

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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. 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

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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 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

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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

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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 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-CRl , 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

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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 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

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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 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.

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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

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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 "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.,*

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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 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

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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

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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).

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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

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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 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,

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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 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,

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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 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 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

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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

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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.

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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 proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set

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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

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

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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 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

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(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

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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 ($P<0.001$), 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

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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.

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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%)	

		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 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

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

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. 16/750,978, filed January 23, 2020, which is a continuation of U.S. Patent No. 10,590,189, issued March 17, 2020, which is a continuation of U.S. Patent No. 9,732,149, issued August 15, 2017, which is a continuation of U.S. Patent No. 9,725,504, issued August 8, 2017, which is a continuation of U.S. Patent No. 9,718,880, issued August 1, 2017, 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 February 28, 2020, is named AXJ-114BUSCN7_Sequence_Listing.txt and is 10,452 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.

lntravascular 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

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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.

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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

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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

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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 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

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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.

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,

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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.

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

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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- 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

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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.

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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 (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

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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. 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

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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 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

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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

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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 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-CRl , 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

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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 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

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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 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.

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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

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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 "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.,*

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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 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

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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

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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).

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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

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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 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,

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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 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,

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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 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

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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 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

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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

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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.

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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 proceed to randomization. The hemoglobin value at which each individual's qualifying transfusion was administered, was defined as the hemoglobin "set

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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

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

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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 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

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(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

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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 ($P<0.001$), 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

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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.

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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

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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Electronic Acknowledgement Receipt

EFS ID:	38859708
Application Number:	16804567
International Application Number:	
Confirmation Number:	7508
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/Melissa St Germain
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN7
Receipt Date:	13-MAR-2020
Filing Date:	28-FEB-2020
Time Stamp:	16:04:09
Application Type:	Utility under 35 USC 111(a)

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Warnings:					

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Warnings:					
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16/804,567	02/28/2020		2720	AXJ-114BUSCN7	30	1

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Inventor(s)

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

Applicant(s)

Alexion Pharmaceuticals, Inc., Boston, MA;

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

Domestic Priority data as claimed by applicant

This application is a CON of 16/750,978 01/23/2020
which is a CON of 15/642,096 07/05/2017 PAT 10590189
which 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: 03/12/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/804,567**

Projected Publication Date: 06/25/2020

Non-Publication Request: No

Early Publication Request: No

Title

TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT

Preliminary Class

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).

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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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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

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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 619

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/804,567

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	300
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10			OR	x 100 =	1000
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 460 =	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	2720

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	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
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.

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
16/804,567	02/28/2020		2720	AXJ-114BUSCN7	30	1

CONFIRMATION NO. 7508

REPLACEMENT FILING RECEIPT

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

OC000000115468112

Date Mailed: 03/17/2020

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Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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Samsung Bioepis Exhibit No. 1002
Page 624

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 13, 2020
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN7
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 16/804,567

Confirmation No.: 7508

Filed: February 28, 2020

Art Unit: Not Yet Assigned

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

SECOND PRELIMINARY AMENDMENT AND RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS UNDER 37 C.F.R. § 1.115

Dear Sir:

In response to the Notice to File Corrected Application Papers dated March 13, 2020, 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

Applicant submits herewith a substitute specification. Please replace the specification filed on February 28, 2020, with the substitute specification submitted herewith. No new matter has been added.

Samsung Bioepis Exhibit No. 1002
Page 626

REMARKS

The Notice to File Corrected Application Papers indicates the specification has unreadable or insufficiently clear text on page 40 (Table 3). In response, Applicant respectfully submits a substitute specification, in both clean and marked-up versions, to remove shading in the table on page 40. No new matter has been added.

Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 50-1196, under Order No. AXJ-114BUSCN7 from which the undersigned is authorized to draw.

Dated: March 13, 2020

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, 30th Floor
Boston, Massachusetts 02109-2127
617-217-4630 (Tel)
617-217-4699 (Fax)
Attorney/Agent For Applicant

To: ipboston.docketing@nelsonmullins.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 133485

Mar 17, 2020 04:12:53 AM

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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
16804567	APP.FILE.REC	03/17/2020	AXJ-114BUSCN7
	APP.FILE.REC	03/17/2020	AXJ-114BUSCN7

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If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7	7508

133485 7590 04/01/2020

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
04/01/2020	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

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/804,567	**Applicant(s)** BELL et al.	
	Examiner BRIAN W BROWN	**Art Unit** OPET	**AIA (FITF) Status** No

1. THE REQUEST FILED 28 February 2020 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to BRIAN BROWN at (571)272-5338. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/BRIAN W BROWN/ Petitions Examiner, OPET	

To: ipboston.docketing@nelsonmullins.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 133485

Apr 02, 2020 10:13:36 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.
16804567	TRACK1.GRANT	04/01/2020	AXJ-114BUSCN7

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

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Thank you for prompt attention to this notice,

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7	7508

133485 7590 04/20/2020

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
04/20/2020	ELECTRONIC

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Office Action Summary	**Application No.** 16/804,567	**Applicant(s)** BELL et al.	
	Examiner JAMES L ROGERS	**Art Unit** 1644	**AIA (FITF) 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 2/28/2020.

☐ 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) 1-30 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) 1-30 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: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

1. Claims 1-30 are pending and under consideration in the instant examination.

2. Applicant's IDSs filed on 3/5/2020 are acknowledged and have been considered.

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 time wise 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 1-30 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-8 of **US Patent 10,590,189** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 189 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4.

With respect to the dependent claims which refer to the particular patient population (claims 6, 9-19, 22-30), the '189 claims treating a "patient" who has PNH, (claim 1), has received at least four transfusions in the 12 months prior to administration of the antibody (claim 2), a platelet count greater than or equal to 100k per microliter prior to administration of the antibody (claim 3), treatment of the patient for at least 26 weeks (claim 8).

With respect to the dosing in dependent claims 2-5, the '189 claims a single unit dosage form comprising 30 mg of the antibody in 30 mL of a sterile, preservative-free solution (claim 1).

The '189 does not specifically claim that the patient is dosed at 600 mg of the antibody via intravenous infusion every 7 days for 4 doses, followed by 900 mg of the antibody via intravenous infusions 7 days later, followed by a maintenance does of 900 mg of the antibody via intravenous infusion every 14 days as in claims 8 and 21 or that the antibody is administered at a dosage level of between 5 and 50 mg per kg per patient per treatment as in claim 7.

The '189 also does not claim that the patient exhibits improved quality of life as measured by a FACIT-Fatigue or EORTC QLQ-C30 score as in claims 17 and 29-30.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have dosed the claimed anti-C5 antibody at the dose claimed in the '189

and to have also used FACIT-Fatigue and EORTC QLQ tests for gauging efficacy. One of skill in the art would have reason to do so because such dosing regimens and tests for gauging efficacy in the treatment of PN were well known in the art as taught by Hillmen. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

5. Claims 1-30 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of **US Patent 9,732,149** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

While the '149 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '149 that the intended use for the antibody is PNH (see abstract of the '149, which lists PNH as one of the complement associated disorders that can be treated by the composition) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

The '149 does not claim the various dosages nor recite the particular characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (Patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

6. Claims 1-30 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of **US Patent 9,725,504,** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and '504 Patent claim the same method of treating PNH by administering an antibody having an H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4.

With respect to the dependent claims, the '504 claims a single unit dosage form (claim 4) and a pharmaceutical composition that includes a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution. The '504 also claims that the patient is dosed at 600 via intravenous infusion every 7 days for 4 doses, followed by 900 mg of antibody 7 days later and then a maintenance does of 900 mg via intravenous infusion every 14 days (claim 8).

The '504 claims that administration results in an immediate and sustained decrease in the mean level s of LDH (claim 9) and that the immediate decrease occurs within one week of administration of the antibody (claim 1).

The '504 differs in that it does not claim that the patient has received at least four transfusions in the 12 months prior to administration of the antibody, a platelet count greater than or equal to 100k per microliter prior to administration of the antibody, treatment of the patient for at least 26 weeks.

The '504 also does not claim that the patient exhibits improved quality of life as measured by a FACIT-Fatigue or EORTC QLQ-C30 score as in claims 17 and 29-30.

Hillmen teaches a patient population for the administration of the anti-C5 antibody eculizumab, that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the dosing schedules claimed in the '504 and to have done so with a patient population with the current platelet count and having at least four transfusions prior in the 12 months prior to administration of the anti-C5 antibody as well as have used FACIT-Fatigue and EORTC QLQ tests for gauging efficacy. One of skill in the art would have reason to do so because such tests for gauging efficacy in the treatment of PNH were well known in the art, and these types of patient populations

were precisely those used for determining clinical efficacy of anti-C5 antibodies as taught by Hillmen. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

7. Claims 1-30 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of **US Patent 9,718,880** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref).

While the '880 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '880 that the intended use for the antibody is PNH (see abstract of the '149, which lists PNH as one of the complement associated disorders that can be treated by the composition) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

The '880 also claims a sterile free, 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml antibody solution.

The '880 does not claim the various other currently claimed dosages nor recite the particular characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the dosing schedule of 600/900 mg and to have done so with a patient population with the current platelet count and having at least four transfusions prior in the 12 months prior to administration of the anti-C5 antibody as well as have used FACIT-Fatigue and EORTC QLQ tests for gauging efficacy. One of skill in the art would have reason to do so because such tests for gauging efficacy in the treatment of PNH were well known in the art, and these types of patient populations were precisely those used for determining clinical efficacy of anti-C5 antibodies as taught by Hillmen. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

8. Claims 1-30 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of **US Patent 9,409,980** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

The '980 Patent claims a method for treating a patient having a complement associated disorder which includes PNH by administering an anti-C5 antibody (claims 1 and 17).

The '980 claims that the anti-C5 antibody which includes an H chain with SEQ ID NO: 13 and L chain with SEQ ID NO: 12 (claim 4).

As shown below with the sequence alignment, SEQ ID NO: 12/13 have 100% sequence identity to currently claimed SEQ ID NO: 2/4.

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100.0% identity in 448 residues overlap; Score: 2397.0; 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
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UserSeq1     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
UserSeq2     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
                 ************************************************************

UserSeq1     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
                 ************************************************************

UserSeq1     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                 ************************************************************

UserSeq1     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                 ****************************

100.0% identity in 214 residues overlap; Score: 1110.0; Gap frequency: 0.0%

UserSeq1       1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
UserSeq2       1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
                 ************************************************************

UserSeq1      61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
UserSeq2      61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
                 ************************************************************

UserSeq1     121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
UserSeq2     121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                 ************************************************************

UserSeq1     181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
UserSeq2     181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
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The ‘980 does not claim the various dosages nor recite the particular characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

9. Claims 1-30 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of **US Patent 9,415,102** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

The ‘102 Patent claims an anti-C5 antibody with published SEQ ID Nos: 13/12 which have 100% sequence identity to the currently claimed SEQ ID Nos: 2/4 for the H and L chain of an antibody that binds C5.

```
100.0% identity in 448 residues overlap; Score: 2397.0; 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 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
                  ************************************************************

UserSeq1      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
                  ************************************************************

UserSeq1      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                  ************************************************************

UserSeq1      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                  ****************************
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100.0% identity in 214 residues overlap; Score: 1110.0; Gap frequency: 0.0%

UserSeq1        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
UserSeq2        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
                  ************************************************************

UserSeq1       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
UserSeq2       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
                  ************************************************************

UserSeq1      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
UserSeq2      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                  ************************************************************

UserSeq1      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
UserSeq2      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
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While the ‘102 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the ‘102 that the intended use for the antibody is PNH (see¶193) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

The ‘102 does not claim the various dosages nor recite the particular characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (Patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

10. Claims 1-30 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of **US Patent 9,556,263** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

The '263 Patent claims a method for treating a patient having PNH by administering an eculizumab (claim 3). The '263 does not specifically recite the sequences. However, it is clear from column 17, line 57-column 18 line 25 that the claimed eculizumab includes published sequences 13/12 for the H and L chain of eculizumab which have 100% sequence identity to currently claimed SEQ ID Nos: 2/4:

```
100.0% identity in 448 residues overlap; Score: 2397.0; 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 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
                  ************************************************************

UserSeq1      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
                  ************************************************************

UserSeq1      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                  ************************************************************

UserSeq1      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                  ****************************
100.0% identity in 214 residues overlap; Score: 1110.0; Gap frequency: 0.0%

UserSeq1        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
UserSeq2        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
                  ************************************************************

UserSeq1       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
UserSeq2       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
                  ************************************************************
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UserSeq1      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
UserSeq2      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                  ************************************************************

UserSeq1      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
UserSeq2      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
                  *********************************
```

The '263 does not claim the various dosages nor recite the particular characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

11. Claims 1-30 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of **US Patent 9,925,262** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

The '262 Patent claims a kit for treating a patient having PNH by administering an anti-C5 antibody which eculizumab having published SEQ ID NO: 13/12 for the H and L chains which have 100% sequences identity to the currently claimed SEQ ID Nos: 2/4:

```
100.0% identity in 448 residues overlap; Score: 2397.0; Gap frequency: 0.0%

UserSeq1        1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
UserSeq2        1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY
                  ************************************************************
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UserSeq1       61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
UserSeq2       61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYFFGSSPNWYFDVWGQGTLVTV
                  ************************************************************

UserSeq1      121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
UserSeq2      121 SSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ
                  ************************************************************

UserSeq1      181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
UserSeq2      181 SSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPS
                  ************************************************************

UserSeq1      241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
UserSeq2      241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
                  ************************************************************

UserSeq1      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
                  ************************************************************

UserSeq1      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                  ************************************************************

UserSeq1      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                  ****************************
100.0% identity in 214 residues overlap; Score: 1110.0; Gap frequency: 0.0%

UserSeq1        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
UserSeq2        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
                  ************************************************************

UserSeq1       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
UserSeq2       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
                  ************************************************************

UserSeq1      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
UserSeq2      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                  ************************************************************

UserSeq1      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
UserSeq2      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
                  **********************************
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The ‘262 does not claim the various dosages nor recite the particular characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

12. Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 9-22 of **US Patent Application 15/261,210** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

This is a provisional rejection because the '210 is not yet patented.

The '261 Application claims a method of treating a patient diagnosed with PNH by administering recombinant eculizumab (claims 17-19). The '210 does not specifically recite the currently claimed sequences. However, it is clear that the sequences match the H and L for the recited eculizumab because the specification at #34 discloses SEQ ID NO: 1 and 2 which have 100% sequence identity to the currently claimed SEQ ID Nos: 2/4:

```
100.0% identity in 448 residues overlap; Score: 2397.0; 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
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                ************************************************************

UserSeq1     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
UserSeq2     241 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
                ************************************************************

UserSeq1     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2     301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
                ************************************************************

UserSeq1     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2     361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                ************************************************************

UserSeq1     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2     421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                ****************************
100.0% identity in 214 residues overlap; Score: 1110.0; Gap frequency: 0.0%

UserSeq1       1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
UserSeq2       1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
                ************************************************************

UserSeq1      61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
UserSeq2      61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
                ************************************************************

UserSeq1     121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
UserSeq2     121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                ************************************************************

UserSeq1     181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
UserSeq2     181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
                ***********************************
```

The ‘261 does not claim the various dosages nor recite the particular characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

13. Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-10, and 12-30 of **US Patent Application 15/560,606** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

This is a provisional rejection because the '606 is not yet patented.

The '606 Application claims a method of treating a human patient having PNH by administering an anti-C5 antibody having SEQ ID NO:s 14/11 (see claims 1 and 9) which have 100% sequence identity to the currently claimed SEQ ID Nos: 2/4:

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100.0% identity in 448 residues overlap; Score: 2397.0; 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 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
                  ************************************************************

UserSeq1      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
                  ************************************************************

UserSeq1      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                  ************************************************************

UserSeq1      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
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                  ****************************
100.0% identity in 214 residues overlap; Score: 1110.0; Gap frequency: 0.0%

UserSeq1        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
UserSeq2        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
                  ************************************************************

UserSeq1       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
UserSeq2       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
                  ************************************************************

UserSeq1      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
UserSeq2      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                  ************************************************************

UserSeq1      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
UserSeq2      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
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The variant constant region recited in the '606 are considered species of the claimed H and L chains, and as species they anticipate the instant claims (see MPEP § 804 II.B.1).

The '606 further claims an initial dose of 600 once a week for 4 weeks (claim 14) followed by a maintenance phase of 900 mg during the 5th week and then a 900 mg maintenance dose (claim 15-16).

The '606 does not recite characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

14. Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5, 7-9, 11-13, 16-19, 21-25, 27 and 31 of **US Patent Application 16/342,462** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

This is a provisional rejection because the '462 is not yet patented.

The '462 Application claims a method of treating a human patient having a "complement disorder" which is defined in the specification at ¶77 as an example of a complement-associated disorder, by administering "eculizumab". (claim 7) "Eculizumab" is defined by the specification as having SEQ ID NOs: 10/11 for the heavy and light chains which have 100% sequence identity to the currently claimed SEQ ID Nos: 2/4:

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100.0% identity in 448 residues overlap; Score: 2397.0; 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 VFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST
                  ************************************************************

UserSeq1      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
UserSeq2      301 YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT
                  ************************************************************

UserSeq1      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
UserSeq2      361 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE
                  ************************************************************

UserSeq1      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
UserSeq2      421 GNVFSCSVMHEALHNHYTQKSLSLSLGK
                  ****************************
100.0% identity in 214 residues overlap; Score: 1110.0; Gap frequency: 0.0%

UserSeq1        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
UserSeq2        1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS
                  ************************************************************

UserSeq1       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
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UserSeq2       61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP
                  ************************************************************

UserSeq1      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
UserSeq2      121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
                  ************************************************************

UserSeq1      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
UserSeq2      181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
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The ‘462 does not recite the particular doses or characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

15. Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of **US Patent Application 16/155,528** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

This is a provisional rejection because the '528 is not yet patented.

The '528 Application claims a method of treating a patient having PNH by administration of an anti-C5 antibody, which is eculizumab (claims 1, 17-18). While the '528 does not specifically recite the currently claimed sequences, Eculizumab is defined in the specification as "Soliris" at ¶133 and is considered to be the same sequence as currently claimed.

The ‘528 does not recite the particular doses or characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

16. Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 103-114 of **US Patent Application 16/425,402** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

This is a provisional rejection because the '402 is not yet patented.

The '402 Application claims a method of treating a patient having PNH by administration of an anti-C5 antibody, which is eculizumab (claim 103). While the '402 does not specifically recite the currently claimed sequences, the '402 has a priority date of March 29, 2013 and it is considered to be the same antibody as currently claimed by SEQ ID NO;s 2/4.

The '042 does not recite the particular doses or characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

17. Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37, 41-46 of **US Patent Application 16/941,080** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

This is a provisional rejection because the '080 is not yet patented.

The '080 Application claims a method of treating a patient in need of treatment with a complement inhibitor which is eculizumab by administration of eculizumab (claim 103). While the '080 does not specifically recite the currently claimed sequences, the '080 effective filing date is November 17, 2014 and ¶52 discloses that eculizumab is Soliris. Accordingly, in absence of evidence to the contrary, "eculizumab" is considered to encompass the currently claimed sequences.

The '080 does not specifically recite treating PNH. However, the specification discloses that patients in need of treatment with the complement inhibitor are those having PNH. (¶77).

The '077 does not recite the particular doses or characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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.

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).

18. Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-33 of **US Patent No: 10,239,937** in view of Hillmen (N Engl J Med 355 1233-1243 (2006), IDS Ref), Evans et al. (US 6,355,245 B1, IDS Ref) and Wang et al. (US 2005/0271660, IDS Ref).

This is a provisional rejection because the '080 is not yet patented.

The '937 Patent claims a method of treating a patient with PNH by administering "eculizumab". While the '937 does not specifically recite the currently claimed sequences, the '937 effective filing date is November 5, 2009 which is after the effective filing date of the current application. Accordingly, in absence of evidence to the contrary, "eculizumab" is considered to encompass the currently claimed sequences.

The '937 does not recite the particular doses or characteristics of the patient population.

Hillmen teaches a phase 3 trial for eculizumab, another antibody against C5, given intravenously at a dose of 600 mg weekly for 4 weeks, followed 1 week later by a 900 mg dose and then 900 mg every other week through week 26 for the treatment of PNH (p. 1233, 2nd ¶).

Hillmen further teaches that excessive intravascular hemolysis in patients in PNH causes anemia (p. 1234, 2nd ¶) and that patients received transfusions when they had symptoms resulting from anemia (p. 1235, 2nd ¶). (patient is anemic; claim 6).

Hillmen teaches that patients had received at least four transfusions during the previous 12 months and had platelet counts of at least 100k per cubic millimeter (p. 1234, 2nd column 1st ¶).

Hillmen further teaches that clinical efficacy was determined using FACIT-Fatigue and EORTC QLC-C30(p. 1235 2nd ¶; p. 1235 last ¶) and that significant improvements were noted for both tests (p. 1239, ¶s 1-2).

Hillmen teaches that lactate dehydrogenase (LDH), a biochemical marker of hemolysis was immediately reduced (p. 1233, 3rd ¶; p. 1240, 1st ¶). Transfusion independence was achieved in 505 of patients in the eculizumab group (p. 1238, 2nd column 1st ¶).

Hillmen does not teach 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 claims 3-4 or that the antibody is diluted to a concentration of 5 mg/mL prior to administration as in claim 5.

Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, 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 PNH 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).

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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).

19. The closest prior was considered to be **Evans** (US 6,355,245, IDS Ref). Evans teaches the antibody 5G1.1. However, Evans does not teach an antibody that binds C5 having SEQ ID NO: 2 for the H chain and SEQ ID NO: 4 for the L chain. The antibody taught by Evans is a mouse antibody (see at least column 37 line 34 – column 38, line 45). Evans does not teach any additional full-length antibodies.

20. The following art was considered pertinent:

(a) Bell et al. (US 2012/0237515)

Bell teaches methods for the treatment of PNH by administering an antibody against C5. Bell further teaches SEQ ID NO: 2/4 which have 100% sequence identity to applicant's currently claimed SEQ ID Nos: 2/4 (see ¶20).

The '515 to Bell constitutes 102(e) art because it makes a claim back to Provisional US application No: 60/783,070, filed on 3/15/2006, whereas the current application claims priority to PCT/US2007/006606 on 3/15/2007. The '515 to bell and the application under examination have different inventive entities, and so are prima facie "by another."

However, the '070 Provisional US Application to which Bell makes a claim of priority does not disclose the currently claims anti-C5 antibody having a SEQ ID NO: 2 for the H chain and SEQ ID NO: 4 for the L chain.

21. 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).

April 10, 2020

/JAMES ROGERS/
Art Unit 1644

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/804,567	BELL et al.
	Examiner	Art Unit
	JAMES L ROGERS	1644

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

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Search Notes		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	03/31/2020	JR
EAST: PGPUB, USPAT, JPO, EPO, DRWNT, INVENTOR SEARCH	03/31/2020	JR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/JAMES L ROGERS/ Examiner, Art Unit 1644	

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

PTO/SB/08a (02-18)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	16804567
Filing Date	2020-02-28
First Named Inventor	Leonard BELL
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	AXJ-114BUSCN7

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	1	European Application No. 16172335.8 Minutes to Oral Proceedings, dated September 5, 2019, 7 pages.	
	2	European Application No. 16172335.8 Bombara Declaration, dated July 2, 2019, 90 pages.	
	3	European Application No. 16172335.8 First Declaration of Dr. Dino Miano, dated March 17, 2018, 27 pages.	
	4	European Application No. 16172335.8 Second Declaration of Dr. Dino Miano, dated January 14, 2019, 3 pages.	
	5	European Application No. 16172335.8 Third Party Observation, dated September 3, 2019, 8 pages.	
	6	European Application No. 16172335.8 Third Party Observation, dated September 4, 2019, 8 pages.	
	7	European Application No. 16172335.8, Summons to Attend Oral Proceedings, dated March 27, 2019, 13 pages.	
	8	European Application No. 16172335.9, Reply To Written Opinion, dated October 30, 2017, 7 pages.	
	9	European Application No. 16195335.9, Decision to Refuse a European Patent, dated February 11, 2020, 51 pages.	
	10	European Application No. 16195335.9, Minutes to Oral Proceedings, dated February 7, 2020, 51 pages.	
	11	European Application No. 16195355.9 Alexion Pharmaceuticals, Inc. Written Submission in Response to Summons to Attend Oral Proceedings, dated July 5, 2019, 18 pages.	

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	12	European Application No. 16195355.9 Third Party Observation, dated September 2, 2019, 5 pages.	
	13	European Application No. 16195355.9 Third Party Observation, dated September 4, 2019, 5 pages.	
	14	European Application No. 16195355.9, Extended European Search Report, dated March 17, 2017, 8 pages.	
	15	European Application No. 16195355.9, Reply to Third Party Communication, dated January 16, 2018, 3 pages.	
	16	European Application No. 16195355.9, Reply To Written Opinion, dated July 10, 2017, 7 pages.	
	17	European Application No. 16195355.9, Summons to Attend Oral Proceeding, dated May 7, 2018, 10 pages.	
	18	European Application No. 16195355.9, Summons to Attend Oral Proceeding, dated May 7, 2018, 10 pages.	
	19	European Application No. 16195355.9, Summons to Attend Oral Proceedings, dated March 27, 2019, 12 pages.	
	20	European Application No. 16195355.9, Table of Alexion European patents and patent applications, cited in Third Party Observation filed on December 12, 2017, 1 page.	
	21	European Application No. 16195355.9, Written Submission in Preparation of Oral Proceedings, dated August 15, 2018, 13 pages.	
	22	European Decision Revoking The European Patent (Art. 101(2). (3)(b) EPC). EP Application No. EP 05712607, 12 pages. dated July 1. 2014.	

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	23	European Examination Report, European Application No. 16172335.8, dated November 23, 2017, 8 pages.	
	24	European Examination Report, European Application No. 16195355.9, dated November 17, 2017, 30 pages.	
	25	European Medicines Agency, EMA/HMPC/16633/2009 section 2, Historical Data on Medicinal Use, 2010, pages 1-40.	
	26	European Patent No. 1720571, Opposition File History, 515 pages.	
	27	European Patent No. 1720571, Pfizer Inc's Opposition statement, dated August 15, 2018, 13 pages.	
	28	European Patent No. 1720571, Third Party Observation filed on December 12, 2017, 1 page.	
	29	European Patent No. 2359834, Graphical representation of D20 Table 2, cited in Opposition on March 22, 2018, 1 page.	
	30	European Patent No. 2359834, Opposition File History, 2685 pages.	
	31	European Patent No. 2359834, Summary of antibodies listed in D20/D21 Tables, cited in Opposition on March 22, 2018.	
	32	European Patent No. 2359834, Summary of antibody products approved by EMA since filing date EMA Approved Antibodies C411599EP, cited in Opposition on March 22, 2018, 2 pages.	
	33	European Patent No. 3167888, File History, 348 pages.	

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	34	EvaluatePharma Orphan Drug Report 2019 6th Edition April 2019, 30 pages.	
	35	Extracts from Kabat et al., Sequences of Proteins of Immunological Interest, US Dept, Health and Human Services, 10 pages (1991).	
	36	Fatimah, A. et al., "Eculizumab in the management of paroxysmal nocturnal hemoglobinuria: patient selection and special considerations," Ther. Clin. Risk Manag., vol. 12: 1161-1170 (2016).	
	37	FDA Approval Letter dated March 16, 2007, 8 pages.	
	38	FDA Medical Review for Application Number 125166 (eculizumab), March 28, 2017, 122 pages.	
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	40	FIGUEROA, et al., "Infectious Diseases Associated with Complement Deficiencies," Clinical Microbiology Reviews, vol. 4(3): 359-395 (1991).	
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	42	Foote, J. et al., "Antibody Framework Residues Affecting the Conformation of the Hypervariable Loops," J. Mol. Biol., vol. 224:487-449 (1992).	
	43	Frokjaer, S. et al., "Protein Drug Stability: A Formulation Challenge," Nature Reviews, Drug Discovery, vol. 4:298-306 (April 2005).	
	44	Fung, M. et al., "Inhibition of complement, neutrophil, and platelet activation by an anti-factor D monoclonal antibody in simulated cardiopulmonary bypass circuits," The Journal of Thoracic and Cardiovascular Surgery, vol. 122(1):113-121 (2001)	

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	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

	45	GARBA, ET AL., "Total serum lactate dehydrogenase activity in acute Plasmodium falciparum malaria infection," Singapore Medical J. 46(11):632-634 (2005).	
	46	GARCIA et al., Effect of Preservatives on IgG aggregation, Complement-activating Effect and Hypotensive Activity of Horse Polyvalent Antivenom Used in Snakebite Envenomation," Biologicals, vol. 30:143-151 (2002).	
	47	Gavilondo, J.V. and Larrick, J.W., "Antibody Engineering at the Millenium," BioTechniques, vol. 29(1): 128-145 (2000).	
	48	Genentech, Inc., Avastin 2004 Package Insert, 27 pages.	
	49	Genentech, Inc., Herceptin 1998 Package Insert, 2 pages.	
	50	Genentech, Inc., Lucentis 2006 Package Insert, 7 pages.	

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EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	04/01/2020

*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.

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	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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)	2020-03-05
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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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.

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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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

```
=> d hist


     (FILE 'PCTGEN' ENTERED AT 16:30:44 ON 31 MAR 2020)
               DEL HIST

     FILE 'AGRICOLA, BIOTECHNO, COMPENDEX, EMBASE, INSPEC, PQSCITECH,
ADISCTI,
     ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, CABA, CAPLUS, CEABA-VTB, CIN,
     ESBIOBASE, FSTA, IFIALL, IMSRESEARCH, KOSMET, MEDLINE, NTIS, PCTGEN,
PS,
     RDISCLOSURE, SCISEARCH, TOXCENTER, ...' ENTERED AT 16:32:57 ON 31 MAR
2020
L1            24 FILE AGRICOLA
L2           451 FILE BIOTECHNO
L3            11 FILE COMPENDEX
L4          6385 FILE EMBASE
L5             3 FILE INSPEC
L6           456 FILE PQSCITECH
L7           163 FILE ADISCTI
L8            43 FILE ADISINSIGHT
L9            98 FILE ADISNEWS
L10            0 FILE ANABSTR
L11         3141 FILE BIOSIS
L12           22 FILE CABA
L13         2029 FILE CAPLUS
L14            0 FILE CEABA-VTB
L15           20 FILE CIN
L16          783 FILE ESBIOBASE
L17            0 FILE FSTA
L18          412 FILE IFIALL
L19           38 FILE IMSRESEARCH
L20            1 FILE KOSMET
L21         3011 FILE MEDLINE
L22            5 FILE NTIS
L23         3037 FILE PCTGEN
L24            0 FILE PS
L25            1 FILE RDISCLOSURE
L26         3859 FILE SCISEARCH
L27          923 FILE TOXCENTER
L28        40563 FILE USGENE
L29         3876 FILE USPATFULL
L30            1 FILE USPATOLD
L31         1240 FILE USPAT2
L32           44 FILE IPA
L33            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L34        70640 S    (PAROXYSMAL (2A) NOCTURNAL) (2A) HEMOGLOBINURIA
L35            9 FILE AGRICOLA
L36            0 FILE BIOTECHNO
L37            1 FILE COMPENDEX
L38         1371 FILE EMBASE
L39            0 FILE INSPEC
L40           65 FILE PQSCITECH
L41           77 FILE ADISCTI
L42           24 FILE ADISINSIGHT
L43           61 FILE ADISNEWS
L44            0 FILE ANABSTR
L45          526 FILE BIOSIS
L46            0 FILE CABA
```

```
L47          334 FILE CAPLUS
L48            0 FILE CEABA-VTB
L49           18 FILE CIN
L50          166 FILE ESBIOBASE
L51            0 FILE FSTA
L52           92 FILE IFIALL
L53           18 FILE IMSRESEARCH
L54            0 FILE KOSMET
L55          404 FILE MEDLINE
L56            0 FILE NTIS
L57           96 FILE PCTGEN
L58            0 FILE PS
L59            0 FILE RDISCLOSURE
L60          677 FILE SCISEARCH
L61          155 FILE TOXCENTER
L62         3098 FILE USGENE
L63          588 FILE USPATFULL
L64            0 FILE USPATOLD
L65          260 FILE USPAT2
L66           28 FILE IPA
L67            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L68         8068 S L34 AND  ((C5 (5A) ANTIBOD?) OR ECULIZUMAB OR SOLIRIS)
L69            0 FILE AGRICOLA
L70            0 FILE BIOTECHNO
L71            0 FILE COMPENDEX
L72           12 FILE EMBASE
L73            0 FILE INSPEC
L74            0 FILE PQSCITECH
L75            1 FILE ADISCTI
L76            9 FILE ADISINSIGHT
L77            1 FILE ADISNEWS
L78            0 FILE ANABSTR
L79            5 FILE BIOSIS
L80            0 FILE CABA
L81            1 FILE CAPLUS
L82            0 FILE CEABA-VTB
L83            0 FILE CIN
L84            0 FILE ESBIOBASE
L85            0 FILE FSTA
L86            4 FILE IFIALL
L87           17 FILE IMSRESEARCH
L88            0 FILE KOSMET
L89            1 FILE MEDLINE
L90            0 FILE NTIS
L91            0 FILE PCTGEN
L92            0 FILE PS
L93            0 FILE RDISCLOSURE
L94            0 FILE SCISEARCH
L95            1 FILE TOXCENTER
L96            0 FILE USGENE
L97           79 FILE USPATFULL
L98            0 FILE USPATOLD
L99           39 FILE USPAT2
L100           0 FILE IPA
L101           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L102         170 S L68 AND ANEMIC
L103           0 FILE AGRICOLA
L104           0 FILE BIOTECHNO
L105           0 FILE COMPENDEX
```

```
L106            3 FILE EMBASE
L107            0 FILE INSPEC
L108            0 FILE PQSCITECH
L109            1 FILE ADISCTI
L110            2 FILE ADISINSIGHT
L111            0 FILE ADISNEWS
L112            0 FILE ANABSTR
L113            2 FILE BIOSIS
L114            0 FILE CABA
L115            0 FILE CAPLUS
L116            0 FILE CEABA-VTB
L117            0 FILE CIN
L118            0 FILE ESBIOBASE
L119            0 FILE FSTA
L120            2 FILE IFIALL
L121           12 FILE IMSRESEARCH
L122            0 FILE KOSMET
L123            0 FILE MEDLINE
L124            0 FILE NTIS
L125            0 FILE PCTGEN
L126            0 FILE PS
L127            0 FILE RDISCLOSURE
L128            0 FILE SCISEARCH
L129            0 FILE TOXCENTER
L130            0 FILE USGENE
L131           28 FILE USPATFULL
L132            0 FILE USPATOLD
L133           10 FILE USPAT2
L134            0 FILE IPA
L135            0 FILE NAPRALERT
      TOTAL FOR ALL FILES
L136           60 S L102 AND (LACTATE (2A) DEHYDROGENASE)
L137            0 FILE AGRICOLA
L138            0 FILE BIOTECHNO
L139            0 FILE COMPENDEX
L140            3 FILE EMBASE
L141            0 FILE INSPEC
L142            0 FILE PQSCITECH
L143            1 FILE ADISCTI
L144            2 FILE ADISINSIGHT
L145            0 FILE ADISNEWS
L146            0 FILE ANABSTR
L147            2 FILE BIOSIS
L148            0 FILE CABA
L149            0 FILE CAPLUS
L150            0 FILE CEABA-VTB
L151            0 FILE CIN
L152            0 FILE ESBIOBASE
L153            0 FILE FSTA
L154            2 FILE IFIALL
L155            7 FILE IMSRESEARCH
L156            0 FILE KOSMET
L157            0 FILE MEDLINE
L158            0 FILE NTIS
L159            0 FILE PCTGEN
L160            0 FILE PS
L161            0 FILE RDISCLOSURE
L162            0 FILE SCISEARCH
L163            0 FILE TOXCENTER
L164            0 FILE USGENE
L165           28 FILE USPATFULL
```

```
L166          0 FILE USPATOLD
L167         10 FILE USPAT2
L168          0 FILE IPA
L169          0 FILE NAPRALERT
      TOTAL FOR ALL FILES
L170         55 S L136 AND TRANSFUSION?
L171          0 FILE AGRICOLA
L172          0 FILE BIOTECHNO
L173          0 FILE COMPENDEX
L174          1 FILE EMBASE
L175          0 FILE INSPEC
L176          0 FILE PQSCITECH
L177          1 FILE ADISCTI
L178          1 FILE ADISINSIGHT
L179          0 FILE ADISNEWS
L180          0 FILE ANABSTR
L181          0 FILE BIOSIS
L182          0 FILE CABA
L183          0 FILE CAPLUS
L184          0 FILE CEABA-VTB
L185          0 FILE CIN
L186          0 FILE ESBIOBASE
L187          0 FILE FSTA
L188          0 FILE IFIALL
L189          1 FILE IMSRESEARCH
L190          0 FILE KOSMET
L191          0 FILE MEDLINE
L192          0 FILE NTIS
L193          0 FILE PCTGEN
L194          0 FILE PS
L195          0 FILE RDISCLOSURE
L196          0 FILE SCISEARCH
L197          0 FILE TOXCENTER
L198          0 FILE USGENE
L199         24 FILE USPATFULL
L200          0 FILE USPATOLD
L201         10 FILE USPAT2
L202          0 FILE IPA
L203          0 FILE NAPRALERT
      TOTAL FOR ALL FILES
L204         38 S L170 AND (PLATELET (2A) COUNT)
L205          0 FILE AGRICOLA
L206          0 FILE BIOTECHNO
L207          0 FILE COMPENDEX
L208          0 FILE EMBASE
L209          0 FILE INSPEC
L210          0 FILE PQSCITECH
L211          1 FILE ADISCTI
L212          1 FILE ADISINSIGHT
L213          0 FILE ADISNEWS
L214          0 FILE ANABSTR
L215          0 FILE BIOSIS
L216          0 FILE CABA
L217          0 FILE CAPLUS
L218          0 FILE CEABA-VTB
L219          0 FILE CIN
L220          0 FILE ESBIOBASE
L221          0 FILE FSTA
L222          0 FILE IFIALL
L223          0 FILE IMSRESEARCH
L224          0 FILE KOSMET
```

```
L225            0 FILE MEDLINE
L226            0 FILE NTIS
L227            0 FILE PCTGEN
L228            0 FILE PS
L229            0 FILE RDISCLOSURE
L230            0 FILE SCISEARCH
L231            0 FILE TOXCENTER
L232            0 FILE USGENE
L233            7 FILE USPATFULL
L234            0 FILE USPATOLD
L235            4 FILE USPAT2
L236            0 FILE IPA
L237            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L238           13 S L204 AND (FACIT (2A) FATIGUE)
L239            0 FILE AGRICOLA
L240            0 FILE BIOTECHNO
L241            0 FILE COMPENDEX
L242            0 FILE EMBASE
L243            0 FILE INSPEC
L244            0 FILE PQSCITECH
L245            1 FILE ADISCTI
L246            1 FILE ADISINSIGHT
L247            0 FILE ADISNEWS
L248            0 FILE ANABSTR
L249            0 FILE BIOSIS
L250            0 FILE CABA
L251            0 FILE CAPLUS
L252            0 FILE CEABA-VTB
L253            0 FILE CIN
L254            0 FILE ESBIOBASE
L255            0 FILE FSTA
L256            0 FILE IFIALL
L257            0 FILE IMSRESEARCH
L258            0 FILE KOSMET
L259            0 FILE MEDLINE
L260            0 FILE NTIS
L261            0 FILE PCTGEN
L262            0 FILE PS
L263            0 FILE RDISCLOSURE
L264            0 FILE SCISEARCH
L265            0 FILE TOXCENTER
L266            0 FILE USGENE
L267            7 FILE USPATFULL
L268            0 FILE USPATOLD
L269            4 FILE USPAT2
L270            0 FILE IPA
L271            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L272           13 S L238 AND (FACIT (2A) FATIGUE)
L273            0 FILE AGRICOLA
L274            0 FILE BIOTECHNO
L275            0 FILE COMPENDEX
L276            0 FILE EMBASE
L277            0 FILE INSPEC
L278            0 FILE PQSCITECH
L279            0 FILE ADISCTI
L280            1 FILE ADISINSIGHT
L281            0 FILE ADISNEWS
L282            0 FILE ANABSTR
L283            0 FILE BIOSIS
```


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```
L284            0 FILE CABA
L285            0 FILE CAPLUS
L286            0 FILE CEABA-VTB
L287            0 FILE CIN
L288            0 FILE ESBIOBASE
L289            0 FILE FSTA
L290            0 FILE IFIALL
L291            0 FILE IMSRESEARCH
L292            0 FILE KOSMET
L293            0 FILE MEDLINE
L294            0 FILE NTIS
L295            0 FILE PCTGEN
L296            0 FILE PS
L297            0 FILE RDISCLOSURE
L298            0 FILE SCISEARCH
L299            0 FILE TOXCENTER
L300            0 FILE USGENE
L301            7 FILE USPATFULL
L302            0 FILE USPATOLD
L303            4 FILE USPAT2
L304            0 FILE IPA
L305            0 FILE NAPRALERT
      TOTAL FOR ALL FILES
L306           12 S L272 AND (26 (2A) WEEKS)
L307           12 DUP REM L306 (0 DUPLICATES REMOVED)
L308            0 FILE AGRICOLA
L309            0 FILE BIOTECHNO
L310            0 FILE COMPENDEX
L311            0 FILE EMBASE
L312            0 FILE INSPEC
L313            0 FILE PQSCITECH
L314            0 FILE ADISCTI
L315            0 FILE ADISINSIGHT
L316            0 FILE ADISNEWS
L317            0 FILE ANABSTR
L318            0 FILE BIOSIS
L319            0 FILE CABA
L320            0 FILE CAPLUS
L321            0 FILE CEABA-VTB
L322            0 FILE CIN
L323            0 FILE ESBIOBASE
L324            0 FILE FSTA
L325            0 FILE IFIALL
L326            0 FILE IMSRESEARCH
L327            0 FILE KOSMET
L328            0 FILE MEDLINE
L329            0 FILE NTIS
L330            0 FILE PCTGEN
L331            0 FILE PS
L332            0 FILE RDISCLOSURE
L333            0 FILE SCISEARCH
L334            0 FILE TOXCENTER
L335            0 FILE USGENE
L336            1 FILE USPATFULL
L337            0 FILE USPATOLD
L338            0 FILE USPAT2
L339            0 FILE IPA
L340            0 FILE NAPRALERT
      TOTAL FOR ALL FILES
L341            1 S L306 AND PY<2008
L342            0 FILE AGRICOLA
```

L343 0 FILE BIOTECHNO
L344 0 FILE COMPENDEX
L345 0 FILE EMBASE
L346 0 FILE INSPEC
L347 0 FILE PQSCITECH
L348 0 FILE ADISCTI
L349 0 FILE ADISINSIGHT
L350 0 FILE ADISNEWS
L351 0 FILE ANABSTR
L352 0 FILE BIOSIS
L353 0 FILE CABA
L354 0 FILE CEABA-VTB
L355 0 FILE CIN
L356 0 FILE ESBIOBASE
L357 0 FILE FSTA
L358 0 FILE IFIALL
L359 0 FILE IMSRESEARCH
L360 0 FILE KOSMET
L361 0 FILE MEDLINE
L362 0 FILE NTIS
L363 0 FILE PCTGEN
L364 0 FILE PS
L365 0 FILE RDISCLOSURE
L366 0 FILE SCISEARCH
L367 0 FILE TOXCENTER
L368 0 FILE USGENE
L369 11 FILE USPATFULL
L370 0 FILE USPATOLD
L371 3 FILE USPAT2
L372 0 FILE IPA
L373 0 FILE NAPRALERT
TOTAL FOR ALL FILES
L374 14 S
DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSR
L375 0 FILE AGRICOLA
L376 0 FILE BIOTECHNO
L377 0 FILE COMPENDEX
L378 0 FILE EMBASE
L379 0 FILE INSPEC
L380 0 FILE PQSCITECH
L381 0 FILE ADISCTI
L382 0 FILE ADISINSIGHT
L383 0 FILE ADISNEWS
L384 0 FILE ANABSTR
L385 0 FILE BIOSIS
L386 0 FILE CABA
L387 0 FILE CEABA-VTB
L388 0 FILE CIN
L389 0 FILE ESBIOBASE
L390 0 FILE FSTA
L391 0 FILE IFIALL
L392 0 FILE IMSRESEARCH
L393 0 FILE KOSMET
L394 0 FILE MEDLINE
L395 0 FILE NTIS
L396 0 FILE PCTGEN
L397 0 FILE PS
L398 0 FILE RDISCLOSURE
L399 0 FILE SCISEARCH
L400 0 FILE TOXCENTER
L401 0 FILE USGENE

```
L402            9 FILE USPATFULL
L403            0 FILE USPATOLD
L404            2 FILE USPAT2
L405            0 FILE IPA
L406            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L407           11 S L374 AND
QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEIL
L408           11 DUP REM L407 (0 DUPLICATES REMOVED)
L409            0 S L408
L410            0 FILE AGRICOLA
L411            0 S L408
L412            0 FILE BIOTECHNO
L413            0 S L408
L414            0 FILE COMPENDEX
L415            0 S L408
L416            0 FILE EMBASE
L417            0 S L408
L418            0 FILE INSPEC
L419            0 S L408
L420            0 FILE PQSCITECH
L421            0 S L408
L422            0 FILE ADISCTI
L423            0 S L408
L424            0 FILE ADISINSIGHT
L425            0 S L408
L426            0 FILE ADISNEWS
L427            0 S L408
L428            0 FILE ANABSTR
L429            0 S L408
L430            0 FILE BIOSIS
L431            0 S L408
L432            0 FILE CABA

     FILE 'AGRICOLA, BIOTECHNO, COMPENDEX, EMBASE, INSPEC, PQSCITECH,
ADISCTI,
     ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, CABA, CAPLUS, CEABA-VTB, CIN,
     ESBIOBASE, FSTA, IFIALL, IMSRESEARCH, KOSMET, MEDLINE, NTIS, PCTGEN,
PS,
     RDISCLOSURE, SCISEARCH, TOXCENTER, ...' ENTERED AT 16:54:44 ON 31 MAR
2020
L433           24 FILE AGRICOLA
L434          451 FILE BIOTECHNO
L435           11 FILE COMPENDEX
L436         6385 FILE EMBASE
L437            3 FILE INSPEC
L438          456 FILE PQSCITECH
L439          163 FILE ADISCTI
L440           43 FILE ADISINSIGHT
L441           98 FILE ADISNEWS
L442            0 FILE ANABSTR
L443         3141 FILE BIOSIS
L444           22 FILE CABA
L445         2029 FILE CAPLUS
L446            0 FILE CEABA-VTB
L447           20 FILE CIN
L448          783 FILE ESBIOBASE
L449            0 FILE FSTA
L450          412 FILE IFIALL
L451           38 FILE IMSRESEARCH
L452            1 FILE KOSMET
```

```
L453        3011 FILE MEDLINE
L454           5 FILE NTIS
L455        3037 FILE PCTGEN
L456           0 FILE PS
L457           1 FILE RDISCLOSURE
L458        3859 FILE SCISEARCH
L459         923 FILE TOXCENTER
L460       40563 FILE USGENE
L461        3876 FILE USPATFULL
L462           1 FILE USPATOLD
L463        1240 FILE USPAT2
L464          44 FILE IPA
L465           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L466       70640 S (PAROXYSMAL (2A) NOCTURNAL) (2A) HEMOGLOBINURIA
L467           0 FILE AGRICOLA
L468           0 FILE BIOTECHNO
L469           0 FILE COMPENDEX
L470           0 FILE EMBASE
L471           0 FILE INSPEC
L472           0 FILE PQSCITECH
L473           0 FILE ADISCTI
L474           0 FILE ADISINSIGHT
L475           0 FILE ADISNEWS
L476           0 FILE ANABSTR
L477           0 FILE BIOSIS
L478           0 FILE CABA
L479           0 FILE CEABA-VTB
L480           0 FILE CIN
L481           0 FILE ESBIOBASE
L482           0 FILE FSTA
L483           0 FILE IFIALL
L484           0 FILE IMSRESEARCH
L485           0 FILE KOSMET
L486           0 FILE MEDLINE
L487           0 FILE NTIS
L488           0 FILE PCTGEN
L489           0 FILE PS
L490           0 FILE RDISCLOSURE
L491           0 FILE SCISEARCH
L492           0 FILE TOXCENTER
L493           0 FILE USGENE
L494          11 FILE USPATFULL
L495           0 FILE USPATOLD
L496           3 FILE USPAT2
L497           0 FILE IPA
L498           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L499          14 S L466 AND
DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGAT
L500          24 FILE AGRICOLA
L501         451 FILE BIOTECHNO
L502          11 FILE COMPENDEX
L503        6385 FILE EMBASE
L504           3 FILE INSPEC
L505         456 FILE PQSCITECH
L506         163 FILE ADISCTI
L507          43 FILE ADISINSIGHT
L508          98 FILE ADISNEWS
L509           0 FILE ANABSTR
L510        3141 FILE BIOSIS
```

```
L511          22 FILE CABA
L512           0 FILE CEABA-VTB
L513          20 FILE CIN
L514         783 FILE ESBIOBASE
L515           0 FILE FSTA
L516         412 FILE IFIALL
L517          38 FILE IMSRESEARCH
L518           1 FILE KOSMET
L519        3011 FILE MEDLINE
L520           5 FILE NTIS
L521        3037 FILE PCTGEN
L522           0 FILE PS
L523           1 FILE RDISCLOSURE
L524        3859 FILE SCISEARCH
L525         923 FILE TOXCENTER
L526       40563 FILE USGENE
L527        3876 FILE USPATFULL
L528           1 FILE USPATOLD
L529        1240 FILE USPAT2
L530          44 FILE IPA
L531           0 FILE NAPRALERT
      TOTAL FOR ALL FILES
L532       68611 S (PAROXYSMAL (2A) NOCTURNAL) (2A) HEMOGLOBINURIA
L533           0 FILE AGRICOLA
L534           0 FILE BIOTECHNO
L535           0 FILE COMPENDEX
L536          30 FILE EMBASE
L537           0 FILE INSPEC
L538           0 FILE PQSCITECH
L539          17 FILE ADISCTI
L540           6 FILE ADISINSIGHT
L541           3 FILE ADISNEWS
L542           0 FILE ANABSTR
L543          27 FILE BIOSIS
L544           0 FILE CABA
L545           0 FILE CEABA-VTB
L546           0 FILE CIN
L547           5 FILE ESBIOBASE
L548           0 FILE FSTA
L549          11 FILE IFIALL
L550           3 FILE IMSRESEARCH
L551           0 FILE KOSMET
L552           7 FILE MEDLINE
L553           0 FILE NTIS
L554           0 FILE PCTGEN
L555           0 FILE PS
L556           0 FILE RDISCLOSURE
L557           7 FILE SCISEARCH
L558           7 FILE TOXCENTER
L559           0 FILE USGENE
L560          10 FILE USPATFULL
L561           0 FILE USPATOLD
L562           4 FILE USPAT2
L563           3 FILE IPA
L564           0 FILE NAPRALERT
      TOTAL FOR ALL FILES
L565         140 S L532 AND (FACIT (2A) FATIGUE)
L566           0 FILE AGRICOLA
L567           0 FILE BIOTECHNO
L568           0 FILE COMPENDEX
L569           9 FILE EMBASE
```


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```
L570            0 FILE INSPEC
L571            0 FILE PQSCITECH
L572            5 FILE ADISCTI
L573            1 FILE ADISINSIGHT
L574            3 FILE ADISNEWS
L575            0 FILE ANABSTR
L576            9 FILE BIOSIS
L577            0 FILE CABA
L578            0 FILE CEABA-VTB
L579            0 FILE CIN
L580            2 FILE ESBIOBASE
L581            0 FILE FSTA
L582            1 FILE IFIALL
L583            0 FILE IMSRESEARCH
L584            0 FILE KOSMET
L585            3 FILE MEDLINE
L586            0 FILE NTIS
L587            0 FILE PCTGEN
L588            0 FILE PS
L589            0 FILE RDISCLOSURE
L590            3 FILE SCISEARCH
L591            1 FILE TOXCENTER
L592            0 FILE USGENE
L593            8 FILE USPATFULL
L594            0 FILE USPATOLD
L595            4 FILE USPAT2
L596            1 FILE IPA
L597            0 FILE NAPRALERT
      TOTAL FOR ALL FILES
L598           50 S L565 AND (EORTC (2A) QLQ)
L599            0 FILE AGRICOLA
L600            0 FILE BIOTECHNO
L601            0 FILE COMPENDEX
L602            0 FILE EMBASE
L603            0 FILE INSPEC
L604            0 FILE PQSCITECH
L605            0 FILE ADISCTI
L606            0 FILE ADISINSIGHT
L607            3 FILE ADISNEWS
L608            0 FILE ANABSTR
L609            4 FILE BIOSIS
L610            0 FILE CABA
L611            0 FILE CEABA-VTB
L612            0 FILE CIN
L613            0 FILE ESBIOBASE
L614            0 FILE FSTA
L615            0 FILE IFIALL
L616            0 FILE IMSRESEARCH
L617            0 FILE KOSMET
L618            0 FILE MEDLINE
L619            0 FILE NTIS
L620            0 FILE PCTGEN
L621            0 FILE PS
L622            0 FILE RDISCLOSURE
L623            0 FILE SCISEARCH
L624            1 FILE TOXCENTER
L625            0 FILE USGENE
L626            1 FILE USPATFULL
L627            0 FILE USPATOLD
L628            0 FILE USPAT2
L629            0 FILE IPA
```

```
L630            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L631            9 S L598 AND PY<2008
L632            8 DUP REM L631 (1 DUPLICATE REMOVED)
L633           24 FILE AGRICOLA
L634          451 FILE BIOTECHNO
L635           11 FILE COMPENDEX
L636         6385 FILE EMBASE
L637            3 FILE INSPEC
L638          456 FILE PQSCITECH
L639          163 FILE ADISCTI
L640           43 FILE ADISINSIGHT
L641           98 FILE ADISNEWS
L642            0 FILE ANABSTR
L643         3141 FILE BIOSIS
L644           22 FILE CABA
L645            0 FILE CEABA-VTB
L646           20 FILE CIN
L647          783 FILE ESBIOBASE
L648            0 FILE FSTA
L649          412 FILE IFIALL
L650           38 FILE IMSRESEARCH
L651            1 FILE KOSMET
L652         3011 FILE MEDLINE
L653            5 FILE NTIS
L654         3037 FILE PCTGEN
L655            0 FILE PS
L656            1 FILE RDISCLOSURE
L657         3859 FILE SCISEARCH
L658          923 FILE TOXCENTER
L659        40563 FILE USGENE
L660         3876 FILE USPATFULL
L661            1 FILE USPATOLD
L662         1240 FILE USPAT2
L663           44 FILE IPA
L664            0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L665        68611 S (PAROXYSMAL (2A) NOCTURNAL) (2A) HEMOGLOBINURIA
L666            0 FILE AGRICOLA
L667           25 FILE BIOTECHNO
L668            0 FILE COMPENDEX
L669          674 FILE EMBASE
L670            0 FILE INSPEC
L671           24 FILE PQSCITECH
L672           95 FILE ADISCTI
L673           30 FILE ADISINSIGHT
L674           72 FILE ADISNEWS
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L676          318 FILE BIOSIS
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L682          149 FILE IFIALL
L683           23 FILE IMSRESEARCH
L684            1 FILE KOSMET
L685          223 FILE MEDLINE
L686            0 FILE NTIS
L687           96 FILE PCTGEN
L688            0 FILE PS
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L689          0 FILE RDISCLOSURE
L690        158 FILE SCISEARCH
L691        122 FILE TOXCENTER
L692         44 FILE USGENE
L693       3679 FILE USPATFULL
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L695       1172 FILE USPAT2
L696          7 FILE IPA
L697          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L698       6953 S L665 AND (DOSE OR DOSAGE)
L699          0 FILE AGRICOLA
L700          0 FILE BIOTECHNO
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L739          0 FILE ADISINSIGHT
L740          0 FILE ADISNEWS
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L797           16 S L764 AND ((30 (2A) ML) (5A) (10 (2A) MG))
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L799            0 FILE BIOTECHNO
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L806            0 FILE ADISNEWS
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Samsung Bioepis Exhibit No. 1002
Page 691

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L807            0 FILE ANABSTR
L808            0 FILE BIOSIS
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L811            0 FILE CIN
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L817            0 FILE MEDLINE
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L819            0 FILE PCTGEN
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L822            0 FILE SCISEARCH
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L828            0 FILE IPA
L829            0 FILE NAPRALERT
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L830            0 S L797 AND PY<2008
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Samsung Bioepis Exhibit No. 1002
Page 692

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=> d hist


     (FILE 'HOME' ENTERED AT 15:51:01 ON 31 MAR 2020)

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L1             0 S
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L2            30 S
DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPSR
L3             0 S
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L4            18 S
QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEYT

     FILE 'REGISTRY' ENTERED AT 15:53:33 ON 31 MAR 2020
L5            30 S
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L6            30 DUP REM L5 (0 DUPLICATES REMOVED)

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                RUN GETSEQ
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L7    RUN STATEMENT CREATED
L8            95 S L7 AND 214/SQL
L9             0 S L8 AND PY<2008

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                RUN GETSEQ
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L10   RUN STATEMENT CREATED
L11            0 S L10 AND PY<2008

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L12           18 S
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     FILE 'USGENE' ENTERED AT 16:28:36 ON 31 MAR 2020
                RUN GETSEQ
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L13   RUN STATEMENT CREATED
L14            0 S L13 AND (ALEXION (2A) PHARMACEUTICALS)
L15            0 S L13 AND PY<2008
L16            0 S L13 AND (ROTHER (2A) BELL)

     FILE 'PCTGEN' ENTERED AT 16:30:44 ON 31 MAR 2020
                RUN GETSEQ
QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEIL
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L17   RUN STATEMENT CREATED
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	16804567
Filing Date	2020-02-28
First Named Inventor	Leonard BELL
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	AXJ-114BUSCN7

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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
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	1							

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NON-PATENT LITERATURE DOCUMENTS Remove

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]

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	1	CORVINI M. et al., "Complement C7 deficiency presenting as recurrent aseptic meningitis," Database accession no. NLM15328683,1 page (2004) DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US October 1992 (1992-10).	
	2	CORVINI, M. et al., "Complement C7 deficiency presenting as recurrent aseptic meningitis," Annals of Allergy, Asthma & Immunology, vol. 93:200-205 (2004).	
	3	Cytogen Corp., ProstaScint 1996 Package Insert, 17 pages.	
	4	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.	
	5	DAUGHERTY, A. et al., "Formulation and Delivery Issues for Monoclonal Antibody Therapeutics," Advanced Drug Delivery Reviews, vol. 58:686-706 (2006).	
	6	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00739, dated August 30, 2019, 65 pages.	
	7	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00740, dated August 30, 2019, 69 pages.	
	8	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00741, dated August 30, 2019, 61 pages.	
	9	Declaration by Dr. Michael Treuheit, dated August 3, 2017, 12 pages.	
	10	Declaration by Prof. Ronald Taylor and Curriculum Vitae, November 21, 2018, 9 pages.	
	11	Declaration of Arturo Casadevall and Curriculum Vitae, dated November 22, 2019, 251 pages.	

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	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

	12	Declaration of Bernhardt L. Trout, Ph.D. and Curriculum Vitae, dated November 22, 2019, 95 pages.	
	13	Declaration of Daniel Bazarko, dated November 22, 2019, 7 pages.	
	14	Declaration of Dr. Alexander Klibanov, dated November 24, 2018, 45 pages.	
	15	Declaration of Dr. Bruce Andrien with Exhibits, dated May 23, 2017, 36 pages.	
	16	Declaration of Dr. Bruce Andrien, dated August 15, 2018, 2 pages.	
	17	Declaration of Dr. Miano, dated March 22, 2018, 27 pages.	
	18	Declaration of Ivan Hofmann, 41 pages, February 14, 2020.	
	19	Declaration of Joseph P. Balthasar, Ph.D. and Curriculum Vitae, dated February 27, 2019, 129 pages.	
	20	Declaration of Michel C. Nussenzweig, M.D., Ph.D. and Curriculum Vitae, dated November 21, 2019, 55 pages.	
	21	Declaration of Stephen A. Saxe, with Exhibits A, B, C, dated January 12, 2018, 10 pages.	
	22	Deposition Transcript of Arturo Casadevall, M.D., Ph.D., Case IPR2019-00739, IPR2019-00740 and IPR2019-00741, 325 pages (January 24, 2020).	

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	Attorney Docket Number	AXJ-114BUSCN7

	23	Deposition Transcript of Bernhardt L. Trout, Case IPR2019-00739 and IPR2019-00740, 217 pages (January 28, 2020).	
	24	Deposition Transcript of Daniel A. Bazarko, Case IPR2019-00739, IPR2019-00740 and IPR2019-00741 (February 6, 2020) 113 pages.	
	25	Deposition Transcript of Joseph P. Balthasar, Ph.D., Amgen, Inc. v. Alexion Pharmaceuticals, Inc., 342 pages (Oct. 23, 2019).	
	26	Deposition Transcript of Michel Nussenzweig, M.D., Ph.D., Case IPR2019-00739, IPR2019-00740 and IPR2019-00741, 106 pages (January 31, 2020).	
	27	Dmytrijuk, A. et al., "FDA Report: Eculizumab (SOLIRIS®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, The Oncologist, vol. 13:993-1000 (2008).	
	28	Eli Lilly & Co., ReoPro 1997 Package Insert, 17 pages.	
	29	EMEA, CPMP, Note for guidance on excipients, antioxidants and antimicrobial preservatives in the dossier for application for marketing authorization of; a medicinal product, February 20, 2003, 10 pages.	
	30	Emery, P. et al., "The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIB randomized, double blind, placebo controlled, dose ranging trial," Arthritis & Rheumatism, vol. 54(5): 1390-1400 (2006).	
	31	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.	
	32	European Application No. 11001632.6 Amgen's Response to the Statement of Grounds of Appeal filed by the Appellant on June 24, 2019, dated November 8, 2019, 47 pages.	
	33	European Application No. 11001632.6 Declaration of Dr. Bruce Andrien, dated May 23, 2017, 23 pages, cited in Opposition.	

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	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

	34	European Application No. 11001632.6 Declaration of Dr. Laural Boone, dated May 11, 2017, 8 pages, cited in Opposition.	
	35	European Application No. 11001632.6 Declaration of Dr. Leonard Bell, dated January 12, 2012, 4 pages, cited in Opposition.	
	36	European Application No. 11001632.6 Declaration of Tom Vink, dated August 6, 2009, 17 pages, cited in Opposition.	
	37	European Application No. 11001632.6 Denosumab, Drug Bank, accessed November 04, 2019, 6 pages, cited in Opposition.	
	38	European Application No. 11001632.6 European Board of Appeals Decision, File number T 386/89, dated March 24, 1992, 16 pages, cited in Opposition.	
	39	European Application No. 11001632.6 Hoffmann Eitle's Response to the Statement of Grounds of Appeal filed by the Appellant on June 24, 2019, dated November 8, 2019, 45 pages.	
	40	European Application No. 11001632.6 Ranibizumab, Drug Bank, accessed November 05, 2019, 6 pages, cited in Opposition.	
	41	European Application No. 11001632.6 Salbutamol Drug Guidelines, 5 pages, cited in Opposition.	
	42	European Application No. 11001632.6 Statement of Grounds of Appeal on Behalf of Alexion Pharmaceuticals, Inc., dated June 24, 2019.	
	43	European Application No. 11001632.6 Third Declaration of Dr. Dino Miano, dated June 21, 2019, 6 pages, cited in Opposition.	
	44	European Application No. 11001632.6 Patentee's Response to Oppositions, dated March 22, 2018, 24 pages.	

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	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

	45	European Application No. 11001632.6, Summons to Attend Oral Proceedings, dated July 5, 2018, 10 pages.	
	46	European Application No. 11001632.6, Urgent Oral Proceedings of the Patentee, dated January 14, 2019, 2 pages.	
	47	European Application No. 11001632.6, Written Submission in Preparation of Oral Proceedings of the Patentee, dated November 24, 2018, 7 pages.	
	48	European Application No. 16172335.8 Alexion Pharmaceuticals, Inc. Written Submission in Response to Summons to Attend Oral Proceedings, dated July 5, 2019, 23 pages.	
	49	European Application No. 16172335.8 Decision of the Examining Division, dated January 20, 2020, 27 pages.	
	50	European Application No. 16172335.8 Decision to Refuse a European Patent, dated January 28, 2020, 27 pages.	

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EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	04/01/2020

*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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	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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)	2020-03-05
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.

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.

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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.

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U.S.PATENTS Remove

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	10590189	B2	2020-03-17	Bell et al.	
	2	4686100		1987-08-11	Raffin et al.	
	3	5135916		1992-08-04	Sims et al.	
	4	5660825		1997-08-26	Sims et al.	
	5	6171586		2001-01-09	Lam et al.	
	6	6180370		2001-01-30	Queen et al.	
	7	6329509		2001-12-11	Jardieu et al.	
	8	6355245		2002-03-12	Evans et al.	

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	9	6407213		2002-06-18	Carter et al.	
	10	7361339		2008-04-22	Bell	
	11	7482435		2009-01-27	Bowdish et al.	
	12	9718880		2017-08-01	Bell et al.	
	13	9725504		2017-08-08	Bell et al.	
	14	9732149		2017-08-15	Bell et al.	

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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	20030202972	A1	2003-10-30	Andya et al.	
	2	20030049260	A1	2003-03-13	Bell	
	3	20030049683	A1	2003-03-13	Bowdish et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

	4	20030232972	A1	2003-12-18	Bowdish et al.	
	5	20040146948	A1	2004-07-29	Britton et al.	
	6	20040219147	A1	2004-11-04	Bell	
	7	20040038308	A1	2004-02-26	Rother et al.	
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	11	20050221382	A1	2005-10-06	Rother	
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	15	20050271660	A1	2005-12-08	Wang	
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	18	20070116710	A1	2007-05-24	Bell et al.	
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	25	20120237515	A1	2012-09-20	Bell et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]¡	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	0411306	EP	A1	1991-02-06	Goetze, Otto Prof. Dr. Med		☒
	2	1720571	EP	B9	2012-10-24	Alexion Pharmaceuticals, Inc		☐
	3	1755674	EP	B1	2014-11-19	Alexion Pharmaceuticals, Inc		☐
	4	1988882	EP	B1	2014-12-17	Alexion Pharmaceuticals, Inc		☒
	5	2 359 834	EP	B1	2016-11-09	Alexion Pharmaceuticals, Inc		☐

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	Attorney Docket Number	AXJ-114BUSCN7

	6	2013235	EP	A1	2009-01-14	Alexion Pharmaceuticals, Inc		☐
	7	2061810	EP	B1	2014-11-12	Alexion Pharmaceuticals, Inc		☐
	8	2089058	EP	A2	2009-08-19	Alexion Pharmaceuticals, Inc		☐
	9	2581113	EP	A1	2013-04-17	Kyowa Hakko Kirin Co., Ltd		☐
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	12	3056218	EP	A1	2016-08-17	Alexion Pharmaceuticals, Inc		☐
	13	2380907	EU	B1	2016-11-30	Alexion Pharmaceuticals, Inc		☐
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	15	2004/029207	WO	A2	2004-04-08	Xencor Inc		☐
	16	2004/035607	WO	A2	2004-04-29	Genmab A/S		☐

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	18	2004/071439	WO	A2	2004-08-26	Elan Pharmaceuticals, Inc		☐
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	Attorney Docket Number	AXJ-114BUSCN7

	28	97/11971	WO	A1	1997-04-03	Alexion Pharmaceuticals, Inc		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

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.	T5
	1	2007 USP Dictionary of USAN and International Drug Names, 85 pages.	
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	9	Alexion Form 10 K for FY 2011 (Excerpts) 3 pages.	
	10	Alexion Form 10-K for FY 2007 (Excerpts) 3 pages	
	11	Alexion Form 10-K for FY 2008 (Excerpts) 3 pages.	
	12	Alexion Form 10-K for FY 2009 (Excerpts) 3 pages.	
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	20	Alexion Form 10K for FY 2012 (Excerpts) 3 pages.	
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EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	04/01/2020

*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.

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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.

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	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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)	2020-03-05
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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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:

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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.

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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.

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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 C.F.R. § 1.6(a)(4).

Dated: March 5, 2020
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN7
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 16/804,567

Confirmation No.: 7508

Filed: February 28, 2020

Art Unit: Not Yet Assigned

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.

For the Examiner's convenience in reviewing this continuation application, Applicant submits a consolidated PTO/SB/08, listing all references cited during the prosecution of the parent applications. The present application is a continuation of U.S. Application No. 16/750,978, filed January 23, 2020 (Atty. Docket No. AXJ-114BUSCN6). 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.

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

Applications			
Serial No.	*Filing Date*	*First Named Inventor*	*Docket No.*
16/750,978	01-23-2020	Leonard Bell	AXJ-114BUSCN6
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Serial No.	Date Mailed from USPTO	Examiner
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13/335,518	11-07-2013	P. Gambel

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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.

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This Information Disclosure Statement is filed within three months of the U.S. filing date (37 C.F.R. § 1.97(b)(1)). Applicant believes no fee is due with this statement. Applicant believes no fee is due with this statement.

Dated: March 5, 2020

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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	Attorney Docket Number	AXJ-114BUSCN7

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).

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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)	2020-03-05
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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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2020-03-05
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

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)	2020-03-05
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.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

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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.

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

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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.

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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.

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To: ipboston.docketing@nelsonmullins.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 133485

Apr 20, 2020 03:45:24 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.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
16804567	CTNF	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7
	1449	04/20/2020	AXJ-114BUSCN7

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Alexion Pharmaceuticals, Inc.

Application No./Patent No.: 16/804,567 Filed/Issue Date: February 28, 2020

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

Alexion Pharmaceuticals, Inc. (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Leonard Bell To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 051981, Frame 0733, or for which a copy thereof is attached.

2. From: Russell P. Rother To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 051981, Frame 0733, or for which a copy thereof is attached.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: Mark J. Evans To: Alexion Pharmaceuticals, Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 051981 , Frame 0733 , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature _____ Date 4/27/20

Todd Spalding
Printed or Typed Name

Vice President, Head of Intellectual Property
Title or Registration Number

PTO/AIA/25 (04-13)
Approved for use through 04/30/2013. 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 displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) AXJ-114BUSCN7

In re Application of: Leonard BELL *et al.*

Application No.: 16/804,567-Conf. #7508

Filed: February 28, 2020

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

The applicant, Alexion Pharmaceuticals, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number (see attached), filed, _____, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

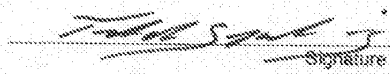
In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent granted on the pending **reference** application expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. [x] The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

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

2. [ ] The undersigned is an attorney or agent of record. Reg. No. _____


Signature

4/27/20
Date

Todd Spalding
Typed or printed name

Vice President, Head of Intellectual Property
Title

_____
Telephone Number

[x] Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SUPPLEMENTAL SHEET FOR TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) AXJ-114BUSCN7

Reference application Nos. applicable to this terminal disclaimer (referenced on first page):

15/261,210 (filed September 9, 2016)
15/560,606 (filed September 22, 2017)
16/342,462 (filed April 16, 2019)
16/155,528 (filed October 9, 2018)
16/425,402 (filed May 29, 2019)
14/941,080 (filed November 13, 2015)
16/750,978 (filed January 23, 2020)

PTO/AIA/28 (04-14)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AXJ-114BUSCN7

In re Application of: Leonard BELL *et al.*

Application No.: 16/804,567-Conf. #7508

Filed: February 28, 2020

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

The applicant, Alexion Pharmaceuticals, Inc., owner of _____ percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. (see attached) as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

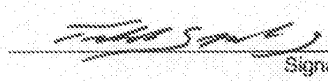
expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. [x] The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

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

2. [ ] The undersigned is an attorney or agent of record. Reg. No. _____



Signature

4/27/20

Date

Todd Spalding

Typed or printed name

Vice President, Head of Intellectual Property

Title

Telephone Number

[x] Terminal disclaimer fee under 37 CFR 1.20(d) included.

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SUPPLEMENTAL SHEET FOR TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AXJ-114BUSCN7

Prior patent Nos. applicable to this terminal disclaimer (referenced on first page):

9,352,035
9,732,149
9,718,880
9,725,504
9,409,980
9,415,102
9,556,263
9,925,262
10,239,937
10,590,189

Electronic Patent Application Fee Transmittal

Application Number:	16804567
Filing Date:	28-Feb-2020
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/Melissa St Germain
Attorney Docket Number:	AXJ-114BUSCN7

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	2	160	320
		Total in USD ($)		**320**

Electronic Acknowledgement Receipt	
EFS ID:	39273959
Application Number:	16804567
International Application Number:	
Confirmation Number:	7508
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/Melissa St Germain
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN7
Receipt Date:	27-APR-2020
Filing Date:	28-FEB-2020
Time Stamp:	17:01:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$320
RAM confirmation Number	E20204QH02134808
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	Amendment/Req. Reconsideration-After Non-Final Reject	AXJ-114BUSCN7_Response_to_Non-Final.pdf	47929 42590c6e4fd7caaf924aee48ff72b649d8975c5b	no	9
Warnings:					
Information:					
2	Assignee showing of ownership per 37 CFR 3.73	AXJ-114BUSCN7_373_Statement.pdf	3641983 77d9c508dbe9dd72ea4fc4c5a6d97ac2fefd3c6	no	2
Warnings:					
Information:					
3	Terminal Disclaimer Filed	AXJ-114BUSCN7_TD_Applications.pdf	3505903 9d6904f16a0993c2c39680521dee611abffd9e98	no	2
Warnings:					
Information:					
4	Terminal Disclaimer Filed	AXJ-114BUSCN7_TD_Patents.pdf	1929288 bd4f5707188e8f50c69ecd7495b495b37efe9fc3	no	2
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30523 19af0fa282a6cfd6520bd4b50326c67c5d512cc9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	9155626		

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, 2020
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN7
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 16/804,567

Confirmation No.: 7508

Filed: February 28, 2020

Art Unit: 1644

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

Examiner: Rogers, James L.

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

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated April 20, 2020, please amend the above-identified U.S. patent application as follows:

A Listing of the Claims begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. **(Original)** A method of treating a patient having paroxysmal nocturnal hemoglobinuria (PNH), wherein the method comprises intravenously 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.

2. **(Original)** The method of claim 1, wherein the antibody is formulated in a pharmaceutical composition comprising a single unit dosage form.

3. **(Original)** The method of claim 2, wherein the single unit dosage form is a 300 mg single unit dosage form.

4. **(Original)** The method of claim 3, wherein the pharmaceutical composition comprises a 300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution.

5. **(Original)** The method of claim 4, wherein the antibody is diluted to a concentration of 5 mg/mL prior to administration.

6. **(Original)** The method of claim 1, wherein the patient is anemic.

7. **(Original)** The method of claim 1, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

8. **(Original)** The method of claim 1, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7 ± 1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7 ± 1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14 ± 2 days.

Samsung Bioepis Exhibit No. 1002
Page 770

9. **(Original)** The method of claim 1, wherein the patient exhibits decreased lactate dehydrogenase levels after treatment with the antibody.

10. **(Original)** The method of claim 1, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

11. **(Original)** The method of claim 10, wherein the immediate decrease occurs within one week of administration of the antibody.

12. **(Original)** The method of claim 1, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

13. **(Original)** The method of claim 1, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

14. **(Original)** The method of claim 12, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

15. **(Original)** The method of claim 1, wherein the patient has about a 51% likelihood of transfusion avoidance after administration of the antibody.

16. **(Original)** The method of claim 1, wherein the patient has less than a 3% likelihood of developing antibodies to the antibody that binds C5 after 26 weeks of treatment.

17. **(Original)** The method of claim 1, wherein the patient exhibits improved quality of life as measured by a FACIT-Fatigue score or an EORTC QLQ-C30 score.

18. **(Original)** The method of claim 5, wherein the patient is treated with the antibody for at least 26 weeks.

19. **(Original)** The method of claim 5, wherein the patient is anemic.

Samsung Bioepis Exhibit No. 1002
Page 771

20. **(Original)** The method of claim 5, wherein the antibody is administered to the patient at a dosage level of between 5 mg per kg and 50 mg per kg per patient per treatment.

21. **(Original)** The method of claim 5, wherein the patient is dosed as follows: 600 mg of the antibody via intravenous infusion every 7 ± 1 days for 4 doses; followed by 900 mg of the antibody via intravenous infusion 7 ± 1 days later; followed by a maintenance dose of 900 mg of the antibody via intravenous infusion every 14 ± 2 days.

22. **(Original)** The method of claim 5, wherein the patient exhibits decreased lactate dehydrogenase levels after treatment with the antibody.

23. **(Original)** The method of claim 5, wherein administration of the antibody results in an immediate and sustained decrease in mean levels of lactate dehydrogenase (LDH).

24. **(Original)** The method of claim 23, wherein the immediate decrease occurs within one week of administration of the antibody.

25. **(Original)** The method of claim 5, wherein the patient has received at least four transfusions in the twelve months prior to administration of the antibody.

26. **(Original)** The method of claim 5, wherein the patient has a platelet count greater than or equal to 100,000 per microliter prior to administration of the antibody.

27. **(Original)** The method of claim 5, wherein the patient has about a 51% likelihood of transfusion avoidance after administration of the antibody.

28. **(Original)** The method of claim 5, wherein the patient has less than a 3% likelihood of developing antibodies to the antibody that binds C5 during the 26 weeks.

29. **(Original)** The method of claim 5, wherein the patient exhibits improved quality of life as measured by a FACIT-Fatigue score.

30. **(Original)** The method of claim 5, wherein the patient exhibits improved quality of life as measured by an EORTC QLQ-C30 score.

REMARKS

Claims 1-30 are pending in the application.

Information Disclosure Statement

Applicants acknowledge with appreciation the Examiner's indication that the Information Disclosure Statement submitted on March 5, 2020 has been considered.

Non-Statutory Double Patenting Rejections

The Examiner has rejected claims 1-30 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the following patents:

1. Claims 1-8 of US Patent 10,590,189, in view of Hillmen (*N. Engl. J. Med.*, 355 1233-1243 (2006));
2. Claim 1 of US Patent 9,732,149, in view of Hillmen, Evans *et al.* (U.S. 6,355,245) and Wang *et al.* (U.S. 2005/0271660);
3. Claims 1-10 of US Patent 9,725,504, in view of Hillmen;
4. Claims 1-3 of US Patent 9,718,880, in view of Hillmen;
5. Claims 1-17 of US Patent 9,409,980, in view of Hillmen, Evans *et al.*, and Wang *et al.*;
6. Claims 1-15 of US Patent 9,415,102, in view of Hillmen, Evans *et al.*, and Wang *et al.*;
7. Claims 1-14 of US Patent 9,556,263, in view of Hillmen, Evans *et al.*, and Wang *et al.*;
8. Claims 1-13 of US Patent 9,925,262, in view of Hillmen, Evans *et al.*, and Wang *et al.*; and
9. Claims 1-33 of US Patent 10,239,937, in view of Hillmen, Evans *et al.*, and Wang *et al.*

While in no way acquiescing to the rejections, Applicants respectfully submit herewith a Terminal Disclaimer over each of the above-referenced patents, *i.e.*, US Patent 10,590,189, US Patent 9,732,149, US Patent 9,725,504, US Patent No: 9,718,880, US Patent No: 9,409,980, US Patent No: 9,415,102, US Patent No: 9,556,263, US Patent 9,925,262, and US Patent 10,239,937.

In addition, Applicant respectfully submits herewith a Terminal Disclaimer over US Patent 9,352,035. The submission of this Terminal Disclaimer should in no way be construed as an admission of nonstatutory obviousness-type double patenting over the claims of the '035 patent.

Provisional Non-Statutory Double Patenting Rejections

Claims 1-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the following patents applications:

1. Claims 1 and 9-22 of US Patent Application 15/261,210, in view of Hillmen, Evans *et al.*, and Wang *et al.;*
2. Claims 1, 7-10 and 12-30 of US Patent Application 15/560,606, in view of Hillmen, Evans *et al.*, and Wang *et al.;*
3. Claims 1-5, 7-9, 11-13, 16-19, 21-25, 27 and 31 of US Patent Application 16/342,462, in view of Hillmen, Evans *et al.*, and Wang *et al.;*
4. Claims 1-19 of US Patent Application 16/155,528, in view of Hillmen, Evans *et al.*, and Wang *et al.;*
5. Claims 103-114 of US Patent Application 16/425,402, in view of Hillmen, Evans *et al.*, and Wang *et al.;* and
6. Claims 37 and 41-46 of US Patent Application 16/941,080, in view of Hillmen, Evans *et al.*, and Wang *et al.*

Applicant respectfully disagrees with these rejections. Notwithstanding, MPEP §1490(v)(D) provides that, if a provisional obviousness-type double patenting rejection ("ODP rejection") is the only rejection remaining in the earlier-filed of two pending applications, but the later-filed application is rejectable on other grounds, the Examiner should then withdraw the provisional ODP rejection and permit the earlier-filed application to issue as a patent without a Terminal Disclaimer.

The earliest non-provisional effective filing date of the present application is March 15, 2007, whereas the earliest non-provisional effective filing date of the '210 application is September 9, 2016. Thus, the present application is the "earlier filed" between the two applications.

The earliest non-provisional effective filing date of the present application is March 15, 2007, whereas the earliest non-provisional effective filing date of the '606 application is March 29, 2016. Thus, the present application is the "earlier filed" between the two applications.

The earliest non-provisional effective filing date of the present application is March 15, 2007, whereas the earliest non-provisional effective filing date of the '462 application is October 26, 2017. Thus, the present application is the "earlier filed" between the two applications.

The earliest non-provisional effective filing date of the present application is March 15, 2007, whereas the earliest non-provisional effective filing date of the '528 application is November 9, 2010. Thus, the present application is the "earlier filed" between the two applications.

The earliest non-provisional effective filing date of the present application is March 15, 2007, whereas the earliest non-provisional effective filing date of the '402 application is March 28, 2014. Thus, the present application is the "earlier filed" between the two applications.

Finally, the Examiner has cited US Patent Application **16**/941,080. Applicant assumes this is a typographical error, that the Examiner intended to cite US Patent Application **14**/941,080, and respectfully requests confirmation. Assuming Applicant's understanding is correct, the earliest non-provisional effective filing date of the present application is March 15, 2007, whereas the earliest non-provisional effective filing date of the '080 application is November 13, 2015. Thus, the present application is the "earlier filed" between the two applications.

In sum, pursuant to MPEP §1490(v)(D), since the present application is the "earlier filed" application in each of the above-cited provisional ODP rejections, these rejections should be withdrawn.

Finally, Applicant respectfully submits herewith a Terminal Disclaimer over US Patent Application 16/750,978. The submission of this Terminal Disclaimer should in no way be construed as an admission of nonstatutory obviousness-type double patenting over the claims of the '978 application.

Remarks with Respect to Double Patenting Rejections

In the non-statutory double patenting rejections discussed above, the Examiner states that "Evans teaches that an anti-C5 antibody 5G1.1, eculizumab, is effective…" (see, for example, page 5 (paragraph 2), page 9 (paragraph 4), page 13 (paragraph 2), page 15 (last paragraph), page 18 (paragraph 6), page 21 (paragraph 4), page 24 (paragraph 2), page 25 (last paragraph), page 28 (paragraph 8), page 30 (paragraph 6), page 32 (paragraph 6), and page 34 (paragraph 4).

Applicant respectfully disagrees. To be clear, as acknowledged by the Examiner in the Interview Summary dated February 3, 2020 for US Application No.: 15/642,096, Evans does ***not***

disclose or even mention "eculizumab". Nor is the only full-length anti-C5 antibody described in Evans – the 5G1.1 mouse antibody – the same antibody as eculizumab.

CONCLUSION

If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 217-4630. Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 50-1196, under Order No. AXJ-114BUSCN7 from which the undersigned is authorized to draw.

Dated: April 27, 2020

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, 30th Floor
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Attorney/Agent For Applicant

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/804,567	Filing Date 02/28/2020	☐ 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	
☐ 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 $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ 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	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	04/27/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $460 =	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

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CORALIA BETANCOURT/
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The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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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Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 16/804,567 *	16/804,567	BELL et al.	
	Examiner	Art Unit	
	ROGERS, JAMES L	1644	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 27 April 2020	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
/CHARRISSA S BROWN/
Technology Center: PLRC
Telephone: (571)272-1558

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 16/804,567 *	16/804,567	BELL et al.	
	Examiner	Art Unit	
	ROGERS, JAMES L	1644	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☐ APPROVED	☑ DISAPPROVED
Date Filed: 27 April 2020	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
/CHARRISSA S BROWN/
Technology Center: PLRC
Telephone: (571)272-1558
Note: The Percentage of Ownership is missing.

PTO/AIA/26 (04-14)
Approved for use through 11/30/2020. OMB 0651-0031
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AXJ-114BUSCN7

In re Application of: Leonard BELL *et al.*

Application No.: 16/804,567-Conf. #7508

Filed: February 28, 2020

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

The applicant, Alexion Pharmaceuticals, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. (see attached) as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. [x] The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

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

2. [ ] The undersigned is an attorney or agent of record. Reg. No. _____

Signature — May 5 2020 (Date)

Todd Spalding
Typed or printed name

Vice President, Head of Intellectual Property
Title

617-840-9824
Telephone Number

[x] Terminal disclaimer fee under 37 CFR 1.20(d) included.

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SUPPLEMENTAL SHEET FOR TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AXJ-114BUSCN7

Prior patent Nos. applicable to this terminal disclaimer (referenced on first page):

9,352,035
9,732,149
9,718,880
9,725,504
9,409,980
9,415,102
9,556,263
9,925,262
10,239,937
10,590,189

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Alexion Pharmaceuticals, Inc.

Application No./Patent No.: 16/804,567 Filed/Issue Date: February 28, 2020

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

Alexion Pharmaceuticals, Inc. (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Leonard Bell To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 051981, Frame 0733, or for which a copy thereof is attached.

2. From: Russell P. Rother To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 051981, Frame 0733, or for which a copy thereof is attached.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: Mark J. Evans To: Alexion Pharmaceuticals, Inc.
The document was recorded in the United States Patent and Trademark Office at
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4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
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☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature _____ Date 4/27/20

Todd Spalding
Printed or Typed Name

Vice President, Head of Intellectual Property
Title or Registration Number

Electronic Patent Application Fee Transmittal

Application Number:	16804567
Filing Date:	28-Feb-2020
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/Melissa St Germain
Attorney Docket Number:	AXJ-114BUSCN7

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
		Total in USD ($)		**160**

Electronic Acknowledgement Receipt	
EFS ID:	39351534
Application Number:	16804567
International Application Number:	
Confirmation Number:	7508
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/Melissa St Germain
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN7
Receipt Date:	05-MAY-2020
Filing Date:	28-FEB-2020
Time Stamp:	14:15:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	E202055E15589870
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Warnings:					
Information:					
2	Assignee showing of ownership per 37 CFR 3.73	AXJ-114BUSCN7_373_Statement.pdf	3641983 77d9c508dbe9dd72ea4fc4c5a6d97ac2fefcf3c6	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30472 a862c0d89c2357a657b677a0775b2e1022c0683e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6979449		

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
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Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 16/804,567 *	16/804,567	BELL et al.	
	Examiner	Art Unit	
	ROGERS, JAMES L	1644	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 05 May 2020	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
/PAMELA A YOUNG/
Technology Center: PLRC
Telephone: (571)272-3622

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

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
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN7

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN7

	1	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen Inc.'s Motion to Exclude Evidence Under C.F.R. § 42.64 (c)," Case IPR2019-00741, filed May 8, 2020, 10 pages.	
	2	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen Inc.'s Objections to Evidence," Case IPR2019-00739, filed May 4, 2020, 4 pages.	
	3	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen Inc.'s Objections to Evidence," Case IPR2019-00740, filed May 4, 2020, 4 pages.	
	4	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen Inc.'s Objections to Evidence," Case IPR2019-00741, filed May 4, 2020, 4 pages.	
	5	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Surreply to Petitioner's Reply," Case IPR2019-00739, filed April 27, 2020, 40 pages.	
	6	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Surreply to Petitioner's Reply," Case IPR2019-00740, filed April 27, 2020, 40 pages.	
	7	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Surreply to Petitioner's Reply," Case IPR2019-00741, filed April 27, 2020, 40 pages.	
	8	ClinicalTrials.Gov, Study No. NCT03818607, "A Study Evaluating the Efficacy and Safety of ABP 959 Compared with Eculizumab in Adult Participants with PNH (DAHLIA)," available at https://clinicaltrials.gov/ct2/show/NCT03818607 (last accessed Apr. 21, 2020) 10 pages.	
	9	Deposition Transcript of Ivan T. Hofmann, Amgen, Inc. v. Alexion Pharmaceuticals, Inc., March 12, 2020, 220 pages. Case IPR2019-00739, IPR2019-00740 and IPR2019-00741	
	10	Deposition Transcript of Joseph P. Balthasar, Ph.D., Amgen, Inc. v. Alexion Pharmaceuticals, Inc., April 22, 2020, 81 pages. Case IPR2019-00739, IPR2019-00740 and IPR2019-00741	
	11	European Application No. 11001632.6, Patentee's Comments on the Arguments Raised in the Response to Grounds of Appeal, dated April 6, 2020, 14 pages.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN7

	12	European Application No. 16172335.8, Notice of Appeal against the Examining Division's Decision of January 28, 2020 to refuse this application, filed March 24, 2020, 4 pages.	
	13	European Application No. 16195355.9, Notice of appeal against the Examining Division's decision of February 11, 2020 to refuse this application, dated July 5, 2019, filed March 24, 2020, 4 pages.	
	14	File History for U.S. Patent No. 10,590,189, 594 pages. Case IPR2019-00739, IPR2019-00740 and IPR2019-00741	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN7

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)	2020-05-13
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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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 Patent Application Fee Transmittal

Application Number:	16804567
Filing Date:	28-Feb-2020
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/Anita Costa
Attorney Docket Number:	AXJ-114BUSCN7

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

Electronic Acknowledgement Receipt	
EFS ID:	39420058
Application Number:	16804567
International Application Number:	
Confirmation Number:	7508
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-114BUSCN7
Receipt Date:	13-MAY-2020
Filing Date:	28-FEB-2020
Time Stamp:	15:36:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$240
RAM confirmation Number	E20205CF36593492
Deposit Account	
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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	Non Patent Literature	AXJ-114BUSCN7_-_MotiontoExclude-941.pdf	198951 244bd66a1605a14d7ef55f758ef26399b6dd6467	no	10
Warnings:					
Information:					
2	Non Patent Literature	AXJ-114BUSCN7_-_2020-05-04_Objections_to_Evidence__739.pdf	135717 4f5311bff37f4cd06cdd135dfad6b79911cc5762	no	4
Warnings:					
Information:					
3	Non Patent Literature	AXJ-114BUSCN7_-_2020-05-04_Objections_to_Evidence_740.pdf	135721 084e1a43c604bf99e05e1768796fdbcce9bbbd85	no	4
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Information:					
4	Non Patent Literature	AXJ-114BUSCN7_-_OBJECTIONEVIDENCE_Case_IPR2019-00741_.pdf	135721 96b18f5f96593c1888639511f5f9df992841ce3f	no	4
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Information:					
5	Non Patent Literature	AXJ-114BUSCN7_-_2020-04-27_ALEXION_504_Surreply_IPR2019-00739.pdf	441878 cfbc2275a79fcda3a982d6c719c8c496be87ef56	no	40
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Information:					
6	Non Patent Literature	AXJ-114BUSCN7_-_2020-04-27_ALEXION_880_Surreply_IPR2019-00740.pdf	442994 0223876b5909c750d06545d5c7eeb8a43e0851e9	no	40
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Information:					

7	Non Patent Literature	AXJ-114BUSCN7_-_SURREPLY_Case_IPR2019-00741_.pdf	440481 d16b414897d63bedd8f84e92561b0a5e80b44a12	no	40
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Information:					
8	Non Patent Literature	AXJ-114BUSCN7_-_EX2096_2096_-_ClinicalTrialsGov_Study_No_NCT03818607.pdf	873380 1942cbb90b8755e363a90e4d0c8bf539b6215fa3	no	10
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9	Non Patent Literature	AXJ-114BUSCN7_-_HOFMAN_DEPO_TRANS.pdf	2294151 7171b60567db39b829de28d22dd43b91109252a7	no	220
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10	Non Patent Literature	AXJ-114BUSCN7_-_Balthasar_Reply_Dep_Tr_Apr_22_2020_EX_2092.pdf	2050333 86add8d37777da09e33c243d4fe2ee4444c7d3dc	no	81
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11	Non Patent Literature	11001632_RESPONSE.pdf	748994 3d377579525889628 5f7276bddba229c7187a75f	no	14
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12	Non Patent Literature	16172335_NOTICE_OF_APPEAL.pdf	113537 0f335c3ad7fd9ce781132d92750c7e083a53473d	no	4
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13	Non Patent Literature	16195355_Notice_of_Appeal.pdf	113482 484f4a3bece8ea8a8a20a4b31f4c99bdf8bafe50	no	4
Warnings:					
Information:					

14	Non Patent Literature	EXH_2095_US_10590189_FH_pp1-594_504.pdf	23057814 4a1dee10947804ffd7844a28e7cfcf92ec6e4cff	no	594
Warnings:					
Information:					
15	Transmittal Letter	IDSTRANS.pdf	26898 5d8980ea1272e0b0414356ff5c0758e450b5e26f	no	2
Warnings:					
Information:					
16	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	1035173 0f2d81f1407f30ca7fdf6a0be6d6ceae3151b782	no	5
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
17	Fee Worksheet (SB06)	fee-info.pdf	30379 ce62038acc28fe7ad8203321f5224650c9bc1c59	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	32275604		

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00741
U.S. Patent No. 9,732,149 B2

AMGEN INC.'S MOTION TO EXCLUDE EVIDENCE UNDER 37 C.F.R. § 42.64(c)

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Alexandria, VA 22313-1450

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Amgen Inc. files this motion pursuant to 37 C.F.R. §§ 42.62 and 42.64(c) and in accordance with Due Date 5 of the Scheduling Order (Paper 16). Amgen requests exclusion of the entirety of Exhibits 2030, 2031, 2033-2040, 2043, 2044, 2047, 2049-2052, 2054, 2055, 2074-2077, 2080-2083, 2086, and 2091; and Amgen requests exclusion of portions of Exhibit 2022. Amgen timely objected to each of these exhibits through written Objections to Evidence, and Alexion has not cured Amgen's objections.

The Federal Rules of Evidence (FRE) govern the admissibility of evidence in *inter partes* review proceedings. 37 C.F.R. § 42.62. As shown herein, the challenged exhibits contain irrelevant prejudicial information under FRE 401, 402, and 403. Accordingly, the Board should exclude the objected-to exhibits.

I. Multiple exhibits were filed in contravention of the Board rule against including new evidence with a surreply

Alexion submitted Exhibits 2094, 2095, and 2096 together with its Patent Owner Surreply, in contravention of the Board's rule not to include new evidence with a surreply. The Trial Practice Guide contains an explicit bar on taking such action, stating that "[t]he ***sur-reply may not be accompanied by new evidence*** other than deposition transcripts of the cross-examination of any reply witness." Patent Trial and Appeal Board Consolidated Trial Practice Guide November 2019, p. 73. None of these three exhibits is a deposition transcript, so the exception allowing expert deposition transcripts to be introduced with a surreply does not

apply to Exhibits 2094, 2095, and 2096. Moreover, none of these exhibits were mentioned or presented during deposition of Amgen's experts Dr. Balthasar (Exhibit 2093) or Mr. Hoffman (Exhibit 2092). Indeed, neither party presented or discussed Exhibits 2094, 2095, and 2096 prior to Alexion's Surreply. Alexion did not seek, much less receive, permission from the Board to submit Exhibits 2094, 2095, and 2096. Therefore, Exhibits 2094, 2095, and 2096 should be excluded from the record.

Exhibits 2094, 2095, and 2096 should also be excluded under FRE 403 because their inclusion in the record would result in significant prejudice to Amgen that outweighs any potential relevance. Inclusion of Exhibits 2094, 2095, and 2096 would be prejudicial to Amgen because Alexion has belatedly used each of these three exhibits to present misleading new arguments as part of its Surreply—and Amgen has had no opportunity to respond to the new evidence and arguments. For example, Alexion cited to Exhibits 2094 and 2095 when noting that the Patent Office allowed claims in a related patent when aware of the Bowdish and Evans references. *See* Surreply, 1. Because Alexion has submitted this evidence at the very end of the proceeding, Amgen will not have an opportunity to brief why the Examiner wrongly allowed those claims based on only a partial record of the IPR

papers and references.[1] Similarly, Alexion presented Exhibit 2096 as part of its new commercial success arguments in its Surreply. *See* Surreply, 26-27. Because Alexion did not use this evidence previously, neither Amgen nor its commercial success expert Mr. Hoffman will be able to discuss Exhibit 2096.

Accordingly, Exhibits 2094, 2095, and 2096 should be excluded as having been submitted in contravention of the rules and as being prejudicial to Amgen.

II. Multiple exhibits are not relevant and/or prejudicial

Alexion submitted many exhibits that it failed to cite in its Response, rendering them irrelevant and/or prejudicial. Exhibits 2030, 2031, 2033-2040, 2043, 2044, 2047, 2049-2052, 2054, 2055, 2074-2077, 2080-2083, and 2091 appear nowhere in Alexion's Response. Amgen timely objected to these Exhibits (Paper 23, 3-4) and Alexion failed to cure these objections.

[1] For example, Amgen will not be able to discuss the significance of the fact that the Examiner was not presented with Amgen's Reply from this or any related proceeding (documents that were in Alexion's possession prior to issuance, but not submitted to the Examiner for consideration), that the Examiner was instead given only Alexion's flawed and misleading patent owner response, or that the Examiner's decision was therefore reached after receiving only Alexion's incomplete and one-sided arguments.

Evidence is relevant if it "has any tendency to make a fact more or less probable than it would be without the evidence" and "the fact is of consequence in determining the action." FRE 401. Alexion's failure to cite Exhibits 2030, 2031, 2033-2040, 2043, 2044, 2047, 2049-2052, 2054, 2055, 2074-2077, 2080-2083, and 2091 demonstrates that these exhibits do not have a tendency to make any fact of consequence more or less probable. If these exhibits related to any fact of consequence in this proceeding, Alexion should have cited them in the Response. The evidence is, therefore, inadmissible as irrelevant. *See* FRE 402 ("Irrelevant evidence is not admissible.").

Exhibits 2030, 2031, 2033-2040, 2043, 2044, 2047, 2049-2052, 2054, 2055, 2074-2077, 2080-2083, and 2091 also should be excluded under FRE 403 as unfairly prejudicial. These exhibits were not cited or discussed in Alexion's Response. If Alexion had appropriately cited and discussed these Exhibits, it would have overshot the word limit of its Response. Because "[a]rguments must not be incorporated by reference from one document into another document," 37 C.F.R. § 42.6(a)(3), any attempt by Alexion to rely upon these exhibits is prejudicial to Amgen. Amgen would be prejudiced if Alexion is allowed to disregard the rules and effectively incorporate this information by reference.

Accordingly, Exhibits 2030, 2031, 2033-2040, 2043, 2044, 2047, 2049-2052, 2054, 2055, 2074-2077, 2080-2083, and 2091 should be excluded as

irrelevant and/or prejudicial.

III. Portions of Exhibit 2022 are irrelevant, prejudicial, and lack probative value

Multiple paragraphs in one of Alexion's supporting expert declarations (Exhibit 2022) were never cited in Alexion's Response. Accordingly, Amgen moves to exclude paragraphs 132, 137, 151-155, 157, 168-170, 182-184, 186, 253-254, 270, 277-278 in Exhibit 2022 as irrelevant, prejudicial, and lacking probative value. Amgen timely objected to these paragraphs of Exhibit 2022 (Paper 23, 1-2) and Alexion failed to cure these objections.

Evidence is relevant if it "has any tendency to make a fact more or less probable than it would be without the evidence" and "the fact is of consequence in determining the action." FRE 401. Alexion's failure to cite these paragraphs demonstrates that they do not have a tendency to make any fact of consequence more or less probable. If these portions of the declaration were related to any fact of consequence in this proceeding, Alexion should have cited them in the Response. These portions of Exhibit 2022 are, therefore, inadmissible as irrelevant. *See* FRE 402 ("Irrelevant evidence is not admissible.").

These uncited paragraphs from Exhibit 2022 should also be excluded under FRE 403 as unfairly prejudicial. These portions were not cited or discussed in Alexion's Response. If Alexion had appropriately cited and discussed the omitted paragraphs, it would have overshot the word limit of its Response. Because

"[a]rguments must not be incorporated by reference from one document into another document," 37 C.F.R. § 42.6(a)(3), any attempt by Alexion to rely upon the uncited paragraphs is prejudicial to Amgen. Amgen would be prejudiced if Alexion is allowed to disregard the rules and effectively incorporate this information by reference.

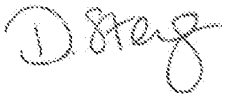
IV. Portions of Exhibit 2022 should be excluded because they rely on inadmissible evidence

Multiple paragraphs in Alexion's supporting expert declaration (Exhibit 2022) relies upon evidence that is inadmissible for the reasons provided in Section II above. Accordingly, Amgen moves to exclude paragraphs 57, 69, 71, 73, 75-79, 82, 83, 86, 91-93, 106, 107, 112, 115-117, 121, 258, 261-263, 265-266, 270 in Exhibit 2022. Allowing those paragraphs to remain in the record would be prejudicial to Amgen under FRE 403 because it would be unfair to allow Alexion's experts to use inadmissible evidence. Accordingly, those paragraphs should be excluded from the record. Amgen timely objected to these paragraphs of Exhibit 2022 (Paper 23, 2-3) and Alexion failed to cure these objections.

V. Conclusion

For the foregoing reasons, the challenged evidence does not meet the threshold for admissibility and should be excluded from the record.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C



Date: May 8, 2020
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Deborah A. Sterling
Registration No. 62,732
Lead Attorney for Petitioner

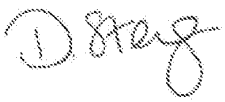
CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **AMGEN INC.'S MOTION TO EXCLUDE EVIDENCE UNDER 37 C.F.R. § 42.64(c)** was served in its entirety on May 8, 2020, upon the following parties via electronic mail:

Gerald J. Flattmann, Jr.
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Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C



Date: May, 8, 2020
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Deborah A. Sterling
Registration No. 62,732
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14992267.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00739
U.S. Patent No. 9,725,504 B2

AMGEN INC.'S
OBJECTIONS TO EVIDENCE

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Petitioner, Amgen Inc. ("Amgen"), objects under the Federal Rules of Evidence (FRE) and 37 C.F.R. § 42.64(b)(1) to the admissibility of Exhibits 2094, 2095, and 2096, filed by Patent Owner Alexion Pharmaceuticals, Inc. ("Alexion") on April 27, 2020, with Alexion's Patent Owner Surreply. Amgen's Objections are timely filed under 37 C.F.R. § 42.64(b)(1), within five business days of the April 27, 2020 Patent Owner Surreply. Amgen files these Objections to provide notice to Alexion that Amgen may move to exclude Exhibits 2094, 2095, and 2096 under 37 C.F.R. § 42.64(c).

I. IDENTIFICATION OF GROUNDS FOR OBJECTIONS

Amgen objects to Alexion's inclusion of Exhibits 2094, 2095, and 2096 with Alexion's Surreply. As noted in the Trial Practice Guide, "[t]he sur-reply may not be accompanied by new evidence other than deposition transcripts of the cross-examination of any reply witness." Patent Trial and Appeal Board Consolidated Trial Practice Guide November 2019, p. 73. Alexion did not introduce any of Exhibits 2094, 2095, and 2096 during the deposition of Dr. Balthasar (Exhibit 2093) or of Mr. Hoffman (Exhibit 2092), and neither party previously referenced Exhibits 2094, 2095, or 2096. Accordingly, Exhibits 2094, 2095, and 2096 are "new" evidence to the Surreply, and introduction of these exhibits at this stage of the proceeding is a clear violation of the PTAB rules of practice.

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Amgen also objects to Exhibit 2096 as lacking authentication under FRE 901. In particular, Amgen objects to Exhibit 2096 because Alexion has failed to provide sufficient evidence that Exhibit 2096 is what Alexion claims it is.

II. CONCLUSION

Should Alexion fail to withdraw or otherwise correct the defects associated with Exhibits 2094, 2095, and 2096 in view of Amgen's objections, Amgen may file a motion to exclude Exhibits 2094, 2095, and 2096 under 37 C.F.R. § 42.64(c).

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that the above-captioned "AMGEN INC.'S OBJECTIONS TO EVIDENCE" was served in its entirety on May 4, 2020, upon the following parties via email:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00740
U.S. Patent No. 9,718,880 B2

AMGEN INC.'S
OBJECTIONS TO EVIDENCE

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2019-00741
U.S. Patent No. 9,732,149 B2

AMGEN INC.'S
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AMGEN INC.
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ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00739
Patent: 9,725,504

PATENT OWNER'S SURREPLY TO PETITIONER'S REPLY

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2068	Alexion Form 10-K for FY 2016 (Excerpts)
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2093	Deposition Transcript of Ivan T. Hofmann, *Amgen, Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, -740, -741 (Mar. 12, 2020)
2094	U.S. Patent No. 10,590,189
2095	File History for U.S. Patent No. 10,590,189
2096	ClinicalTrials.Gov, Study No. NCT03818607, "A Study Evaluating the Efficacy and Safety of ABP 959 Compared with Eculizumab in Adult Participants with PNH (DAHLIA)," *available at* https://clinicaltrials.gov/ct2/show/NCT03818607 (last accessed Apr. 21, 2020)

I. INTRODUCTION

Amgen still fails to prove the unpatentability of claims 1-10 of the '504 patent. On March 17, 2020, the USPTO confirmed that claims covering treatment of PNH with SEQ ID NOs: 2 and 4 were patentable over Bowdish and Evans (and the other art and arguments throughout Amgen's Petitions) when it issued U.S. Patent No. 10,590,189, a continuation of the '504 patent. (ALXN2094; ALXN2095, 552-54, 586.) There is no basis to conclude differently here.

Ground 1, alleging anticipation over Hillmen, fails because Hillmen did not disclose SEQ ID NOs: 2 and 4 or its properties. Amgen cannot fill in those missing claim elements with present-day knowledge not publicly available before March 15, 2007, or with other documents under the guise of "enablement."

Grounds 2-7, alleging obviousness, rely on improper hindsight and disregard the prior art as a whole. Amgen asserts that publications reporting "successful eculizumab PNH clinical trials" would have "motivated a POSA to make and use a pharmaceutical composition comprising eculizumab for the treatment of patients with PNH." (Paper 29 ("Reply"), 7.) But a POSA would not have arrived at ***SEQ ID NOs: 2 and 4***, when those publications consistently taught that "eculizumab" had a different sequence – an ***IgG4*** isotype as described in Thomas. Instead, Amgen uses hindsight to construct the now-known, claimed sequence piecemeal from a combination of sequences in other documents that never mention

"eculizumab," its anti-C5 activity, or its clinical properties. Then, with no basis, Amgen claims that a POSA would have known that its cobbled-together sequence was the "eculizumab" antibody of the clinical literature – despite that literature uniformly identifying "eculizumab" as Thomas's ***IgG4*** antibody.

Amgen's contention that the literature cited Thomas for general "humanization" techniques contradicts the conclusions of the '504 patent Examiner and this Board. And the isolated, ambiguous statement in Tacken (AMG1034) on which Amgen pins its case (despite not having asserted Tacken in any of its Grounds) would not have dissuaded a POSA from the art's overwhelming pronouncement that "eculizumab" was Thomas's IgG4 antibody.

Critically, nothing in the art connected "eculizumab" – the successful, clinically tested antibody – to SEQ ID NOs: 2 and 4. As Alexion's experts explained, a POSA could not have reasonably expected that the untested, uncharacterized antibody sequence Amgen pieces together in hindsight would have bound C5 and prevented its cleavage, treated PNH, or been suitable for any pharmaceutical composition.

Dr. Balthasar's Reply Declaration (AMG1081) lacks credibility, repeatedly contradicting his prior sworn testimony. Notably, Amgen's counsel supplied Dr. Balthasar with all of his new cited references, and only select portions of Dr.

Casadevall's and Dr. Trout's deposition transcripts. (ALXN2092, 12:15-17, 16:13-22, 25:4-8, 25:20-28:7, 29:9-13.)

II. A POSA HAD NO BASIS TO ASSOCIATE "ECULIZUMAB" WITH SEQ ID NOS: 2 AND 4

Amgen's Grounds depend on the mistaken assumption that a POSA would have associated "eculizumab," the clinically successful anti-C5 antibody described in the prior art, with SEQ ID NOs: 2 and 4. But the opposite is true: the literature before March 15, 2007 consistently taught that "***eculizumab is***" the antibody of Thomas – an ***IgG4*** isotype antibody, having a different sequence from SEQ ID NOs: 2 and 4.[1] (Paper 22 ("POR"), 14-19.) Nothing in the art taught that an antibody with SEQ ID NOs: 2 and 4 – then an unknown, uncharacterized sequence – would have met the '504 patent's claimed requirements of binding C5 and use in a pharmaceutical composition to treat PNH. *See, e.g.*, *PersonalWeb Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 989, 993 (Fed. Cir. 2017).

A. The Literature Consistently Taught a POSA that "Eculizumab" Was the *IgG4*-Isotype Antibody of Thomas

Before March 15, 2007, the only plausible conclusion was that "eculizumab" was the IgG4 antibody of Thomas. As Amgen concedes, a POSA would have had

[1] Unless otherwise noted, all emphasis is added, and internal citations and quotation marks are omitted.

the goal of "recreating a[] … method of treating PNH with … eculizumab, which clinical trials had repeatedly demonstrated to be successful." (AMG1081, ¶10; *id.* ¶68; Reply, 7, 14; ALXN2092, 35:9-38:19.) A POSA would have looked to the literature regarding "eculizumab" and its clinical properties, which Amgen relies on for that exact purpose. (*E.g.*, AMG1002, ¶¶12, 36-42.) That literature consistently pointed to Thomas for information on what "eculizumab is"; and Thomas in turn identified a humanized IgG4 antibody with potent anti-C5 and anti-hemolytic activity. (ALXN2022, ¶140.)

The '504 patent Examiner and this Board have agreed that the clinical literature pointed to Thomas for the structure of "eculizumab." (ALXN2092, 78:1-80:7, 81:22-85:17, 87:3-93:19.) The Examiner, in issuing an obviousness rejection, concluded that Hillmen (AMG1004) "refers to reference number 15 (Thomas) as disclosing more information about eculizumab," and "Thomas in turn discloses that eculizumab is the humanized antibody h5G1.1."[2] (POR, 30-31; AMG1014, 557, 559.) And this Board determined that Hillmen and Hill "at least invoked a molecule having the IgG4 isotype taught in Thomas." (Paper 15, 34;

[2] Alexion overcame the rejection after explaining that Hillmen and Thomas guided a POSA to a different sequence than SEQ ID NOs: 2 and 4. (AMG1014, 586-87, 591 ¶¶3-5.)

Paper 15, IPR2019-00740, 37.) This plain reading cannot be "patently false" (Reply, 3) when everyone but Amgen agrees.

Amgen contends Thomas does not say "eculizumab," and dismisses Thomas as "one of the earliest disclosures." (Reply, 8, 10-11.) But the literature consistently cited to Thomas ***for*** "eculizumab," including in March 2007. (*See, e.g.*, POR, 14-19, 27; ALXN2022, ¶¶121-124, 151; AMG1077, 76:10-19, 127:3-18, 136:8-18; ALXN2028, 31 & Ref. 6.) In contrast, Bowdish, Mueller, and Evans (from which Amgen pieces together SEQ ID NOs: 2 and 4) never mention "eculizumab," and were never cited for what "eculizumab is." (Section II.C *infra*.)

The art did not cite Thomas merely for generalized "methods of humanizing antibodies." (*Cf.* Reply, 10-11.) As Dr. Balthasar testified, the prior art cited Thomas for "***what*** eculizumab is." (ALXN2032, 128:20-129:10, 129:13-130:22; ALXN2022, ¶140.) For example, Hillmen 2006 states "***Eculizumab (Soliris, Alexion Pharmaceuticals) is*** a humanized monoclonal antibody directed against the terminal complement protein C5," and cites Thomas. (AMG1012, 1234.) The plain reading of that statement, like those in Hillmen, Hill, and Hill 2007, is that Thomas identifies ***what*** "eculizumab" is. (POR, 15-19.) Amgen concedes as much, admitting that the literature cited Thomas for "information about ***eculizumab's*** ability to bind C5." (AMG1081, ¶29; Reply, 10-11.)

Nor does Bell cite Thomas for "humanization" methods when it states that "[m]ethods for the preparation of h5G1.1-mAb" are described in Thomas. (AMG1081, ¶29; AMG1005, ¶[0052].) As Dr. Balthasar concedes, this sentence "provid[es] 'methods for the preparation of ***h5G1.1-mAb***,' which ***is how Bell referred to eculizumab***," and then cites to Thomas. (AMG1081, ¶92; ALXN2092, 70:4-71:17, 74:5-75:20; ALXN2022, ¶¶195-199).)

B. Tacken Would *Not* Have Changed a POSA's Understanding That "Eculizumab" Was an IgG4 Isotype Antibody

Despite the overwhelming evidence identifying "eculizumab" as an IgG4 antibody, Amgen clings to a ***single*** publication, Tacken (AMG1034), as allegedly teaching that "eculizumab is an IgG2/IgG4 antibody." (Reply, 3.) Amgen uses Tacken to connect (1) publications describing "eculizumab" as a successful PNH treatment (Hillmen, Hill, Bell) – which do not include any sequences, with (2) documents Amgen combines in hindsight to obtain SEQ ID NOs: 2 and 4 (Bowdish, Mueller, Evans) – which do not mention "eculizumab." (*See, e.g.*, AMG1081, ¶¶38, 69, 90-91.) Notably, Tacken does not cite any of the references from Amgen's Grounds.[3]

[3] Because Amgen relies on Tacken to supply missing claim elements, but did not include Tacken in ***any*** of its seven Grounds (POR, 24 n.3), Amgen's Grounds

Tacken does not show that "eculizumab" was known as an IgG2/IgG4 isotype. A POSA would not have considered Tacken at all; and even if they had, the prior art "viewed ***as a whole***" identified "eculizumab" as an IgG4 antibody. *Impax Labs., Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018). Amgen's focus on Tacken, to the exclusion of the art as a whole, reveals improper hindsight. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

A POSA motivated to recreate "eculizumab" for treating PNH would not have disregarded the clinical literature demonstrating its success and focused on one statement buried in Tacken – a publication concerning "anti-DC SIGN" antibodies for vaccination strategies. *See Impax*, 893 F.3d at 1379-80 (discounting reference that, "as a whole," was "not about" and "barely mentioned" the claimed compound). None of the clinical literature cited Tacken for "eculizumab"; and a

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fail for that reason alone. *See PersonalWeb*, 848 F.3d at 989, 993 (vacating Board's obviousness determination where final written decision "did not adequately support its findings that the prior art [combination of the Petition] disclosed all elements of the challenged claims"); *Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1335 (Fed. Cir. 2020) (institution is limited to the Grounds stated in the Petition).

POSA would not have scoured the "materials and methods" sections of "basic research" articles that, like Tacken, do not mention "eculizumab" or C5-binding in their titles or abstracts, and do not discuss PNH at all. (*Cf.* AMG1081, ¶24; *see* ALXN2032, 72:23-73:2, 73:12-74:1, 74:18-21, 92:21-93:1, 108:17-109:10.) Dr. Balthasar only looked at Tacken because Amgen's counsel handed it to him. (ALXN2032, 64:23-65:7, 65:12-14.)

Even if a POSA had considered Tacken, it would not have changed their understanding that "eculizumab" was Thomas's IgG4 antibody. A POSA would not have disregarded the clinical publications about using "eculizumab" for treating PNH, and instead credited an isolated sentence buried in Tacken that mentioned "eculizamab [*sic*]" just once. Nor could a POSA have seen Tacken as the "culminat[ion]" of an "iterative development process" leading to "eculizumab" (*cf.* AMG1081, ¶19), when the literature ***after*** Tacken identified "eculizumab" as Thomas's IgG4 antibody. (POR, 26-27.)

Because Tacken cites to Thomas, the most reasonable reading would have been that (1) "eculizumab" was an ***IgG4*** antibody, as the literature consistently cited Thomas for "eculizumab"; (2) Tacken's IgG2/IgG4 "isotype control" was a ***different*** "h5G1.1" antibody; and (3) Tacken conflated the broad terminology "5G1.1"/"h5G1.1" – which a POSA would have understood to typically refer to broad classes of antibodies, sometimes to "eculizumab," and sometimes to a

specific mouse antibody (ALXN2032, 98:2-99:8, 159:1-10, 169:6-18, 202:24-203:14) – with the specific term "eculizumab."[4] (ALXN2022, ¶¶141-147; POR, 25-27.) The one unreasonable conclusion is that an isolated, ambiguous sentence in Tacken would have upended a POSA's understanding of "eculizumab" from the consistent teachings of the art.

Amgen's reading of Tacken is also not supported by non-prior art statements in the unrelated "'438 application" prosecution history.[5] These statements, which refer to ***2002*** (Reply, 9), could not have been based on Tacken, published in ***2005***. These statements cited only Mueller II (AMG1049, 838-39), which did not

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[4] A POSA would have also been confused by the "-a-" sub-stem in "eculizamab [*sic*]," suggesting a rat antibody. (ALXN2046, 27.)

[5] *Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286 (Fed. Cir. 2014) does not control. *Apple* found that claim scope may be disavowed by narrowing arguments made during prosecution of a ***related*** ex-U.S. application with the ***same specification*** and ***same claim language*** as a U.S. patent. *Id.* at 1311-1313. Here, claim construction is not in issue, the '438 application is unrelated to the '504 patent, and "mutated Fc receptor" (AMG1049, 838-39) appears nowhere in the '504 patent claims.

mention "eculizumab," and did not specifically identify any anti-C5 antibody. (ALXN2032, 98:15-99:8, 159:1-10, 241:23-242:12.)

Significantly, the "CAS Registry" noted by Dr. Balthasar (AMG1081, ¶¶9, 17, 20) would have only increased the confusion. The Registry disclosed an ***incorrect*** sequence for "eculizumab," and was not corrected until 2009. (Paper 2, 9-10, n.6; AMG1054, 237, 247-254, 292-293; ALXN2092, 93:20-95:4, 96:12-100:6.) Amgen fails to explain why a POSA looking to make "eculizumab" would have focused on Tacken (or Bowdish, Mueller, or Evans), rather than all of the "eculizumab" art, including the CAS Registry.

C. Nothing in the Prior Art Linked SEQ ID NOs: 2 and 4 to "Eculizumab"

Amgen's Grounds also fail because nothing in the prior art connected "eculizumab" (including its clinical properties) with SEQ ID NOs: 2 and 4. *See PersonalWeb*, 848 F.3d at 991 ("[A] finding of obviousness cannot be predicated on the mere identification in the prior art of individual components of claimed limitations."). A POSA would not have known of, and would not have been motivated to make, SEQ ID NOs: 2 and 4. (POR, 21-22, 44-56, 59-62; Section IV.A *infra*.) And nothing in the art taught that SEQ ID NOs: 2 and 4 was "***eculizumab***" – the clinically successful antibody that blocks C5 cleavage and treats PNH. SEQ ID NOs: 2 and 4 would have been an unknown, uncharacterized

antibody, with biological, clinical and physicochemical properties that could not be reasonably predicted. (POR, 21-22, 43-44, 56-58, 62-64; Section IV.B *infra*.)

Nothing in Bowdish, Mueller, or Evans guided a POSA to connect "eculizumab" with SEQ ID NOs: 2 and 4. Bowdish, Mueller and Evans never mention "eculizumab." (ALXN2032, 102:10-16, 199:9-17; POR, 49, 61.) Evans does not disclose ***any*** full-length humanized antibodies – only structurally-distinct fragments that never belonged to a full-length antibody. (ALXN2032, 163:5-15; POR, 50.) Neither Bowdish nor Mueller were cited by the literature on "eculizumab" and its clinical properties. (ALXN2032, 139:8-140:5, 140:13-141:2, 141:11-19, 170:5-171:1, 195:22-196:4.) And, as Dr. Balthasar testified, the terminology "5G1.1" (used in Bowdish) and "h5G1.1" (used in Mueller) was ***not*** specific to "eculizumab" – it could refer to multiple antibodies with different sequences. (ALXN2032, 202:24-203:14.) For example, Dr. Balthasar admitted that the "h5G1.1"/isotype terminology used in Mueller could ***not*** have been used to determine a specific sequence. (ALXN2032, 241:23-242:12.)

Amgen uses improper hindsight when it disregards the literature ***actually*** concerning "eculizumab" and its clinical properties and relies on documents saying nothing about "eculizumab." A POSA seeking to recreate "eculizumab" would not have discarded the literature's consistent teaching regarding what "eculizumab is," and turned to an isolated statement regarding "[c]onstruction of 5G1.1" in Bowdish

– a patent application regarding peptide mimetics; or an isolated statement regarding an "h5G1.1" control antibody in Mueller – a patent application regarding anti-VCAM antibodies.

Tacken likewise did not connect "eculizumab" to SEQ ID NOs: 2 and 4. Tacken did not identify its IgG2/IgG4 "control" antibody as "eculizumab" (Section II.B *supra*), and nothing in Tacken provided the sequence of that antibody. Tacken does not cite Bowdish, Mueller or Evans. And if a POSA had looked at Thomas (cited for Tacken's control antibody) and Mueller II (cited for "a hybrid IgG2/IgG4 constant domain"), it would not have led them to SEQ ID NOs: 2 and 4, because (1) Thomas describes an IgG4 antibody with a different sequence from SEQ ID NOs: 2 and 4; (2) Thomas's variable region differs from SEQ ID NO: 4 at variable light chain amino acid 38; and (3) Mueller II's constant region is missing an amino acid present in SEQ ID NO: 2. (Section II.A *supra*; ALXN2022, ¶¶251, 253.) Amgen does not explain how a POSA would overlook these deficiencies to arrive at the claimed sequence.

III. AMGEN'S ANTICIPATION AND OBVIOUSNESS ARGUMENTS REGARDING HILLMEN ARE MISTAKEN ON THE FACTS AND LAW

On Ground 1, alleged anticipation of claims 1-3 and 7-10 over Hillmen, Amgen's Reply repeats the same arguments already rejected by the Board and introduces new legal theories with no basis. Nothing in Hillmen expressly or

inherently disclosed SEQ ID NOs: 2 and 4 or its properties. (POR, 32-34; Paper 15, 33-35.) Amgen's Grounds 2-3 fail at least because no combination of Hillmen, Bell or Wang disclosed "SEQ ID NOs: 2 and 4" or its use in the claimed compositions to treat PNH. (POR, 35-36; Paper 15, 35-36.)

The undisputed facts are fatal to Amgen's theory: (1) the name "eculizumab" alone would not have told a POSA the sequence of "eculizumab"; and (2) nothing within Hillmen disclosed or would have guided a POSA to SEQ ID NOs: 2 and 4. (POR, 32-34; ALXN2032, 139:8-140:5, 140:13-141:19; ALXN2092, 43:11-44:24, 45:19-25.) Rather, Hillmen's citation to Thomas for what "eculizumab is" would have directed a POSA to an ***IgG4*** antibody with a different sequence. (Section II.A *supra*.)

Ground 1 is also wrong on the law. Amgen conflates Hillmen – a publication reporting clinical trial results – with the underlying clinical trial. (Reply, 1, 4-5.) But only the ***publication*** is available as prior art.[6] 35 U.S.C. § 311(b). While we know today that the clinically-tested antibody actually had the claimed sequence, nothing within the "four corners" of ***Hillmen*** disclosed that to a POSA. *See, e.g.*, *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed.

[6] Amgen does not contend that clinical supplies of eculizumab were publicly available. (ALXN2092, 149:4-150:5, 152:4-17.)

Cir. 2008). As in *Endo* and *Bayer*, Hillmen's mere use of the name "eculizumab" was not a disclosure of its chemical composition, *i.e.*, sequence. *See Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-79, 1381-83 (Fed. Cir. 2018) (publication of clinical study using a "castor oil" vehicle did not inherently disclose the vehicle's chemical composition); *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018) (publications disclosing compound name "KIH-485" did not inherently disclose the compound's chemical composition).[7]

Amgen's own case law confirms that an inherently disclosed element must ***necessarily*** flow from the ***disclosure*** within "the single anticipating reference." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1375-78 (Fed. Cir. 2003) (disclosed administration of loratadine necessarily produced the claimed metabolite); *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1372-73 (Fed. Cir.

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[7] *In re Crish,* 393 F.3d 1253 (Fed. Cir. 2004) remains distinguishable. (Paper 15, 33.) As the Board found, the anticipatory publication in *Crish* provided sufficient information (size and location of a claimed promoter region) for a POSA to obtain the claimed sequence using conventional techniques. (*Id.* (quoting *Crish*, 393 F.3d at 1257-59.) Hillmen, in contrast, did not "'specifically identify' … eculizumab" as having SEQ ID NOs: 2 and 4. (Paper 15, 33.)

2007) (disclosed manufacturing process necessarily produced the claimed "separating layer"); *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1348 (Fed. Cir. 1999) (disclosed compositions necessarily produced the claimed "sufficient aeration"). Hillmen, in contrast, did not disclose any process that would have necessarily produced SEQ ID NOs: 2 and 4. *See Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348-49 (Fed. Cir. 2004).

Amgen erroneously uses documents ***outside*** Hillmen (Bowdish, Mueller, Evans, and Tacken) to supply SEQ ID NOs: 2 and 4. (Reply, 6; AMG1081, ¶38; ALXN2092, 57:25-58:6, 60:21-61:12, 64:8-12, 67:21-69:7.) In doing so, Amgen "conflates the principles of enablement and anticipation," and "makes the impermissible leap from enablement to disclosure." *See Galderma Labs., L.P. v. Teva Pharms. USA, Inc.*, No. 2019-2396, 2020 WL 467933, at *5-6 (Fed. Cir. Jan. 29, 2020). The claimed sequence does not "necessarily result" from practicing Hillmen (*id.* at *6-7), because the name "eculizumab" does not disclose a sequence, and Hillmen pointed to Thomas's IgG4 antibody as "eculizumab."

IV. AMGEN FAILS TO SHOW HOW CLAIMS 1-10 WOULD HAVE BEEN OBVIOUS TO A POSA

A. The Claimed Sequence Would *Not* Have Been Obvious in View of Bell, Bowdish and Evans, or Bell, Evans and Mueller

A POSA motivated by Bell (AMG1005) to recreate "eculizumab" would not have turned to Bowdish (Grounds 4-5) or Mueller (Grounds 6-7) – documents with

no mention of Bell, "eculizumab," or PNH. Nor would a POSA have combined sequences from Evans and Bowdish or Mueller in the selective way that Amgen does to arrive at SEQ ID NOs: 2 and 4.

Bowdish: Without hindsight, a POSA seeking to recreate "eculizumab" would not have leapt from Bell to Bowdish. (Reply, 14-15; AMG1081, ¶¶68-72.) Bell and Bowdish do not cite one another. (ALXN2032, 170:5-10, 195:22-196:4.) Dr. Balthasar concedes that Bell and other clinical literature gave a POSA a "strong motivation to make and use eculizumab to treat PNH" (AMG1081, ¶68) – but that literature uniformly pointed to ***Thomas*** for "eculizumab." (*See* Section II.A *supra*.) Bell in particular cited Thomas for "[m]ethods for the preparation of [eculizumab]." (AMG1005, ¶[0052]; AMG1081, ¶92; ALXN2092, 70:4-71:17, 74:5-75:20.) A POSA would not have disregarded Bell's citation to Thomas's IgG4 antibody for "eculizumab," and instead turned to Bowdish – a document regarding "peptide mimetic" compounds having nothing to do with anti-C5 activity or treating PNH. (POR, 47-49.)

Nor would a POSA have connected Bell and Bowdish in view of their incorporations by reference of Evans or the '283 application, respectively. (*Cf.* Reply, 15; AMG1081, ¶¶69, 76.) Bell incorporates both Evans and Thomas when it discusses "***eculizumab***." (AMG1005, ¶[0052]; POR, 46-47.) Bowdish, in contrast, refers to the '283 application for "[c]onstruction of ***5G1.1***" (AMG1006,

¶[0191]) – a term that Dr. Balthasar admitted can refer to many different antibodies, and in the context of Evans, refers to a mouse antibody. (ALXN2032, 98:2-99:8, 169:6-18, 202:24-203:14; AMG1077, 103:16-105:16; POR, 13-14, 19-21, 50.)

The term "5G1.1" in one example of Bowdish would not have connected Bowdish to Bell. (*Cf.* Reply, 14-15; AMG1081, ¶¶71-72.) As Dr. Balthasar testified, "5G1.1" does ***not*** refer specifically to "eculizumab" unless a reference expressly says so (ALXN2032, 98:2-99:8, 199:9-12, 202:24-203:14) – and Bowdish does not. A POSA seeking to recreate "eculizumab" for treating PNH would not have searched all documents with "5G1.1" buried in the text, and disregarded the clinical literature identifying "eculizumab" as Thomas's IgG4 antibody. (Section II.A *supra*.)

A POSA would not have connected Bell and Bowdish based on "knowledge of eculizumab's structure." (AMG1081, ¶¶69, 73-75.) A POSA understood "eculizumab" to be ***IgG4***, not IgG2/IgG4. (*See* Sections II.A-B *supra*.) And even if, hypothetically, "eculizumab" were thought to be IgG2/IgG4, a POSA would not have turned to Bowdish. Bowdish is silent on isotype (ALXN2032, 212:22-213:2, 214:2-7); and a POSA seeking to make "eculizumab" would have had no reason to pick up Bowdish and undertake the sequence analyses that Dr. Balthasar proposes to determine the isotype of its "5G1.1-TPO" compound. (POR, 52; *cf.* AMG1081,

¶¶73-74.) A POSA would not have gone through such a complicated ordeal rather than follow the clear teaching of the clinical literature.[8]

Bowdish did not teach SEQ ID NOs: 2 and 4. Amgen recreates that sequence in hindsight by combining Bowdish with humanized "fragment" sequences from Evans. (Reply, 15; AMG1081, ¶76.) But a POSA would have understood Bowdish's reference to "[c]onstruction of 5G1.1" to refer to Evans's ***mouse*** "5G1.1" antibody, not humanized fragments. (POR, 19-21, 50; ALXN2022, ¶¶ 127-128, 164-165, 213-214.) In Bowdish, "5G1.1" refers to a "whole," "full" antibody; and Evans's only full-length antibody is the ***mouse*** antibody "5G1.1." (AMG1006, ¶¶[0191]-[0193]; ALXN2032, 169:13-18.) Bowdish could not have referred to humanized "fragments," which a POSA understood to be structurally distinct from, and never part of, a full-length humanized antibody. (ALXN2032, 163:5-15, 228:2-16; ALXN2022, ¶127.) Nor could "[c]onstruction of 5G1.1" refer to a full-length humanized antibody, because,

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[8] Nor may Amgen attempt to fill gaps by combining Bowdish with Mueller (AMG1008) and Rother (AMG1032) – documents that are outside Grounds 4-5 and have no connection to Bowdish or "eculizumab." (AMG1081, ¶¶73-74; ALXN2092, 100:14-101:19, 106:14-107:2, 107:23-108:17, 111:7-112:24, 113:20-114:20, 114:25-115:22, 116:18-118:18; Section II.B *supra*.)

as Dr. Balthasar admits, nothing in Evans disclosed ***any*** full-length humanized antibody. (*Id.*)

Seeing the non-overlap between Bowdish's sequences and Evans's "5G1.1" mouse antibody (ALXN2092, 137:25-141:23), a POSA would have stopped there. Amgen's new argument that a POSA would have combined Bowdish with Evans's ***mouse*** antibody defies common sense. (*Cf.* AMG1081, ¶77.) A POSA would not have put on blinders and selectively combined Bowdish with Evans's mouse antibody, while ignoring the extensive sequence mismatch. (ALXN2022, ¶¶214-216, POR, 53-54.) Evans also provided multiple CDR definitions – and a POSA could not have determined the specific sequence Bowdish replaced with its TPO-mimetic peptide. (ALXN2022, ¶220; AMG1077, 242:17-243:19, 244:18-22, 249:13-17, 250:18-23.)

Mueller: Amgen's leap from Bell to Mueller is pure hindsight. Neither Bell nor Evans cite Mueller, or vice versa. (ALXN2032, 170:11-171:20, 243:16-20.) Bell cites ***Thomas***, not Mueller, for "the preparation of [eculizumab]." (AMG1081, ¶92; POR, 46-47, 59.)

A POSA motivated to make "eculizumab" to treat PNH would not have turned to Mueller, concerning anti-VCAM antibodies for blocking transplant rejection. (ALXN2032, 232:6-16; POR, 60-61.) Mueller never mentions "eculizumab," and referred to "h5G1.1" only in describing "control" antibodies for

experiments unrelated to anti-C5 activity or PNH. (ALXN2032, 102:10-16, 235:11-19; POR, 61.) As Dr. Balthasar testified, nothing in Mueller allowed a POSA to identify either of the two "h5G1.1" control antibodies as "eculizumab"; Mueller's "h5G1.1"/isotype terminology would not have indicated any ***specific*** sequence; and Mueller identified only its ***IgG4*** "h5G1.1" control antibody as "anti-C5." (ALXN2032, 102:10-16, 234:9-21, 235:6-19, 237:25-238:5, 238:13-19, 241:23-243:14; AMG1077, 114:10-115:11.)

Amgen now also attempts to supplant Mueller (AMG1008) with Tacken and Mueller II (AMG1031) – documents that should be disregarded as outside the asserted combinations of Amgen's Grounds. (Section II.B *supra*; *cf.* AMG1081, ¶91.) Tacken would not have changed a POSA's understanding that the clinical literature consistently identified "eculizumab" as Thomas's ***IgG4*** antibody. (*See* Section II.B *supra*.) And even if, hypothetically, a POSA had combined sequences from Thomas and Mueller II, it could not have led to SEQ ID NOs: 2 and 4. (*See* Section II.C *supra*.)

Amgen fails to explain why a POSA would have combined sequences from Mueller and Evans in exactly the way Amgen does in hindsight to obtain SEQ ID NOs: 2 and 4. Mueller provides ***no*** anti-C5 antibody sequences (ALXN2032, 232:17-21); and as the Board correctly found, Mueller and Evans provide no guidance on whether, or how, sequences from one document should be combined

with the other.[9] (Paper 15, 52-54; POR, 61-62.) Mueller's use of "CO12" in naming full-length humanized antibodies also would not have connected it to Evans – which Dr Balthasar admits did not disclose ***any*** full-length humanized antibodies, and only provided humanized recombinant fragments. (ALXN2032, 163:5-15; ALXN2022, ¶246.)

B. A POSA Would Not Have Had Any Motivation to Make, or Reasonable Expectation of Success With, SEQ ID NOs: 2 and 4

Even if SEQ ID NOs: 2 and 4 were known to a POSA – which they were not – nothing would have told a POSA that they comprised "***eculizumab***," and thus had the biological, clinical and physicochemical properties attributed to "eculizumab." (Section II.C *supra*.) A POSA would not have reasonably expected success with SEQ ID NOs: 2 and 4 – which to them was an unknown, uncharacterized antibody that had never been tested for anti-C5 activity, pharmaceutical formulation, or safety and efficacy. A POSA also would not have

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[9] In *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804 (Fed. Cir. 1989), a combination "***specifically named*** in the prior art" was found obvious-to-try. *See Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA*, 748 F.3d 1354, 1360-61 (Fed. Cir. 2014) (citing *Merck*, 874 F.2d at 808-09). Nothing in Mueller or Evans specifically named SEQ ID NOs: 2 and 4.

been motivated to make and study a "new, untested antibody" with a different sequence and structure from the "eculizumab" proven to treat PNH. (Reply, 14.)

OSI Pharms., LLC v. Apotex Inc., 939 F.3d 1375 (Fed. Cir. 2019) controls, because Amgen's "asserted references contained no data at all – no 'clinical (human) data or preclinical (animal) data,' nor any 'in vitro (test tube) data'" regarding the anti-C5 activity, safety or efficacy of SEQ ID NOs: 2 and 4. (Reply, 15-16 (quoting *OSI*, 939 F.3d at 1383).) Bowdish and Mueller provided no such data. (ALXN2032, 175:19-176:6, 188:18-23, 235:11-19, 247:13-248:6; POR, 49, 56-57, 62-63.) Neither did Bell (Reply, 16) – which does not disclose SEQ ID NOs: 2 and 4 or IgG2/IgG4 constant regions (ALXN2032, 146:17-25, 151:3-12, 160:7-9, 194:11-24; POR, 45), and cited Thomas for "[m]ethods for preparing [eculizumab]" (*see* Section II.A *supra*). Neither did Evans (Reply, 16), which did not disclose ***any*** full-length humanized antibodies or IgG2/IgG4 constant regions, let alone SEQ ID NOs: 2 and 4. (ALXN2032, 163:5-15, 163:25-164:8; POR, 63.)

Without data for SEQ ID NOs: 2 and 4, a POSA would not have reasonably expected it to "bind[] C5" or "treat a patient suffering from [PNH]" as claimed. (POR, 36-38, 43, 56-58, 62-63; ALXN2022, ¶¶136, 173, 225-234, 255-262.) Even small sequence changes could impact critical antibody characteristics including binding affinity, specificity, and immunogenicity. (ALXN2022, ¶¶105-118; POR, 10-11.) "Fine specificity" (binding to a certain location) was especially critical,

because an effective anti-C5 antibody would need to block cleavage into components C5a and C5b. (ALXN2022, ¶¶229-231; AMG1039, 840; AMG1023, 1398-99; ALXN2092, 169:3-170:7.) Amgen provides no data showing that a POSA could have reasonably expected SEQ ID NOs: 2 and 4 to have the same anti-C5 properties as "eculizumab."

Amgen also provides no data that would have given a POSA a reasonable expectation that SEQ ID NOs: 2 and 4, or any IgG2/IgG4 antibody, would be safe. (ALXN2022, ¶¶78, 87, 135-136, 160, 172-173, 207.) Dr. Balthasar contends there were "extensive disclosures in the prior art … regarding antibodies with hybrid IgG2/IgG4 constant regions" (AMG1081, ¶94 (citing Mueller, Mueller II, and Tacken)) – but ***none*** of those documents clinically tested safety and immunogenicity of any IgG2/IgG4 antibodies. Any purported "advantages" of IgG2/IgG4 constant regions (Reply, 12) were speculative. (ALXN2022, ¶136; POR, 57.)

Amgen's rebuttal on "reasonable expectation of success" is meritless. (Reply, 13; AMG1081, ¶¶80-84.) A POSA understood that constant region changes could critically (and unpredictably) impact binding, specificity, and immunogenicity – and this overarching principle would apply equally to IgG2/IgG4 antibodies. (ALXN2022, ¶¶105-118; AMG1077, 200:13-202:11, 203:20-205:7, 208:10-209:5.) That few prior art references reported on switching

to "IgG2/IgG4" isotypes highlights a POSA's uncertainty in treating humans with a little-studied, clinically untested, non-natural isotype. (ALXN2022, ¶¶82-83, 87; ALXN2092, 172:6-173:2.)

Dr. Balthasar points to Tacken and Mueller II as evidence that "switching to an IgG2/IgG4 isotype" caused "no significant alteration" in antibody function. (AMG1081, ¶82.) But Tacken and Mueller II did not study the impact of isotype switching on anti-C5 activity, "fine specificity" or blocking cleavage – critical factors for an anti-C5 antibody treating PNH. (ALXN2032, 92:21-93:1; ALXN2092, 156:17-164:7, 165:10-166:21; ALXN2022, ¶¶229-231.) Dr. Balthasar also cites Bell, Evans and Thomas to assert that 5G1.1 antibodies retain their function when changing isotype. (AMG1081, ¶¶ 80, 83.) But neither Evans nor Thomas studied IgG2/IgG4 antibodies (ALXN2032, 90:8-22, 97:7-21, 163:25-164:8; ALXN2092, 166:22-170:25); and Bell reported clinical data only for "eculizumab," identified as Thomas's IgG4 antibody (ALXN2092, 152:22-154:16; Section II.A *supra*).

A POSA also would not have reasonably expected success in formulating SEQ ID NOs: 2 and 4 – an unstudied antibody that might not be stable in ***any*** pharmaceutical composition. (ALXN2024, ¶¶64-75; ALXN2092, 119:14-121:24; Section II.C *supra*.) And if, hypothetically, SEQ ID NOs: 2 and 4 were equated with "eculizumab," Amgen fails to show how a "300 mg single-use formulation of

30 ml of a 10 mg/ml sterile, preservative free solution" (claim 6) would have been obvious in view of Bell and Wang (AMG1028). (ALXN2024, ¶¶76-91.) Wang did not "teach[] that eculizumab can be stably formulated for nebulization at a concentration of 1-30 mg/ml" (Reply, 22), because Wang's "1-30 mg/ml" range was generic, not specific to "eculizumab," and nothing in Wang tested the ***stability*** of any "eculizumab" pharmaceutical composition, let alone a 10 mg/ml "eculizumab" solution. (ALXN2024, ¶¶80-89, ALXN2092, 123:6-124:1.) It is undisputed that a POSA considered stability over time to be a key factor in the success of a pharmaceutical composition. (AMG1002, ¶113; AMG1081, ¶46; ALXN2024, ¶70; ALXN2092, 122:4-12, 127:1-20, 129:2-137:24.) Amgen still provides no such prior-art stability data for a 10 mg/ml solution of "eculizumab" in a 300 mg single-use formulation. (ALXN2024, ¶¶47-48, 77-90; AMG1078, 184:25-185:10; AMG1085, 16; ALXN2092, 123:6-124:1, 125:17-126:1, 130:8-131:18, 135:8-24.)

C. Amgen Fails to Rebut the Strong Evidence of Objective Indicia of Non-Obviousness

Amgen cannot dispute the objective indicia of nonobviousness. On commercial success, nexus is presumed because the claims cover SOLIRIS®, and SOLIRIS® has significant sales in the relevant market. (ALXN2093, 69:4-72:4; ALXN2056, ¶¶1-9, App'x A; POR, 64-65.) SOLIRIS® sales cannot be due to

elements in the prior art (AMG1088, ¶¶15, 24-27) because a POSA did ***not*** know of an antibody having SEQ ID NOs: 2 and 4 and its utility in treating PNH. (Section II.C *supra*.) Nor can SOLIRIS® sales be attributed to an "Orphan Drug Exclusivity" period that expired in 2014 (AMG1088, ¶¶38-42), rather than the remarkable clinical properties of the claimed antibody. (ALXN2022, ¶¶265-268.) SOLIRIS® had substantial sales, despite its very small patient population, because of the ***value*** it brought in successfully treating a rare condition that lacked adequate treatment. (ALXN2093, 131:25-133:24, 134:12-135:1, 135:11-136:24, 144:22-146:17, 147:16-148:18, 149:4-21, 151:21-153:5; AMG1092, 2-3, 5; AMG1095, 1; AMG1096, 1.)

Amgen's "blocking patent" theory is wrong on the facts and the law. As Mr. Hofmann conceded, the existence of an earlier patent is not *per se* evidence against commercial success. (ALXN2093, 49:21-50:11, 50:25-51:5.) Mr. Hofmann failed to consider whether another company might have been motivated to, *e.g.*, develop the claimed invention before March 12, 2002 (the start of the alleged "disincentive"); engage in research and development under the § 271(e)(1) safe harbor; or license innovations beyond Evans to Alexion. (ALXN2093, 51:23-52:5, 56:4-57:18, 117:10-12.) Amgen is presently developing its eculizumab product in the U.S. within the term of both Evans and the '504 patent. (ALXN2093, 11:25-13:1, 63:24-64:3, 64:19-65:16, 67:18-68:9; ALXN2096.) Amgen's theory that

companies would have avoided developing products covered by Alexion's patents is belied by Amgen and others attempting exactly that.

Amgen also fails to rebut the evidence that the claimed invention fulfilled a long-felt but unmet need and received significant industry praise. (ALXN2092, 144:8-145:18, 147:13-148:5.) Amgen's position that PNH was suitably treated by frequent "blood transfusions" is not credible. (*Cf.* Reply, 24.) SOLIRIS® was a groundbreaking, life-saving therapy that substantially improved quality of life for PNH patients – including reducing frequent blood transfusions that were previously a necessary measure. (ALXN2022, ¶¶270-279.)

Amgen also cannot dispute that it, and others, are currently developing purported "biosimilar" products that ***exactly*** copy SEQ ID NOs: 2 and 4. (ALXN2092, 143:4-144:6.) They are doing so, rather than designing their own antibodies, because SEQ ID NOs: 2 and 4 is the antibody that safely and effectively treats PNH. (POR, 66.)

V. CONCLUSION

Alexion respectfully submits that the Board should confirm the patentability of claims 1-10.

Respectfully submitted,

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PATENT OWNER'S SURREPLY TO PETITIONER'S REPLY and EXHIBITS 2092-2096** were served via electronic mail April 27, 2020, in their entirety on the following:

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CERTIFICATION OF WORD COUNT

The undersigned hereby certifies that the portions of the above-captioned **PATENT OWNER'S SURREPLY TO PETITIONER'S REPLY** specified in 37 C.F.R. § 42.24 has 5,576 words, in compliance with the 5,600 word limit set forth in 37 C.F.R. § 42.24. This word count was prepared using Microsoft Word.

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

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

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2079	Chang & Hershenson, "Practical Approaches to Protein Formulation Development," Ch. 1, 1-25, PHARMACEUTICAL BIOTECHNOLOGY VOL. 13: RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS, THEORY AND PRACTICE (Carpenter & Manning, eds., 2002)
2080	Wang, Instability, stabilization, and formulation of liquid protein pharmaceuticals, INTERNATIONAL JOURNAL OF PHARMACEUTICS, 185(2):129-188 (1999)
2081	Hermeling, et al., Structure-Immunogenicity Relationships of Therapeutic Proteins, PHARMACEUTICAL RESEARCH, 21(6):897-903 (2004)
2082	Frokjaer & Otzen, Protein Drug Stability: A Formulation Challenge, NATURE REVIEWS DRUG DISCOVERY, 4(4):298-306 (2005)
2083	Rosenberg, Effects of Protein Aggregates: An Immunologic Perspective, THE AAPS JOURNAL, 8(3):E501-E507 (2006)
2084	European Medicines Agency, ICH Topic Q5C, "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products" (July 1996)
2085	U.S. Depart of Health and Human Services, FDA, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products," ICH Rev. 2 (Nov. 2003)
2086	Stebbings, et al., After TGN1412: Recent developments in cytokine release assays, J. IMMUNOTOXICOLOGY, 10(1):75-82 (2013)
2087	GenScript, "Project Proposal for Monoclonal Antibody Sequencing Service," (Nov. 5, 2019)
2088	Amgen, "Amgen Biosimilars: Our Pipeline," https://www.amgenbiosimilars.com/products/our-pipeline/
2089	Generium Pharmaceutical, "Our Products: Elizaria®," http://www.generium.ru/en/products/elizaria/

Exh. No.	Description
2090	Samsung Bioepis, "Our Pipeline," https://www.samsungbioepis.com/en/product/product02.do
2091	"Antibody Molecules," Ch. 15, 622-625, ANTIBODIES, A LABORATORY MANUAL (Harlow & Lane, eds., 1988)
2092	Deposition Transcript of Joseph P. Balthasar, Ph.D., *Amgen, Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, -740, -741 (Apr. 22, 2020)
2093	Deposition Transcript of Ivan T. Hofmann, *Amgen, Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, -740, -741 (Mar. 12, 2020)
2094	U.S. Patent No. 10,590,189
2095	File History for U.S. Patent No. 10,590,189
2096	ClinicalTrials.Gov, Study No. NCT03818607, "A Study Evaluating the Efficacy and Safety of ABP 959 Compared with Eculizumab in Adult Participants with PNH (DAHLIA)," *available at* https://clinicaltrials.gov/ct2/show/NCT03818607 (last accessed Apr. 21, 2020)

I. INTRODUCTION

Amgen still fails to prove the unpatentability of claims 1-3 of the '880 patent. On March 17, 2020, the USPTO confirmed that claims covering treatment of PNH with SEQ ID NOs: 2 and 4 were patentable over Bowdish and Evans (and the other art and arguments throughout Amgen's Petitions) when it issued U.S. Patent No. 10,590,189, a continuation of the '880 patent. (ALXN2094; ALXN2095, 552-54, 586.) There is no basis to conclude differently here.

Grounds 1-2, alleging anticipation over Hillmen or Hill, fail because Hillmen and Hill did not disclose SEQ ID NOs: 2 and 4 or its properties. Amgen cannot fill in those missing claim elements with present-day knowledge not publicly available before March 15, 2007, or with other documents under the guise of "enablement."

Grounds 3-6, alleging obviousness, rely on improper hindsight and disregard the prior art as a whole. Amgen asserts that publications reporting "successful eculizumab PNH clinical trials" would have "motivated a POSA to make … pharmaceutical compositions comprising eculizumab…." (Paper 29 ("Reply"), 7.) But a POSA would not have arrived at ***SEQ ID NOs: 2 and 4***, when those publications consistently taught that "eculizumab" had a different sequence – an ***IgG4*** isotype as described in Thomas. Instead, Amgen uses hindsight to construct the now-known, claimed sequence piecemeal from a combination of sequences in

other documents that never mention "eculizumab," its anti-C5 activity, or its clinical properties. Then, with no basis, Amgen claims that a POSA would have known that its cobbled-together sequence was the "eculizumab" antibody of the clinical literature – despite that literature uniformly identifying "eculizumab" as Thomas's ***IgG4*** antibody.

Amgen's contention that the literature cited Thomas for general "humanization" techniques contradicts the conclusions of the '880 patent Examiner and this Board. And the isolated, ambiguous statement in Tacken (AMG1034) on which Amgen pins its case (despite not having asserted Tacken in any of its Grounds) would not have dissuaded a POSA from the art's overwhelming pronouncement that "eculizumab" was Thomas's IgG4 antibody.

Critically, nothing in the art connected "eculizumab" – the successful, clinically tested antibody – to SEQ ID NOs: 2 and 4. As Alexion's experts explained, a POSA could not have reasonably expected that the untested, uncharacterized antibody sequence Amgen pieces together in hindsight would have bound C5 and prevented its cleavage, treated PNH, or been suitable for any pharmaceutical composition.

Dr. Balthasar's Reply Declaration (AMG1081) lacks credibility, repeatedly contradicting his prior sworn testimony. Notably, Amgen's counsel supplied Dr. Balthasar with all of his new cited references, and only select portions of Dr.

Casadevall's and Dr. Trout's deposition transcripts. (ALXN2092, 12:15-17, 16:13-22, 25:4-8, 25:20-28:7, 29:9-13.)

II. A POSA HAD NO BASIS TO ASSOCIATE "ECULIZUMAB" WITH SEQ ID NOS: 2 AND 4

Amgen's Grounds depend on the mistaken assumption that a POSA would have associated "eculizumab," the clinically successful anti-C5 antibody described in the prior art, with SEQ ID NOs: 2 and 4. But the opposite is true: the literature before March 15, 2007 consistently taught that "***eculizumab is***" the antibody of Thomas – an ***IgG4*** isotype antibody, having a different sequence from SEQ ID NOs: 2 and 4.[1] (Paper 22 ("POR"), 15-19.) Nothing in the art taught that an antibody with SEQ ID NOs: 2 and 4 – then an unknown, uncharacterized sequence – would have met the '880 patent's claimed requirements of binding C5 and use in a pharmaceutical composition to treat PNH. *See, e.g.*, *PersonalWeb Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 989, 993 (Fed. Cir. 2017).

A. The Literature Consistently Taught a POSA that "Eculizumab" Was the *IgG4*-Isotype Antibody of Thomas

Before March 15, 2007, the only plausible conclusion was that "eculizumab" was the IgG4 antibody of Thomas. As Amgen concedes, a POSA would have had

[1] Unless otherwise noted, all emphasis is added, and internal citations and quotation marks are omitted.

the goal of "recreating a[] … pharmaceutical composition comprising … eculizumab, which clinical trials had repeatedly demonstrated to be successful." (AMG1081, ¶10; *id.* ¶69; Reply, 7, 14; ALXN2092, 35:9-38:19.) A POSA would have looked to the literature regarding "eculizumab" and its clinical properties, which Amgen relies on for that exact purpose. (*E.g.*, AMG1002, ¶¶12, 36-42.) That literature consistently pointed to Thomas for information on what "eculizumab is"; and Thomas in turn identified a humanized IgG4 antibody with potent anti-C5 and anti-hemolytic activity. (ALXN2022, ¶139.)

The Examiner and this Board have agreed that the clinical literature pointed to Thomas for the structure of "eculizumab." (ALXN2092, 78:1-80:7, 81:22-85:17, 87:3-93:19.) In issuing a rejection for the related '504 patent, the Examiner concluded that Hillmen (AMG1004) "refers to reference number 15 (Thomas) as disclosing more information about eculizumab," and "Thomas in turn discloses that eculizumab is the humanized antibody h5G1.1."[2] (POR, 30; AMG1014, 557, 559.) And this Board determined that Hillmen and Hill "at least invoked a molecule having the IgG4 isotype taught in Thomas." (Paper 15, 34, 37.) This

[2] Alexion overcame the rejection after explaining that Hillmen and Thomas guided a POSA to a different sequence than SEQ ID NOs. 2 and 4. (AMG1014, 586-87, 591 ¶¶3-5.)

plain reading cannot be "patently false" (Reply, 3) when everyone but Amgen agrees.

Amgen contends Thomas does not say "eculizumab," and dismisses Thomas as "one of the earliest disclosures." (Reply, 8, 10-11.) But the literature consistently cited to Thomas ***for*** "eculizumab," including in March 2007. (*See, e.g.*, POR, 15-19, 27; ALXN2022, ¶¶120-123, 150; AMG1077, 76:10-19, 127:3-18, 136:8-18; ALXN2028, 31 & Ref. 6.) In contrast, Bowdish, Mueller, and Evans (from which Amgen pieces together SEQ ID NOs: 2 and 4) never mention "eculizumab," and were never cited for what "eculizumab is." (Section II.C *infra*.)

The art did not cite Thomas merely for generalized "methods of humanizing antibodies." (*Cf.* Reply, 11.) As Dr. Balthasar testified, the prior art cited Thomas for "***what*** eculizumab is." (ALXN2032, 128:20-129:10, 129:13-130:22; ALXN2022, ¶139.) For example, Hillmen 2006 states "***Eculizumab (Soliris, Alexion Pharmaceuticals) is*** a humanized monoclonal antibody directed against the terminal complement protein C5," and cites Thomas. (AMG1012, 1234.) The plain reading of that statement, like those in Hillmen, Hill, and Hill 2007, is that Thomas identifies ***what*** "eculizumab" is. (POR, 15-19.) Amgen concedes as much, admitting that the literature cited Thomas for "information about ***eculizumab's*** ability to bind to C5." (AMG1081, ¶29; Reply, 11.)

Nor does Bell cite Thomas for "humanization" methods when it states that "[m]ethods for the preparation of h5G1.1-mAb" are described in Thomas. (AMG1081, ¶29; AMG1005, ¶[0052].) As Dr. Balthasar concedes, this sentence "provid[es] 'methods for the preparation of ***h5G1.1-mAb***,' which ***is how Bell referred to eculizumab***," and then cites to Thomas. (AMG1081, ¶95; ALXN2092, 70:4-71:17, 74:5-75:20; ALXN2022, ¶¶194-198.)

B. Tacken Would *Not* Have Changed a POSA's Understanding That "Eculizumab" Was an IgG4 Isotype Antibody

Despite the overwhelming evidence identifying "eculizumab" as an IgG4 antibody, Amgen clings to a ***single*** publication, Tacken (AMG1034), as allegedly teaching that "eculizumab is an IgG2/IgG4 antibody." (Reply, 3.) Amgen uses Tacken to connect (1) publications describing "eculizumab" as a successful PNH treatment (Hillmen, Hill, Bell) – which do not include any sequences, with (2) documents Amgen combines in hindsight to obtain SEQ ID NOs: 2 and 4 (Bowdish, Mueller, Evans) – which do not mention "eculizumab." (*See, e.g.*, AMG1081, ¶¶38, 70, 93-94.) Notably, Tacken does not cite any of the references from Amgen's Grounds.[3]

[3] Because Amgen relies on Tacken to supply missing claim elements, but did not include Tacken in ***any*** of its six Grounds (POR, 24 n.3), Amgen's Grounds fail

Tacken does not show that "eculizumab" was known as an IgG2/IgG4 isotype. A POSA would not have considered Tacken at all; and even if they had, the prior art "viewed ***as a whole***" identified "eculizumab" as an IgG4 antibody. *Impax Labs., Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018). Amgen's focus on Tacken, to the exclusion of the art as a whole, reveals improper hindsight. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

A POSA motivated to recreate "eculizumab" for treating PNH would not have disregarded the clinical literature demonstrating its success and focused on one statement buried in Tacken – a publication concerning "anti-DC SIGN" antibodies for vaccination strategies. *See Impax*, 893 F.3d at 1379-80 (discounting reference that, "as a whole," was "not about" and "barely mentioned" the claimed compound). None of the clinical literature cited Tacken for "eculizumab"; and a

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for that reason alone. *See, e.g.*, *PersonalWeb*, 848 F.3d at 989, 993 (vacating Board's obviousness determination where final written decision "did not adequately support its findings that the prior art [combination of the Petition] disclosed all elements of the challenged claims"); *Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1335 (Fed. Cir. 2020) (institution is limited to the Grounds stated in the Petition).

POSA would not have scoured the "materials and methods" sections of "basic research" articles that, like Tacken, do not mention "eculizumab" or C5-binding in their titles or abstracts, and do not discuss PNH at all. (*Cf.* AMG1081, ¶24; *see* ALXN2032, 72:23-73:2, 73:12-74:1, 74:18-21, 92:21-93:1, 108:17-109:10.) Dr. Balthasar only looked at Tacken because Amgen's counsel handed it to him. (ALXN2032, 64:23-65:7, 65:12-14.)

Even if a POSA had considered Tacken, it would not have changed their understanding that "eculizumab" was Thomas's IgG4 antibody. A POSA would not have disregarded the clinical publications about using "eculizumab" for treating PNH, and instead credited an isolated sentence buried in Tacken that mentioned "eculizamab [*sic*]" just once. Nor could a POSA have seen Tacken as the "culminat[ion]" of an "iterative development process" leading to "eculizumab" (*cf.* AMG1081, ¶19), when the literature ***after*** Tacken identified "eculizumab" as Thomas's IgG4 antibody. (POR, 26-27.)

Because Tacken cites to Thomas, the most reasonable reading would have been that (1) "eculizumab" was an ***IgG4*** antibody, as the literature consistently cited Thomas for "eculizumab"; (2) Tacken's IgG2/IgG4 "isotype control" was a ***different*** "h5G1.1" antibody; and (3) Tacken conflated the broad terminology "5G1.1"/"h5G1.1" – which a POSA would have understood to typically refer to broad classes of antibodies, sometimes to "eculizumab," and sometimes to a

specific mouse antibody (ALXN2032, 98:2-99:8, 159:1-10, 169:6-18, 202:24-203:14) – with the specific term "eculizumab."[4] (ALXN2022, ¶¶140-146; POR, 25-27.) The one unreasonable conclusion is that an isolated, ambiguous sentence in Tacken would have upended a POSA's understanding of "eculizumab" from the consistent teachings of the art.

Amgen's reading of Tacken is also not supported by non-prior art statements in the unrelated "'438 application" prosecution history.[5] These statements, which refer to ***2002*** (Reply, 9), could not have been based on Tacken, published in ***2005***. These statements cite only Mueller II (AMG1049, 838-39), which did not mention

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[4] A POSA would have also been confused by the "-a-" sub-stem in "eculizamab [*sic*]," suggesting a rat antibody. (ALXN2046, 27.)

[5] *Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286 (Fed. Cir. 2014) does not control. *Apple* found that claim scope may be disavowed by narrowing arguments made during prosecution of a ***related*** ex-U.S. application with the ***same specification*** and ***same claim language*** as a U.S. patent. *Id.* at 1311-1313. Here, claim construction is not in issue, the '438 application is unrelated to the '880 patent, and "mutated Fc receptor" (AMG1049, 838-39) appears nowhere in the '880 patent claims.

"eculizumab," and did not specifically identify any anti-C5 antibody. (ALXN2032, 98:15-99:8, 159:1-10, 241:23-242:12.)

Significantly, the "CAS Registry" noted by Dr. Balthasar (AMG1081, ¶¶9, 17, 20) would have only increased the confusion. The Registry disclosed an ***incorrect*** sequence for "eculizumab," and was not corrected until 2009. (Paper 2, 9-10, n.6; AMG1054, 237, 247-254, 292-293; ALXN2092, 93:20-95:4, 96:12-100:6.) Amgen fails to explain why a POSA looking to make "eculizumab" would have focused on Tacken (or Bowdish, Mueller, or Evans), rather than all of the "eculizumab" art, including the CAS Registry.

C. Nothing in the Prior Art Linked SEQ ID NOs: 2 and 4 to "Eculizumab"

Amgen's Grounds also fail because nothing in the prior art connected "eculizumab" (including its clinical properties) with SEQ ID NOs: 2 and 4. *See PersonalWeb*, 848 F.3d at 991 ("[A] finding of obviousness cannot be predicated on the mere identification in the prior art of individual components of claimed limitations."). A POSA would not have known of, and would not have been motivated to make, SEQ ID NOs: 2 and 4. (POR, 21-22, 44-56, 58-61; Section IV.A *infra*.) And nothing in the art taught that SEQ ID NOs: 2 and 4 was "***eculizumab***" – the clinically successful antibody that blocks C5 cleavage and treats PNH. SEQ ID NOs: 2 and 4 would have been an unknown, uncharacterized

antibody, with biological, clinical and physicochemical properties that could not be reasonably predicted. (POR, 21-22, 43-44, 56-58, 63-64; Section IV.B *infra*.)

Nothing in Bowdish, Mueller, or Evans guided a POSA to connect "eculizumab" with SEQ ID NOs: 2 and 4. Bowdish, Mueller and Evans never mention "eculizumab." (ALXN2032, 102:10-16, 199:9-17; POR, 49, 61-62.) Evans does not disclose ***any*** full-length humanized antibodies – only structurally-distinct fragments that never belonged to a full-length antibody. (ALXN2032, 163:5-15; POR, 50.) Neither Bowdish nor Mueller were cited by the literature on "eculizumab" and its clinical properties. (ALXN2032, 139:8-140:5, 140:13-141:2, 141:11-19, 170:5-171:1, 195:22-196:4.) And, as Dr. Balthasar testified, the terminology "5G1.1" (used in Bowdish) and "h5G1.1" (used in Mueller) was ***not*** specific to "eculizumab" – it could refer to multiple antibodies with different sequences. (ALXN2032, 202:24-203:14.) For example, Dr. Balthasar admitted that the "h5G1.1"/isotype terminology used in Mueller could ***not*** have been used to determine a specific sequence. (ALXN2032, 241:23-242:12.)

Amgen uses improper hindsight when it disregards the literature ***actually*** concerning "eculizumab" and its clinical properties and relies on documents saying nothing about "eculizumab." A POSA seeking to recreate "eculizumab" would not have discarded the literature's consistent teaching regarding what "eculizumab is,"

and turned to an isolated statement regarding "[c]onstruction of 5G1.1" in Bowdish – a patent application regarding peptide mimetics; or an isolated statement regarding an "h5G1.1" control antibody in Mueller – a patent application regarding anti-VCAM antibodies.

Tacken likewise did not connect "eculizumab" to SEQ ID NOs: 2 and 4. Tacken did not identify its IgG2/IgG4 "control" antibody as "eculizumab" (Section II.B *supra*), and nothing in Tacken provided the sequence of that antibody. Tacken does not cite Bowdish, Mueller or Evans. And if a POSA had looked at Thomas (cited for Tacken's control antibody) and Mueller II (cited for "a hybrid IgG2/IgG4 constant domain"), it would not have led them to SEQ ID NOs: 2 and 4, because (1) Thomas describes an IgG4 antibody with a different sequence from SEQ ID NOs: 2 and 4; (2) Thomas's variable region differs from SEQ ID NO: 4 at variable light chain amino acid 38; and (3) Mueller II's constant region is missing an amino acid present in SEQ ID NO: 2. (Section II.A *supra*; ALXN2022, ¶¶250, 252.) Amgen does not explain how a POSA would overlook these deficiencies to arrive at the claimed sequence.

III. AMGEN'S ANTICIPATION AND OBVIOUSNESS ARGUMENTS REGARDING HILLMEN AND HILL ARE MISTAKEN ON THE FACTS AND LAW

On Grounds 1-2, alleged anticipation of claim 2 over Hillmen or Hill, Amgen's Reply repeats the same arguments already rejected by the Board and

introduces new legal theories with no basis. Nothing in Hillmen or Hill expressly or inherently disclosed SEQ ID NOs: 2 and 4 or its properties. (POR, 32-34; Paper 15, 33-37.) Amgen's Grounds 3-4 fail at least because no combination of Hillmen, Hill, Bell or Wang disclosed "SEQ ID NOs: 2 and 4" or its use in the claimed compositions to treat PNH. (POR, 35-36; Paper 15, 37-38.)

The undisputed facts are fatal to Amgen's theory: (1) the name "eculizumab" alone would not have told a POSA the sequence of "eculizumab"; and (2) nothing within Hillmen or Hill disclosed or would have guided a POSA to SEQ ID NOs: 2 and 4. (POR, 32-34; ALXN2032, 139:8-140:5, 140:13-141:19; ALXN2092, 43:11-44:24, 45:19-25.) Rather, Hillmen and Hill's citations to Thomas for what "eculizumab is" would have directed a POSA to an ***IgG4*** antibody with a different sequence. (Section II.A *supra*.)

Grounds 1-2 are also wrong on the law. Amgen conflates Hillmen and Hill – publications reporting clinical trial results – with the underlying clinical trials. (Reply, 1, 4-5.) But only the ***publication*** is available as prior art.[6] 35 U.S.C. § 311(b). While we know today that the clinically-tested antibody actually had the claimed sequence, nothing within the "four corners" of ***Hillmen or Hill*** disclosed

[6] Amgen does not contend that clinical supplies of eculizumab were publicly available. (ALXN2092, 149:4-150:5, 152:4-17.)

that to a POSA. *See, e.g.*, *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). As in *Endo* and *Bayer*, Hillmen's and Hill's mere use of the name "eculizumab" was not a disclosure of its chemical composition, *i.e.*, sequence. *See Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-79, 1381-83 (Fed. Cir. 2018) (publication of clinical study using a "castor oil" vehicle did not inherently disclose the vehicle's chemical composition); *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018) (publications disclosing compound name "KIH-485" did not inherently disclose the compound's chemical composition).[7]

Amgen's own case law confirms that an inherently disclosed element must ***necessarily*** flow from the ***disclosure*** within "the single anticipating reference." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1375-78 (Fed. Cir. 2003) (disclosed administration of loratadine necessarily produced the claimed

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[7] *In re Crish,* 393 F.3d 1253 (Fed. Cir. 2004) remains distinguishable. (Paper 15, 33.) As the Board found, the anticipatory publication in *Crish* provided sufficient information (size and location of a claimed promoter region) for a POSA to obtain the claimed sequence using conventional techniques. (*Id.* (quoting *Crish*, 393 F.3d at 1257-59.) Hillmen, in contrast, did not "'specifically identify' … eculizumab" as having SEQ ID NOs: 2 and 4. (Paper 15, 33.)

metabolite); *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1372-73 (Fed. Cir. 2007) (disclosed manufacturing process necessarily produced the claimed "separating layer"); *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1348 (Fed. Cir. 1999) (disclosed compositions necessarily produced the claimed "sufficient aeration"). Hillmen and Hill, in contrast, did not disclose any process that would have necessarily produced SEQ ID NOs: 2 and 4. *Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348-49 (Fed. Cir. 2004).

Amgen erroneously uses documents ***outside*** Hillmen and Hill (Bowdish, Mueller, Evans, and Tacken) to supply SEQ ID NOs: 2 and 4. (Reply, 6-7; AMG1081, ¶38; ALXN2092, 57:25-58:6, 60:21-61:12, 64:8-12, 67:21-69:7.) In doing so, Amgen "conflates the principles of enablement and anticipation," and "makes the impermissible leap from enablement to disclosure." *Galderma Labs., L.P. v. Teva Pharms. USA, Inc.*, No. 2019-2396, 2020 WL 467933, at *5-6 (Fed. Cir. Jan. 29, 2020). The claimed sequence does not "necessarily result" from practicing Hillmen or Hill (*id.* at *6-7), because the name "eculizumab" does not disclose a sequence, and Hillmen and Hill pointed to Thomas's IgG4 antibody as "eculizumab."

IV. AMGEN FAILS TO SHOW HOW CLAIMS 1-3 WOULD HAVE BEEN OBVIOUS TO A POSA

A. The Claimed Sequence Would *Not* Have Been Obvious in View of Bell, Bowdish and Evans, or Bell, Evans and Mueller

A POSA motivated by Bell (AMG1005) to recreate "eculizumab" would not have turned to Bowdish (Ground 5) or Mueller (Ground 6) – documents with no mention of Bell, "eculizumab," or PNH. Nor would a POSA have combined sequences from Evans and Bowdish or Mueller in the selective way that Amgen does to arrive at SEQ ID NOs: 2 and 4.

Bowdish: Without hindsight, a POSA seeking to recreate "eculizumab" would not have leapt from Bell to Bowdish. (Reply, 15; AMG1081, ¶¶69-73.) Bell and Bowdish do not cite one another. (ALXN2032, 170:5-10, 195:22-196:4.) Dr. Balthasar concedes that Bell and other clinical literature gave a POSA a "strong motivation to make a pharmaceutical composition comprising eculizumab" (AMG1081, ¶69) – but that literature uniformly pointed to ***Thomas*** for "eculizumab." (*See* Section II.A *supra*.) Bell in particular cited Thomas for "[m]ethods for the preparation of [eculizumab]." (AMG1005, ¶[0052]; AMG1081, ¶95; ALXN2092, 70:4-71:17, 74:5-75:20.) A POSA would not have disregarded Bell's citation to Thomas's IgG4 antibody for "eculizumab," and instead turned to Bowdish – a document regarding "peptide mimetic" compounds having nothing to do with anti-C5 activity or treating PNH. (POR, 47-49.)

Nor would a POSA have connected Bell and Bowdish in view of their incorporations by reference of Evans or the '283 application, respectively. (*Cf.* Reply, 15; AMG1081, ¶¶70, 77.) Bell incorporates both Evans and Thomas when it discusses "***eculizumab***." (AMG1005, ¶[0052]; POR, 46-47.) Bowdish, in contrast, refers to the '283 application for "[c]onstruction of ***5G1.1***" (AMG1006, ¶[0191]) – a term that Dr. Balthasar admitted can refer to many different antibodies, and in the context of Evans, refers to a mouse antibody. (ALXN2032, 98:2-99:8, 169:6-18, 202:24-203:14; AMG1077, 103:16-105:16, POR, 13-14, 19-21, 50.)

The term "5G1.1" in one example of Bowdish would not have connected Bowdish to Bell. (*Cf.* Reply, 15; AMG1081, ¶¶72-73.) As Dr. Balthasar testified, "5G1.1" does ***not*** refer specifically to "eculizumab" unless a reference expressly says so (ALXN2032, 98:2-99:8, 199:9-12, 202:24-203:14) – and Bowdish does not. A POSA seeking to recreate "eculizumab" for treating PNH would not have searched all documents with "5G1.1" buried in the text, and disregarded the clinical literature identifying "eculizumab" as Thomas's IgG4 antibody. (Section II.A *supra*.)

A POSA would not have connected Bell and Bowdish based on "knowledge of eculizumab's structure." (AMG1081, ¶¶70, 74-76.) A POSA understood "eculizumab" to be ***IgG4***, not IgG2/IgG4. (*See* Sections II.A-B *supra*.) And even

if, hypothetically, "eculizumab" were thought to be IgG2/IgG4, a POSA would not have turned to Bowdish. Bowdish is silent on isotype (ALXN2032, 212:22-213:2, 214:2-7); and a POSA seeking to make "eculizumab" would have had no reason to pick up Bowdish and undertake the sequence analyses that Dr. Balthasar proposes to determine the isotype of its "5G1.1-TPO" compound. (POR, 52; *cf.* AMG1081, ¶¶74-75.) A POSA would not have gone through such a complicated ordeal rather than follow the clear teaching of the clinical literature.[8]

Bowdish did not teach SEQ ID NOs: 2 and 4. Amgen recreates that sequence in hindsight by combining Bowdish with humanized "fragment" sequences from Evans. (Reply, 15; AMG1081, ¶77.) But a POSA would have understood Bowdish's reference to "[c]onstruction of 5G1.1" to refer to Evans's ***mouse*** "5G1.1" antibody, not humanized fragments. (POR, 19-21, 50; ALXN2022, ¶¶126-127, 163-164, 212-213.) In Bowdish, "5G1.1" refers to a "whole," "full" antibody; and Evans's only full-length antibody is the ***mouse***

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[8] Nor may Amgen attempt to fill gaps by combining Bowdish with Mueller (AMG1008) and Rother (AMG1032) – documents that are outside Ground 5 and have no connection to Bowdish or "eculizumab." (AMG1081, ¶¶74-75; ALXN2092, 100:14-101:19, 106:14-107:2, 107:23-108:17, 111:7-112:24, 113:20-114:20, 114:25-115:22, 116:18-118:18; Section II.B *supra*.)

antibody "5G1.1." (AMG1006, ¶¶[0191]-[0193]; ALXN2032, 169:13-18.) Bowdish could not have referred to humanized "fragments," which a POSA understood to be structurally distinct from, and never part of, a full-length humanized antibody. (ALXN2032, 163:5-15, 228:2-16; ALXN2022, ¶126.) Nor could "[c]onstruction of 5G1.1" refer to a full-length humanized antibody, because, as Dr. Balthasar admits, nothing in Evans disclosed ***any*** full-length humanized antibody. (*Id.*)

Seeing the non-overlap between Bowdish's sequences and Evans's "5G1.1" mouse antibody (ALXN2092, 137:25-141:23), a POSA would have stopped there. Amgen's new argument that a POSA would have combined Bowdish with Evans's ***mouse*** antibody defies common sense. (*Cf.* AMG1081, ¶78.) A POSA would not have put on blinders and selectively combined Bowdish with Evans's mouse antibody, while ignoring the extensive sequence mismatch. (ALXN2022, ¶¶213-215, POR, 53-54.) Evans also provided multiple CDR definitions – and a POSA could not have determined the specific sequence Bowdish replaced with its TPO-mimetic peptide. (ALXN2022, ¶219; AMG1077, 242:17-243:19, 244:18-22, 249:13-17, 250:18-23.)

Mueller: Amgen's leap from Bell to Mueller is pure hindsight. Neither Bell nor Evans cite Mueller, or vice versa. (ALXN2032, 170:11-171:20, 243:16-

20.) Bell cites ***Thomas***, not Mueller, for "the preparation of [eculizumab]." (AMG1081, ¶95; POR, 46-47, 60.)

A POSA motivated to make "eculizumab" to treat PNH would not have turned to Mueller, concerning anti-VCAM antibodies for blocking transplant rejection. (ALXN2032, 232:6-16; POR, 61.) Mueller never mentions "eculizumab," and referred to "h5G1.1" only in describing "control" antibodies for experiments unrelated to anti-C5 activity or PNH. (ALXN2032, 102:10-16, 235:11-19; POR, 61.) As Dr. Balthasar testified, nothing in Mueller allowed a POSA to identify either of the two "h5G1.1" control antibodies as "eculizumab"; Mueller's "h5G1.1"/isotype terminology would not have indicated any ***specific*** sequence; and Mueller identified only its ***IgG4*** "h5G1.1" control antibody as "anti-C5." (ALXN2032, 102:10-16; 234:9-21, 235:6-19, 237:25-238:5, 238:13-19, 241:23-243:14; AMG1077, 114:10-115:11.)

Amgen now also attempts to supplant Mueller (AMG1008) with Tacken and Mueller II (AMG1031) – documents that should be disregarded as outside the asserted combinations of Amgen's Grounds. (Section II.B *supra*; *cf.* AMG1081, ¶94.) Tacken would not have changed a POSA's understanding that the clinical literature consistently identified "eculizumab" as Thomas's ***IgG4*** antibody. (*See* Section II.B *supra*.) And even if, hypothetically, a POSA had combined sequences

from Thomas and Mueller II, it could not have led to SEQ ID NOs: 2 and 4. (*See* Section II.C *supra*.)

Amgen fails to explain why a POSA would have combined sequences from Mueller and Evans in exactly the way Amgen does in hindsight to obtain SEQ ID NOs: 2 and 4. Mueller provides ***no*** anti-C5 antibody sequences (ALXN2032, 232:17-21); and as the Board correctly found, Mueller and Evans provide no guidance on whether, or how, sequences from one document should be combined with the other.[9] (Paper 15, 54-55; POR, 62-63.) Mueller's use of "CO12" in naming full-length humanized antibodies also would not have connected it to Evans – which Dr Balthasar admits did not disclose ***any*** full-length humanized antibodies, and only provided humanized recombinant fragments. (ALXN2032, 163:5-15; ALXN2022, ¶245.)

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[9] In *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804 (Fed. Cir. 1989), a combination "***specifically named*** in the prior art" was found obvious-to-try. *See Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA*, 748 F.3d 1354, 1360-61 (Fed. Cir. 2014) (citing *Merck*, 874 F.2d at 808-09). Nothing in Mueller or Evans specifically named SEQ ID NOs: 2 and 4.

B. A POSA Would Not Have Had Any Motivation to Make, or Reasonable Expectation of Success With, SEQ ID NOs: 2 and 4

Even if SEQ ID NOs: 2 and 4 were known to a POSA – which they were not – nothing would have told a POSA that they comprised "***eculizumab***," and thus had the biological, clinical and physicochemical properties attributed to "eculizumab." (Section II.C *supra*.) A POSA would not have reasonably expected success with SEQ ID NOs: 2 and 4 – which to them was an unknown, uncharacterized antibody that had never been tested for anti-C5 activity, pharmaceutical formulation, or safety and efficacy. A POSA also would not have been motivated to make and study a "new, untested antibody" with a different sequence and structure from the "eculizumab" proven to treat PNH. (Reply, 14.)

OSI Pharms., LLC v. Apotex Inc., 939 F.3d 1375 (Fed. Cir. 2019) controls, because Amgen's "asserted references contained no data at all – no 'clinical (human) data or preclinical (animal) data,' nor any 'in vitro (test tube) data'" regarding the anti-C5 activity, safety or efficacy of SEQ ID NOs: 2 and 4. (Reply, 15-16 (quoting *OSI*, 939 F.3d at 1383).) Bowdish and Mueller provided no such data. (ALXN2032, 175:19-176:6, 188:18-23, 235:11-19, 247:13-248:6; POR, 49, 56-57, 62-63.) Neither did Bell (Reply, 16) – which does not disclose SEQ ID NOs: 2 and 4 or IgG2/IgG4 constant regions (ALXN2032, 146:17-25, 151:3-12, 160:7-9, 194:11-24; POR, 45), and cited Thomas for "[m]ethods for preparing

[eculizumab]" (*see* Section II.A *supra*.) Neither did Evans (Reply, 16-17), which did not disclose ***any*** full-length humanized antibodies or IgG2/IgG4 constant regions, let alone SEQ ID NOs: 2 and 4. (ALXN2032, 163:5-15, 163:25-164:8; POR, 64.)

Without data for SEQ ID NOs: 2 and 4, a POSA would not have reasonably expected it to be "anti-C5" or suitable "for use in treating a patient afflicted with [PNH]" as claimed. (POR, 36-38, 43, 56-58, 63-64; ALXN2022, ¶¶135, 172, 224-233, 254-260.) Even small sequence changes could impact critical antibody characteristics including binding affinity, specificity, and immunogenicity. (ALXN2022, ¶¶104-117; POR, 10-11.) "Fine specificity" (binding to a certain location) was especially critical, because an effective anti-C5 antibody would need to block cleavage into components C5a and C5b. (ALXN2022, ¶¶228-230; AMG1039, 840; AMG1023, 1398-99; ALXN2092, 169:3-170:7.) Amgen provides no data showing that a POSA could have reasonably expected SEQ ID NOs: 2 and 4 to have the same anti-C5 properties as "eculizumab."

Amgen also provides no data that would have given a POSA a reasonable expectation that SEQ ID NOs: 2 and 4, or any IgG2/IgG4 antibody, would be safe. (ALXN2022, ¶¶77, 86, 134-135, 159, 171-172, 206.) Dr. Balthasar contends there were "extensive disclosures in the prior art … regarding antibodies with hybrid IgG2/IgG4 constant regions" (AMG1081, ¶97 (citing Mueller, Mueller II, and

Tacken)) – but ***none*** of those documents clinically tested safety and immunogenicity of any IgG2/IgG4 antibodies. Any purported "advantages" of IgG2/IgG4 constant regions (Reply, 12) were speculative. (ALXN2022, ¶135; POR, 57-58.)

Amgen's rebuttal on "reasonable expectation of success" is meritless. (Reply, 13; AMG1081, ¶¶81-85.) A POSA understood that constant region changes could critically (and unpredictably) impact binding, specificity, and immunogenicity – and this overarching principle would apply equally to IgG2/IgG4 antibodies. (ALXN2022, ¶¶104-117; AMG1077, 200:13-202:11, 203:20-205:7, 208:10-209:5.) That few prior art references reported on switching to "IgG2/IgG4" isotypes highlights a POSA's uncertainty in treating humans with a little-studied, clinically untested, non-natural isotype. (ALXN2022, ¶¶81-82, 86; ALXN2092, 172:6-173:2.)

Dr. Balthasar points to Tacken and Mueller II as evidence that "switching to an IgG2/IgG4 isotype" caused "no significant alteration" in antibody function. (AMG1081, ¶83.) But Tacken and Mueller II did not study the impact of isotype switching on anti-C5 activity, "fine specificity" or blocking cleavage – critical factors for an anti-C5 antibody treating PNH. (ALXN2032, 92:21-93:1; ALXN2092, 156:17-164:7, 165:10-166:21; ALXN2022, ¶¶228-230.) Dr. Balthasar also cites Bell, Evans and Thomas to assert that 5G1.1 antibodies retain

their function when changing isotype. (AMG1081, ¶¶81, 84.) But neither Evans nor Thomas studied IgG2/IgG4 antibodies (ALXN2032, 90:8-22, 97:7-21, 163:25-164:8; ALXN2092, 166:22-170:25); and Bell reported clinical data only for "eculizumab," identified as Thomas's IgG4 antibody (ALXN2092, 152:22-154:16; Section II.A *supra*).

A POSA also would not have reasonably expected success in formulating SEQ ID NOs: 2 and 4 – an unstudied antibody that might not be stable in ***any*** pharmaceutical composition. (ALXN2024, ¶¶62-73; ALXN2092, 119:14-121:24; Section II.C *supra*.) And if, hypothetically, SEQ ID NOs: 2 and 4 were equated with "eculizumab," Amgen fails to show how a "300 mg single-use formulation of 30 ml of a 10 mg/ml sterile, preservative free solution" (claims 1, 3) would have been obvious in view of Bell and Wang (AMG1028). (ALXN2024, ¶¶74-89.) Wang did not "teach[] that eculizumab can be stably formulated for nebulization at a concentration of 1-30 mg/ml" (Reply, 22-23), because Wang's "1-30 mg/ml" range was generic, not specific to "eculizumab," and nothing in Wang tested the ***stability*** of any "eculizumab" pharmaceutical composition, let alone a 10 mg/ml "eculizumab" solution. (ALXN2024, ¶¶78-87; ALXN2092, 123:6-124:1.) It is undisputed that a POSA considered stability over time to be a key factor in the success of a pharmaceutical composition. (AMG1002, ¶105; AMG1081, ¶47; ALXN2024, ¶68; ALXN2092, 122:4-12, 127:1-20, 129:2-137:24.) Amgen still

provides no such prior-art data for a 10 mg/ml solution of "eculizumab" in a 300 mg single-use formulation. (ALXN2024, ¶¶45-46, 75-88; AMG1078, 184:25-185:10; AMG1085, 16; ALXN2092, 123:6-124:1, 125:17-126:1, 130:8-131:18, 135:8-24.)

C. Amgen Fails to Rebut the Strong Evidence of Objective Indicia of Non-Obviousness

Amgen cannot dispute the objective indicia of non-obviousness. On commercial success, nexus is presumed because the claims cover SOLIRIS®, and SOLIRIS® has significant sales in the relevant market. (ALXN2093, 69:4-72:4; ALXN2056, ¶¶1-9, App'x A; POR, 64-65.) SOLIRIS® sales cannot be due to elements in the prior art (AMG1088, ¶¶15, 24-27) because a POSA did ***not*** know of an antibody having SEQ ID NOs: 2 and 4 and its utility in treating PNH. (Section II.C *supra*.) Nor can SOLIRIS® sales be attributed to an "Orphan Drug Exclusivity" period that expired in 2014 (AMG1088, ¶¶37-41), rather than the remarkable clinical properties of the claimed antibody. (ALXN2022, ¶¶263-267.) SOLIRIS® had substantial sales, despite its very small patient population, because of the ***value*** it brought in successfully treating a rare condition that lacked adequate treatment. (ALXN2093, 131:25-133:24, 134:12-135:1, 135:11-136:24, 144:22-146:17, 147:16-148:18, 149:4-21, 151:21-153:5; AMG1092, 2-3, 5; AMG1095, 1; AMG1096, 1.)

Amgen's "blocking patent" theory is wrong on the facts and the law. As Mr. Hofmann conceded, the existence of an earlier patent is not *per se* evidence against commercial success. (ALXN2093, 49:21-50:11, 50:25-51:5.) Mr. Hofmann failed to consider whether another company might have been motivated to, *e.g.*, develop the claimed invention before March 12, 2002 (the start of the alleged "disincentive"); engage in research and development under the § 271(e)(1) safe harbor; or license innovations beyond Evans to Alexion. (ALXN2093, 51:23-52:5, 56:4-57:18, 117:10-12.) Amgen is presently developing its eculizumab product in the U.S. within the term of both Evans and the '880 patent. (ALXN2093, 11:25-13:1, 63:24-64:3, 64:19-65:16, 67:18-68:9; ALXN2096.) Amgen's theory that companies would have avoided developing products covered by Alexion's patents is belied by Amgen and others attempting exactly that.

Amgen also fails to rebut the evidence that the claimed invention fulfilled a long-felt but unmet need and received significant industry praise. (ALXN2092, 144:8-145:18, 147:13-148:5.) Amgen's position that PNH was suitably treated by frequent "blood transfusions" is not credible. (*Cf.* Reply, 24.) SOLIRIS® was a groundbreaking, life-saving therapy that substantially improved quality of life for PNH patients – including reducing frequent blood transfusions that were previously a necessary measure. (ALXN2022, ¶¶268-277.)

Amgen also cannot dispute that it, and others, are currently developing purported "biosimilar" products that ***exactly*** copy SEQ ID NOs: 2 and 4. (ALXN2092, 143:4-144:6.) They are doing so, rather than designing their own antibodies, because SEQ ID NOs: 2 and 4 is the antibody that safely and effectively treats PNH. (POR, 66.)

V. CONCLUSION

Alexion respectfully submits that the Board should confirm the patentability of claims 1-3.

Respectfully submitted,

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CERTIFICATION OF SERVICE

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN INC.
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner.

Case No. IPR2019-00741
Patent: 9,732,149

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2054	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris(TM) (eculizumab)," (Sept. 20, 2006)
2055	Alexion Press Release, "Alexion Submits Market Authorization Application for Soliris(TM) (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency," (Sept. 26, 2006)
2056	Declaration of Daniel Bazarko
2057	***Intentionally left blank***
2058	***Intentionally left blank***
2059	Alexion Form 10-K for FY 2007 (Excerpts)
2060	Alexion Form 10-K for FY 2008 (Excerpts)
2061	Alexion Form 10-K for FY 2009 (Excerpts)
2062	Alexion Form 10-K for FY 2010 (Excerpts)
2063	Alexion Form 10-K for FY 2011 (Excerpts)
2064	Alexion Form 10-K for FY 2012 (Excerpts)
2065	Alexion Form 10-K for FY 2013 (Excerpts)
2066	Alexion Form 10-K for FY 2014 (Excerpts)
2067	Alexion Form 10-K for FY 2015 (Excerpts)
2068	Alexion Form 10-K for FY 2016 (Excerpts)
2069	Alexion Form 10-K for FY 2017 (Excerpts)
2070	Alexion Form 10-K for FY 2018 (Excerpts)
2071	Alexion Form 10-Q for Q1 of FY 2019 (Excerpts)

Exh. No.	Description
2072	Alexion Form 10-Q for Q2 of FY 2019 (Excerpts)
2073	Alexion Form 10-Q for Q3 of FY 2019 (Excerpts)
2074	American Type Culture Collection, "Product Sheet, Hybridoma: 5G1.1 ("HB-11625"), https://www.atcc.org/~/ps/HB-11625.ashx
2075	GenScript, "Final Report – Antibody Full Length Sequencing of Hybridoma 5G1.1 T175," Order Number: U856UEK140-1 (Nov. 15, 2019)
2076	GenScript, "Part 1. mAb sequencing: Samples summary" (Nov. 2019)
2077	GenScript, Chain of Custody Log
2078	ATCC Packing Slip
2079	Chang & Hershenson, "Practical Approaches to Protein Formulation Development," Ch. 1, 1-25, PHARMACEUTICAL BIOTECHNOLOGY VOL. 13: RATIONAL DESIGN OF STABLE PROTEIN FORMULATIONS, THEORY AND PRACTICE (Carpenter & Manning, eds., 2002)
2080	Wang, Instability, stabilization, and formulation of liquid protein pharmaceuticals, INTERNATIONAL JOURNAL OF PHARMACEUTICS, 185(2):129-188 (1999)
2081	Hermeling, et al., Structure-Immunogenicity Relationships of Therapeutic Proteins, PHARMACEUTICAL RESEARCH, 21(6):897-903 (2004)
2082	Frokjaer & Otzen, Protein Drug Stability: A Formulation Challenge, NATURE REVIEWS DRUG DISCOVERY, 4(4):298-306 (2005)
2083	Rosenberg, Effects of Protein Aggregates: An Immunologic Perspective, THE AAPS JOURNAL, 8(3):E501-E507 (2006)
2084	European Medicines Agency, ICH Topic Q5C, "Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products" (July 1996)
2085	U.S. Depart of Health and Human Services, FDA, "Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products," ICH Rev. 2 (Nov. 2003)
2086	Stebbings, et al., After TGN1412: Recent developments in cytokine release assays, J. IMMUNOTOXICOLOGY, 10(1):75-82 (2013)
2087	GenScript, "Project Proposal for Monoclonal Antibody Sequencing Service," (Nov. 5, 2019)
2088	Amgen, "Amgen Biosimilars: Our Pipeline," https://www.amgenbiosimilars.com/products/our-pipeline/
2089	Generium Pharmaceutical, "Our Products: Elizaria®," http://www.generium.ru/en/products/elizaria/

Exh. No.	Description
2090	Samsung Bioepis, "Our Pipeline," https://www.samsungbioepis.com/en/product/product02.do
2091	"Antibody Molecules," Ch. 15, 622-625, ANTIBODIES, A LABORATORY MANUAL (Harlow & Lane, eds., 1988)
2092	Deposition Transcript of Joseph P. Balthasar, Ph.D., *Amgen, Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, -740, -741 (Apr. 22, 2020)
2093	Deposition Transcript of Ivan T. Hofmann, *Amgen, Inc. v. Alexion Pharmaceuticals, Inc.*, IPR2019-00739, -740, -741 (Mar. 12, 2020)
2094	U.S. Patent No. 10,590,189
2095	File History for U.S. Patent No. 10,590,189
2096	ClinicalTrials.Gov, Study No. NCT03818607, "A Study Evaluating the Efficacy and Safety of ABP 959 Compared with Eculizumab in Adult Participants with PNH (DAHLIA)," *available at* https://clinicaltrials.gov/ct2/show/NCT03818607 (last accessed Apr. 21, 2020)

I. INTRODUCTION

Amgen still fails to prove the unpatentability of claim 1 of the '149 patent. On March 17, 2020, the USPTO confirmed that claims covering treatment of PNH with SEQ ID NOs: 2 and 4 were patentable over Bowdish and Evans (and the other art and arguments throughout Amgen's Petitions) when it issued U.S. Patent No. 10,590,189, a continuation of the '149 patent. (ALXN2094; ALXN2095, 552-54, 586.) There is no basis to conclude differently here.

Grounds 1-2, alleging anticipation over Hillmen or Hill, fail because Hillmen and Hill did not disclose SEQ ID NOs: 2 and 4 or its properties. Amgen cannot fill in those missing claim elements with present-day knowledge not publicly available before March 15, 2007, or with other documents under the guise of "enablement."

Ground 3, alleging anticipation over Bowdish, likewise fails. Amgen cannot show that Bowdish clearly and unambiguously disclosed SEQ ID NOs: 2 and 4 – a sequence found ***nowhere*** in Bowdish, even if fully combined with Evans (which Bowdish does not cite). Nor can Amgen show anything in Bowdish disclosing "an antibody that binds C5" as recited in claim 1.

Grounds 4-5, alleging obviousness, rely on improper hindsight and disregard the prior art as a whole. Amgen asserts that a POSA would have had the goal of "recreating" eculizumab for treating PNH. (AMG1081, ¶ 10.) But a POSA would

not have arrived at ***SEQ ID NOs: 2 and 4***, when the literature consistently taught that "eculizumab" had a different sequence – an ***IgG4*** isotype as described in Thomas. Instead, Amgen uses hindsight to construct the now-known, claimed sequence piecemeal from a combination of sequences in other documents that never mention "eculizumab," its anti-C5 activity, or its clinical properties. Then, with no basis, Amgen claims that a POSA would have known that its cobbled-together sequence was the "eculizumab" antibody of the clinical literature – despite that literature uniformly identifying "eculizumab" as Thomas's ***IgG4*** antibody.

Amgen's contention that the literature cited Thomas for general "humanization" techniques contradicts the conclusions of the '149 patent Examiner and this Board. And the isolated, ambiguous statement in Tacken (AMG1034) on which Amgen pins its case (despite not having asserted Tacken in any of its Grounds) would not have dissuaded a POSA from the art's overwhelming pronouncement that "eculizumab" was Thomas's IgG4 antibody.

Critically, nothing in the art connected "eculizumab" – the successful, clinically tested antibody – to SEQ ID NOs: 2 and 4. As Alexion's experts explained, a POSA could not have reasonably expected that the untested, uncharacterized antibody sequence Amgen pieces together in hindsight would have bound C5 and prevented its cleavage or treated conditions like PNH.

Dr. Balthasar's Reply Declaration (AMG1081) lacks credibility, repeatedly contradicting his prior sworn testimony. Notably, Amgen's counsel supplied Dr. Balthasar with all of his new cited references, and only select portions of Dr. Casadevall's and Dr. Trout's deposition transcripts. (ALXN2092, 12:15-17, 16:13-22, 25:4-8, 25:20-28:7, 29:9-13.)

II. A POSA HAD NO BASIS TO ASSOCIATE "ECULIZUMAB" WITH SEQ ID NOS: 2 AND 4

Amgen's Grounds depend on the mistaken assumption that a POSA would have associated "eculizumab," the clinically successful anti-C5 antibody described in the prior art, with SEQ ID NOs: 2 and 4. But the opposite is true: the literature before March 15, 2007 consistently taught that "***eculizumab is***" the antibody of Thomas – an ***IgG4*** isotype antibody, having a different sequence from SEQ ID NOs: 2 and 4.[1] (Paper 22 ("POR"), 13-17.) Nothing in the art taught that an antibody with SEQ ID NOs: 2 and 4 – then an unknown, uncharacterized sequence – would have met the '149 patent's claimed requirement of binding C5. *See, e.g.*, *PersonalWeb Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 989, 993 (Fed. Cir. 2017).

[1] Unless otherwise noted, all emphasis is added, and internal citations and quotation marks are omitted.

A. The Literature Consistently Taught a POSA that "Eculizumab" Was the *IgG4*-Isotype Antibody of Thomas

Before March 15, 2007, the only plausible conclusion was that "eculizumab" was the IgG4 antibody of Thomas. As Amgen concedes, a POSA would have had the goal of "recreating [eculizumab] for use in … treating PNH, which clinical trials had repeatedly demonstrated to be successful." (AMG1081, ¶10; *id.* ¶55; ALXN2092, 35:9-38:19.) A POSA would have looked to the literature regarding "eculizumab" and its clinical properties, which Amgen relies on for that exact purpose. (*E.g.*, AMG1002, ¶¶12, 34-40.) That literature consistently pointed to Thomas for information on what "eculizumab is"; and Thomas in turn identified a humanized IgG4 antibody with potent anti-C5 and anti-hemolytic activity. (ALXN2022, ¶138.)

The '149 patent Examiner and this Board agreed that the clinical literature pointed to Thomas for the structure of "eculizumab." (ALXN2092, 78:1-80:7, 81:22-85:17, 87:3-93:19.) In issuing a rejection for the related '504 patent, the Examiner concluded that Hillmen (AMG1004) "refers to reference number 15 (Thomas) as disclosing more information about eculizumab," and "Thomas in turn

discloses that eculizumab is the humanized antibody h5G1.1."[2] (POR, 28-29; AMG1014, 557, 559.) And this Board determined that Hillmen and Hill "at least invoked a molecule having the IgG4 isotype taught in Thomas." (Paper 15, 25, 27.) This plain reading cannot be "patently false" (Reply, 3) when everyone but Amgen agrees.

Amgen contends Thomas does not say "eculizumab," and dismisses Thomas as "one of the earliest disclosures." (Reply, 11, 14.) But the literature consistently cited to Thomas ***for*** "eculizumab," including in March 2007. (*See, e.g.*, POR, 13-17, 26; ALXN2022, ¶¶120-123, 150; AMG1077, 76:10-19, 127:3-18, 136:8-18; ALXN2028, 31 & Ref. 6.) In contrast, Bowdish, Mueller, and Evans (from which Amgen pieces together SEQ ID NOs: 2 and 4) never mention "eculizumab," and were never cited for what "eculizumab is." (Section II.C *infra*.)

The art did not cite Thomas merely for generalized "methods of humanizing antibodies." (*Cf.* Reply, 14.) As Dr. Balthasar testified, the prior art cited Thomas for "***what*** eculizumab is." (ALXN2032, 128:20-129:10, 129:13-130:22; ALXN2022, ¶139.) For example, Hillmen 2006 states "***Eculizumab (Soliris,***

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[2] Alexion overcame the rejection after explaining that Hillmen and Thomas guided a POSA to a different sequence than SEQ ID NOs. 2 and 4. (AMG1014, 586-87, 591 ¶¶3-5.)

Alexion Pharmaceuticals) is a humanized monoclonal antibody directed against the terminal complement protein C5," and cites Thomas. (AMG1012, 1234.) The plain reading of that statement, like those in Hillmen, Hill, and Hill 2007, is that Thomas identifies ***what*** "eculizumab" is. (POR, 14-17.) Amgen concedes as much, admitting that the literature cited Thomas for "information about ***eculizumab's*** ability to bind C5." (AMG1081, ¶29; Reply, 14.)

Nor does Bell cite Thomas for "humanization" methods when it states that "[m]ethods for the preparation of h5G1.1-mAb" are described in Thomas. (AMG1081, ¶29; AMG1005, ¶[0052].) As Dr. Balthasar concedes, this sentence "provid[es] 'methods for the preparation of ***h5G1.1-mAb***,' which ***is how Bell referred to eculizumab***," and then cites to Thomas. (AMG1081, ¶77; ALXN2092, 70:4-71:17, 74:5-75:20; ALXN2022, ¶¶204-208).)

B. Tacken Would *Not* Have Changed a POSA's Understanding That "Eculizumab" Was an IgG4 Isotype Antibody

Despite the overwhelming evidence identifying "eculizumab" as an IgG4 antibody, Amgen clings to a ***single*** publication, Tacken (AMG1034), as allegedly teaching that "eculizumab is an IgG2/IgG4 antibody." (Reply, 3.) Amgen uses Tacken to connect (1) publications describing "eculizumab" as a successful PNH treatment (Hillmen, Hill, Bell) – which do not include any sequences, with (2) documents Amgen combines in hindsight to obtain SEQ ID NOs: 2 and 4

(Bowdish, Mueller, Evans) – which do not mention "eculizumab." (*See, e.g.*, AMG1081, ¶¶38, 56, 75-76.) Notably, Tacken does not cite any of the references from Amgen's Grounds.[3]

Tacken does not show that "eculizumab" was known as an IgG2/IgG4 isotype. A POSA would not have considered Tacken at all; and even if they had, the prior art "viewed ***as a whole***" identified "eculizumab" as an IgG4 antibody. *Impax Labs., Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018). Amgen's focus on Tacken, to the exclusion of the art as a whole, reveals improper hindsight. *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

A POSA motivated to recreate "eculizumab" for treating PNH would not have disregarded the clinical literature demonstrating its success and focused on one statement buried in Tacken – a publication concerning "anti-DC SIGN"

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[3] Because Amgen relies on Tacken to supply missing claim elements, but did not include Tacken in ***any*** of its five Grounds (POR, 23 n.3), Amgen's Grounds fail for that reason alone. *See, e.g.*, *PersonalWeb*, 848 F.3d at 989, 993 (vacating Board's obviousness determination where final written decision "did not adequately support its findings that the prior art [combination of the Petition] disclosed all elements of the challenged claims").

antibodies for vaccination strategies. *See Impax*, 893 F.3d at 1379-80 (discounting reference that, "as a whole," was "not about" and "barely mentioned" the claimed compound). None of the clinical literature cited Tacken for "eculizumab"; and a POSA would not have scoured the "materials and methods" sections of "basic research" articles that, like Tacken, do not mention "eculizumab" or C5-binding in their titles or abstracts, and do not discuss PNH at all. (*Cf.* AMG1081, ¶24; *see* ALXN2032, 72:23-73:2, 73:12-74:1, 74:18-21, 92:21-93:1, 108:17-109:10.) Dr. Balthasar only looked at Tacken because Amgen's counsel handed it to him. (ALXN2032, 64:23-65:7, 65:12-14.)

Even if a POSA had considered Tacken, it would not have changed their understanding that "eculizumab" was Thomas's IgG4 antibody. A POSA would not have disregarded the clinical publications about using "eculizumab" for treating PNH, and instead credited an isolated sentence buried in Tacken that mentioned "eculizamab [*sic*]" just once. Nor could a POSA have seen Tacken as the "culminat[ion]" of an "iterative development process" leading to "eculizumab" (*cf.* AMG1081, ¶19), when the literature ***after*** Tacken identified "eculizumab" as Thomas's IgG4 antibody. (POR, 25-26.)

Because Tacken cites to Thomas, the most reasonable reading (if Tacken were considered at all) would have been that (1) "eculizumab" was an ***IgG4*** antibody, as the literature consistently cited Thomas for "eculizumab"; (2)

Tacken's IgG2/IgG4 "isotype control" was a ***different*** "h5G1.1" antibody; and (3) Tacken conflated the broad terminology "5G1.1"/"h5G1.1" – which a POSA would have understood to typically refer to broad classes of antibodies, sometimes to "eculizumab," and sometimes to a specific mouse antibody (ALXN2032, 98:2-99:8, 159:1-10, 169:6-18, 202:24-203:14) – with the specific term "eculizumab."[4] (ALXN2022, ¶¶140-146; POR, 24-26.) The one unreasonable conclusion is that an isolated, ambiguous sentence in Tacken would have upended a POSA's understanding of "eculizumab" from the consistent teachings of the art.

Amgen's reading of Tacken is also not supported by non-prior art statements in the unrelated "'438 application" prosecution history.[5] These statements, which

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[4] A POSA would have also been confused by the "-a-" sub-stem in "eculizamab [*sic*]," suggesting a rat antibody. (ALXN2046, 27.)

[5] *Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286 (Fed. Cir. 2014) does not control. *Apple* found that claim scope may be disavowed by narrowing arguments made during prosecution of a ***related*** ex-U.S. application with the ***same specification*** and ***same claim language*** as a U.S. patent. *Id.* at 1311-1313. Here, claim construction is not in issue, the '438 application is unrelated to the '149 patent, and "mutated Fc receptor" (AMG1049, 838-39) appears nowhere in the '149 patent claims.

refer to ***2002*** (Reply, 13), could not have been based on Tacken, published in ***2005***. These statements cited only Mueller II (AMG1049, 838-39), which does not mention "eculizumab," and did not specifically identify any anti-C5 antibody. (ALXN2032, 98:15-99:8, 159:1-10, 241:23-242:12.)

Significantly, the "CAS Registry" noted by Dr. Balthasar (AMG1081, ¶¶9, 17, 20) would have only increased the confusion. The Registry disclosed an ***incorrect*** sequence for "eculizumab," and was not corrected until 2009. (Paper 2, 11-12, n.8; AMG1054, 237, 247-254, 292-293; ALXN2092, 93:20-95:4, 96:12-100:6.) Amgen fails to explain why a POSA looking to make "eculizumab" would have focused on Tacken (or Bowdish, Mueller, or Evans), rather than all of the "eculizumab" art, including the CAS Registry.

C. Nothing in the Prior Art Linked SEQ ID NOs: 2 and 4 to "Eculizumab"

Amgen's Grounds also fail because nothing in the prior art connected "eculizumab" (including its clinical properties) with SEQ ID NOs: 2 and 4. *See PersonalWeb*, 848 F.3d at 991 ("[A] finding of obviousness cannot be predicated on the mere identification in the prior art of individual components of claimed limitations."). A POSA would not have known of, and would not have been motivated to make, SEQ ID NOs: 2 and 4. (POR, 20-21, 33-48, 51-62, 64-66; Section V.A *infra*.) And nothing in the art taught that SEQ ID NOs: 2 and 4 was

"***eculizumab***" – the clinically successful antibody that blocks C5 cleavage and treats PNH. SEQ ID NOs: 2 and 4 would have been an unknown, uncharacterized antibody, with biological and clinical properties that could not be reasonably predicted. (POR, 20-21, 62-64; Section V.B *infra*.)

Nothing in Bowdish, Mueller, or Evans guided a POSA to connect "eculizumab" with SEQ ID NOs: 2 and 4. Bowdish, Mueller and Evans never mention "eculizumab." (ALXN2032, 102:10-16, 199:9-17; POR, 51, 56, 65.) Evans does not disclose ***any*** full-length humanized antibodies – only structurally-distinct fragments that never belonged to a full-length antibody. (ALXN2032, 163:5-15; POR, 43, 57.) Neither Bowdish nor Mueller were cited by the literature on "eculizumab" and its clinical properties. (ALXN2032, 139:8-140:5, 140:13-141:2, 141:11-19, 170:5-171:1, 195:22-196:4.) And, as Dr. Balthasar testified, the terminology "5G1.1" (used in Bowdish) and "h5G1.1" (used in Mueller) was ***not*** specific to "eculizumab" – it could refer to multiple antibodies with different sequences. (ALXN2032, 202:24-203:14.) For example, Dr. Balthasar admitted that the "h5G1.1"/isotype terminology used in Mueller could ***not*** have been used to determine a specific sequence. (ALXN2032, 241:23-242:12.)

Amgen uses improper hindsight when it disregards the literature ***actually*** concerning "eculizumab" and its clinical properties and relies on documents saying

nothing about "eculizumab." A POSA seeking to recreate "eculizumab" would not have discarded the literature's consistent teaching regarding what "eculizumab is," and turned to an isolated statement regarding "[c]onstruction of 5G1.1" in Bowdish – a patent application regarding peptide mimetics; or an isolated statement regarding an "h5G1.1" control antibody in Mueller – a patent application regarding anti-VCAM antibodies.

Tacken likewise did not connect "eculizumab" to SEQ ID NOs: 2 and 4. Tacken did not identify its IgG2/IgG4 "control" antibody as "eculizumab" (Section II.B *supra*), and nothing in Tacken provided the sequence of that antibody. Tacken does not cite Bowdish, Mueller or Evans. And if a POSA had looked at Thomas (cited for Tacken's control antibody) and Mueller II (cited for "a hybrid IgG2/IgG4 constant domain"), it would not have led them to SEQ ID NOs: 2 and 4, because (1) Thomas describes an IgG4 antibody with a different sequence from SEQ ID NOs: 2 and 4; (2) Thomas's variable region differs from SEQ ID NO: 4 at variable light chain amino acid 38; and (3) Mueller II's constant region is missing an amino acid present in SEQ ID NO: 2. (Section II.A *supra*; ALXN2022, ¶¶244, 246.) Amgen does not explain how a POSA would overlook these deficiencies to arrive at the claimed sequence.

III. AMGEN'S ANTICIPATION AND OBVIOUSNESS ARGUMENTS REGARDING HILLMEN AND HILL ARE MISTAKEN ON THE FACTS AND LAW

On Grounds 1-2, alleged anticipation over Hillmen or Hill, Amgen's Reply repeats the same arguments already rejected by the Board and introduces new legal theories with no basis in the facts. Nothing in Hillmen or Hill expressly or inherently disclosed SEQ ID NOs: 2 and 4 or its properties. (POR, 30-33; Paper 15, 23-27.)

The undisputed facts are fatal to Amgen's theory: (1) the name "eculizumab" alone would not have told a POSA the sequence of "eculizumab"; and (2) nothing within Hillmen or Hill disclosed or would have guided a POSA to SEQ ID NOs: 2 and 4. (POR, 32-33; ALXN2032, 139:8-140:5, 140:13-141:19; ALXN2092, 43:11-44:24, 45:19-25.) Rather, Hillmen and Hill's citations to Thomas for what "eculizumab is" would have directed a POSA to an ***IgG4*** antibody with a different sequence. (Section II.A *supra*.)

Grounds 1-2 are also wrong on the law. Amgen conflates Hillmen and Hill – publications reporting clinical trial results – with the underlying clinical trials. (Reply, 1, 4-5.) But only the ***publication*** is available as prior art.[6] 35 U.S.C.

[6] Amgen does not contend that clinical supplies of eculizumab were publicly available. (ALXN2092, 149:4-150:5, 152:4-17.)

§ 311(b). While we know today that the clinically-tested antibody actually had the claimed sequence, nothing within the "four corners" of ***Hillmen or Hill*** disclosed that to a POSA. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). As in *Endo* and *Bayer*, Hillmen's and Hill's mere use of the name "eculizumab" was not a disclosure of its chemical composition, *i.e.*, sequence. *See Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378-79, 1381-83 (Fed. Cir. 2018) (publication of clinical study using a "castor oil" vehicle did not inherently disclose the vehicle's chemical composition); *Bayer CropScience LP v. Syngenta Ltd.*, IPR2017-01332, Paper 15 at 3-6 (Apr. 2, 2018) (publications disclosing compound name "KIH-485" did not inherently disclose the compound's chemical composition).[7]

Amgen's own case law confirms that an inherently disclosed element must ***necessarily*** flow from the ***disclosure*** within "the single anticipating reference."

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[7] *In re Crish,* 393 F.3d 1253 (Fed. Cir. 2004) remains distinguishable. (Paper 15, 23-24.) As the Board found, the anticipatory publication in *Crish* provided sufficient information (size and location of a claimed promoter region) for a POSA to obtain the claimed sequence using conventional techniques. (*Id.* (quoting *Crish*, 393 F.3d at 1257-59.) Hillmen, in contrast, did not "'specifically identify' … eculizumab" as having SEQ ID NOs: 2 and 4. (Paper 15, 23-24.)

Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1375-78 (Fed. Cir. 2003) (disclosed administration of loratadine necessarily produced the claimed metabolite); *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1372-73 (Fed. Cir. 2007) (disclosed manufacturing process necessarily produced the claimed "separating layer"); *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1348 (Fed. Cir. 1999) (disclosed compositions necessarily produced the claimed "sufficient aeration"). Hillmen and Hill, in contrast, did not disclose any process that would have necessarily produced SEQ ID NOs: 2 and 4. *See Glaxo Grp. Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348-49 (Fed. Cir. 2004).

Amgen erroneously uses documents ***outside*** Hillmen and Hill (Bowdish, Mueller, Evans, and Tacken) to supply SEQ ID NOs: 2 and 4. (Reply, 6; AMG1081, ¶38; ALXN2092, 57:25-58:6, 60:21-61:12, 64:8-12, 67:21-69:7.) In doing so, Amgen "conflates the principles of enablement and anticipation," and "makes the impermissible leap from enablement to disclosure." *Galderma Labs., L.P. v. Teva Pharms. USA, Inc.*, No. 2019-2396, 2020 WL 467933, at *5-6 (Fed. Cir. Jan. 29, 2020). The claimed sequence does not "necessarily result" from practicing Hillmen or Hill (*see id.* at *6-7), because the name "eculizumab" does not disclose a sequence, and Hillmen and Hill pointed to Thomas's IgG4 antibody as "eculizumab."

IV. AMGEN FAILS TO SHOW HOW CLAIM 1 WAS ANTICIPATED BY BOWDISH

Amgen still fails to show that Bowdish disclosed all elements of claim 1, either expressly, or inherently. Critically, Bowdish did not expressly or inherently disclose SEQ ID NOs: 2 and 4. Amgen recreates that sequence in hindsight by combining Bowdish with humanized "fragment" sequences from Evans. (Reply, 8-10; AMG1081, ¶46.) But Amgen does not dispute that (1) Bowdish references the ***'283 application***, not Evans, for "[c]onstruction of 5G1.1," and (2) the '283 application is not of record in this proceeding. (POR, 33-34.)

Even if Bowdish had referenced Evans – which it did not – nothing in Bowdish clearly and unambiguously disclosed SEQ ID NOs: 2 and 4. (POR, 34-48.) Amgen misstates the scope of Bowdish's incorporation of Evans, which is limited to "[c]onstruction of 5G1.1" – a mouse antibody – ***not*** Evans in its entirety. (POR, 34, 37-44.)[8] Because Amgen's anticipation argument depends on

[8] *Paice LLC v. Ford Motor Co.*, 881 F.3d 894 (Fed. Cir. 2018) does not control. In *Paice*, the court found that an incorporation by reference was not limited by the sentence ***following*** it, which said nothing about incorporation. *Id.* at 907-08. In Bowdish, however, the incorporation by reference of the '283 application expressly pertains to "[c]onstruction of 5G1.1." (POR, 42-44.)

humanized fragments from Evans "Example 11" that were not incorporated by Bowdish (Reply, 8-9), it fails for that reason alone.

And even if Bowdish had incorporated Evans in its entirety, it still would not have ***necessarily*** disclosed SEQ ID NOs: 2 and 4. (POR, 44-48.) By referring to "[c]onstruction of 5G1.1," Bowdish would have directed a POSA to look at Evans's ***mouse*** "5G1.1" antibody, not humanized fragments. (POR, 18-20, 57; ALXN2022, ¶¶126-127, 162-163, 189-190.) In Bowdish, "5G1.1" refers to a "whole," "full" antibody; and Evans's only full-length antibody is the ***mouse*** antibody "5G1.1." (AMG1006, ¶¶[0191]-[0193]; ALXN2032, 169:13-18.) Bowdish could not have referred to humanized "fragments," which a POSA understood to be structurally distinct from, and never part of, a full-length humanized antibody. (ALXN2032, 163:5-15, 228:2-16; ALXN2022, ¶126.) Nor could "[c]onstruction of 5G1.1" refer to a full-length humanized antibody, because, as Dr. Balthasar admits, nothing in Evans disclosed ***any*** full-length humanized antibody. (*Id.*)

Seeing the extensive mismatch between Bowdish's TPO-mimetic sequences and Evans's "5G1.1" mouse antibody, a POSA could not have envisaged SEQ ID NOs: 2 and 4. (POR, 39-43, 60-62; ALXN2092, 137:25-141:23.) Amgen's new argument that a POSA would have nonetheless combined Bowdish with Evans's ***mouse*** antibody defies common sense. (*Cf.* AMG1081, ¶47.) A POSA reading

Bowdish would not have put on blinders and selectively combined Bowdish with Evans's mouse antibody, while ignoring the extensive sequence mismatch. (ALXN2022, ¶¶ 190-191, 197, 214-215; POR, 39-43.) Evans also provided multiple CDR definitions – and a POSA could not have determined the specific sequence Bowdish replaced with its TPO-mimetic peptide. (ALXN2022, ¶195; AMG1077, 242:17-243:19, 244:18-22, 249:13-17, 250:18-23.)

Amgen also still fails to show any disclosure in Bowdish of "an antibody that binds C5" as recited in claim 1. (POR, 48-50.) It is undisputed that Bowdish does not disclose any C5-binding data for its TPO-mimetic compound or the starter scaffold; and Evans did not disclose ***any*** full-length humanized antibodies. (*Id.*) And the term "5G1.1" alone, without supporting data, would not have indicated to a POSA that Bowdish's "scaffold" bound to C5. (ALXN2032, 98:2-99:8, 202:24-203:14; AMG1077, 103:16-105:16.)

V. AMGEN FAILS TO SHOW HOW CLAIM 1 WOULD HAVE BEEN OBVIOUS TO A POSA

A. The Claimed Sequence Would *Not* Have Been Obvious in View of Bell, Bowdish and Evans, or Evans and Mueller

A POSA motivated to recreate "eculizumab" would not have turned to Bowdish (Ground 4) or Mueller (Ground 5) – documents with no mention of "eculizumab" or PNH. Nor would a POSA have combined sequences from Evans

and Bowdish or Mueller in the selective way that Amgen does to arrive at SEQ ID NOs: 2 and 4.

Bowdish: Without hindsight, a POSA seeking to recreate "eculizumab" would not have leapt from Bell to Bowdish. (Reply, 17-18; AMG1081, ¶¶55-59.) Bell and Bowdish do not cite one another. (ALXN2032, 170:5-10, 195:22-196:4.) Dr. Balthasar concedes that Bell and other clinical literature gave a POSA a "strong motivation to make and use eculizumab to treat PNH" (AMG1081, ¶55) – but that literature uniformly pointed to ***Thomas*** for "eculizumab." (*See* Section II.A *supra*.) Bell in particular cited Thomas for "[m]ethods for the preparation of [eculizumab]." (AMG1005, ¶[0052]; AMG1081, ¶77; ALXN2092, 70:4-71:17, 74:5-75:20.) A POSA would not have disregarded Bell's citation to Thomas's IgG4 antibody for "eculizumab," and instead turned to Bowdish – a document regarding "peptide mimetic" compounds having nothing to do with anti-C5 activity or treating PNH. (POR, 54-56.)

Nor would a POSA have connected Bell and Bowdish in view of their incorporations by reference of Evans or the '283 application, respectively. (*Cf.* AMG1081, ¶¶56, 63.) Bell incorporates both Evans and Thomas when it discusses "***eculizumab***." (AMG1005, ¶[0052]; POR, 53-54.) Bowdish, in contrast, simply refers to the '283 application for "[c]onstruction of ***5G1.1***" (AMG1006, ¶[0191]) – a term that Dr. Balthasar admitted can refer to many different antibodies, and in the

context of Evans, refers to a mouse antibody. (ALXN2032, 98:2-99:8, 169:6-18, 202:24-203:14; AMG1077, 103:16-105:16, POR, 12-13, 18-20, 57.)

The term "5G1.1" in one example of Bowdish would not have connected Bowdish to Bell. (*Cf.* AMG1081, ¶¶58-59.) As Dr. Balthasar testified, "5G1.1" does ***not*** refer specifically to "eculizumab" unless a reference expressly says so (ALXN2032, 98:2-99:8, 199:9-12, 202:24-203:14) – and Bowdish does not. A POSA seeking to recreate "eculizumab" for treating PNH would not have searched all documents with "5G1.1" buried in the text, and disregarded the clinical literature identifying "eculizumab" as Thomas's IgG4 antibody. (Section II.A *supra*.)

A POSA would not have connected Bell and Bowdish based on "knowledge of eculizumab's structure." (AMG1081, ¶¶56, 60-62.) A POSA understood "eculizumab" to be ***IgG4***, not IgG2/IgG4. (*See* Sections II.A-B *supra*.) And even if, hypothetically, "eculizumab" were thought to be IgG2/IgG4, a POSA would not have turned to Bowdish. Bowdish is silent on isotype (ALXN2032, 212:22-213:2, 214:2-7); and a POSA seeking to make "eculizumab" would have had no reason to pick up Bowdish and undertake the sequence analyses that Dr. Balthasar proposes to determine the isotype of its "5G1.1-TPO" compound. (POR, 59; *cf.* AMG1081,

¶¶60-61.) A POSA would not have gone through such a complicated ordeal rather than follow the clear teaching of the clinical literature.[9]

Even if a POSA had considered Bell, Bowdish and Evans together, they would not have disclosed the claimed sequence. Nothing in Bell disclosed SEQ ID NOs: 2 and 4 (ALXN2032, 146:17-25, 194:11-24); and no combination of Bowdish and Evans would have led a POSA without hindsight to that sequence. (Section IV *supra*.)

Mueller: A POSA motivated to make "eculizumab" to treat PNH would not have turned to Mueller, concerning anti-VCAM antibodies for blocking transplant rejection. (ALXN2032, 232:6-16; POR, 63-65.) Mueller never mentions "eculizumab," and referred to "h5G1.1" only in describing "control" antibodies for experiments unrelated to anti-C5 activity or PNH. (ALXN2032, 102:10-16, 235:11-19; POR, 64-65.) As Dr. Balthasar testified, nothing in Mueller allowed a POSA to identify either of the two "h5G1.1" control antibodies as "eculizumab";

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[9] Nor may Amgen attempt to fill gaps by combining Bowdish with Mueller (AMG1008) and Rother (AMG1032) – documents that are outside Ground 4 and have no connection to Bowdish or "eculizumab." (AMG1081, ¶¶60-61; ALXN2092, 100:14-101:19, 106:14-107:2, 107:23-108:17, 111:7-112:24, 113:20-114:20, 114:25-115:22, 116:18-118:18; Section II.B *supra*.)

Mueller's "h5G1.1"/isotype terminology would not have indicated any ***specific*** sequence; and Mueller identified only its ***IgG4*** "h5G1.1" control antibody as "anti-C5." (ALXN2032, 102:10-16; 234:9-21, 235:6-19, 237:25-238:5, 238:13-19, 241:23-243:14; AMG1077, 114:10-115:11.)

Amgen now also attempts to supplant Mueller (AMG1008) with Tacken and Mueller II (AMG1031) – documents that should be disregarded as outside the asserted combinations of Amgen's Grounds. (Section II.B *supra*; *cf.* AMG1081, ¶76.) Tacken would not have changed a POSA's understanding that the clinical literature consistently identified "eculizumab" as Thomas's ***IgG4*** antibody. (*See* Section II.B *supra*.) And even if, hypothetically, a POSA had combined sequences from Thomas and Mueller II, it could not have led to SEQ ID NOs: 2 and 4. (*See* Section II.C *supra*.)

Amgen still fails to explain why a POSA would have combined sequences from Mueller and Evans in exactly the way Amgen does in hindsight to obtain SEQ ID NOs: 2 and 4. Mueller provides ***no*** anti-C5 antibody sequences (ALXN2032, 232:17-21); and as the Board correctly found, Mueller and Evans provide no guidance on whether, or how, sequences from one document should be combined with the other. (Paper 15, 52-54; POR, 65-66.)

B. A POSA Would Not Have Had Any Motivation to Make, or Reasonable Expectation of Success With, SEQ ID NOs: 2 and 4

Even if SEQ ID NOs: 2 and 4 were known to a POSA – which they were not – nothing would have told a POSA that they comprised "***eculizumab***," and thus had the biological and clinical properties attributed to "eculizumab." (Section II.C *supra*.) A POSA would not have reasonably expected success with SEQ ID NOs: 2 and 4 – which to them was an unknown, uncharacterized antibody that had never been tested for anti-C5 activity or safety and efficacy. A POSA also would not have been motivated to make and study a "new, untested antibody" with a different sequence and structure from the "eculizumab" proven to treat PNH. (Reply, 17.)

OSI Pharms., LLC v. Apotex Inc., 939 F.3d 1375 (Fed. Cir. 2019) controls, because Amgen's "asserted references contained no data at all – no 'clinical (human) data or preclinical (animal) data,' nor any 'in vitro (test tube) data'" regarding the anti-C5 activity, safety or efficacy of SEQ ID NOs: 2 and 4. (Reply, 19 (quoting *OSI*, 939 F.3d at 1383).) Bowdish and Mueller provided no such data. (ALXN2032, 175:19-176:6, 188:18-23, 235:11-19, 247:13-248:6; POR, 49, 56-57, 62-63.) Neither did Bell (Reply, 19) – which does not disclose SEQ ID NOs: 2 and 4 or IgG2/IgG4 constant regions (ALXN2032, 146:17-25, 151:3-12, 160:7-9, 194:11-24; POR, 52), and cited Thomas for "[m]ethods for preparing [eculizumab]" (*see* Section II.A *supra*). Neither did Evans (Reply, 19-20), which

did not disclose ***any*** full-length humanized antibodies or IgG2/IgG4 constant regions, let alone SEQ ID NOs: 2 and 4. (ALXN2032, 163:5-15, 163:25-164:8; POR, 63.)

Without data for SEQ ID NOs: 2 and 4, a POSA would not have reasonably expected it to "bind[] C5" as claimed. (POR, 34, 48-50, 51, 62-65; ALXN2022, ¶¶135, 171, 200-201, 221-229, 248-252.) Even small sequence changes could impact critical antibody characteristics including binding affinity, specificity, and immunogenicity. (ALXN2022, ¶¶104-117; POR, 9-10.) "Fine specificity" (binding to a certain location) was especially critical, because an effective anti-C5 antibody would need to block cleavage into components C5a and C5b. (ALXN2022, ¶¶224-227; AMG1039, 840; AMG1023, 1398-99; ALXN2092, 169:3-170:7.) Amgen provides no data showing that a POSA could have reasonably expected SEQ ID NOs: 2 and 4 to have the same anti-C5 properties as "eculizumab."

Amgen also provides no data that would have given a POSA a reasonable expectation that SEQ ID NOs: 2 and 4, or any IgG2/IgG4 antibody, would be safe. (ALXN2022, ¶¶77, 86, 134-135, 158, 170-171, 218.) Dr. Balthasar contends there were "extensive disclosures in the prior art … regarding antibodies with hybrid IgG2/IgG4 constant regions" (AMG1081, ¶79 (citing Mueller, Mueller II, and Tacken)) – but ***none*** of those documents clinically tested safety and

immunogenicity of any IgG2/IgG4 antibodies. Any purported "advantages" of IgG2/IgG4 constant regions (Reply, 12) were speculative. (ALXN2022, ¶135.)

Amgen's rebuttal on "reasonable expectation of success" is meritless. (Reply, 16-17; AMG1081, ¶¶67-71.) A POSA understood that constant region changes could critically (and unpredictably) impact binding, specificity, and immunogenicity – and this overarching principle would apply equally to IgG2/IgG4 antibodies. (ALXN2022, ¶¶104-117; AMG1077, 200:13-202:11, 203:20-205:7, 208:10-209:5.) That few prior art references reported on switching to "IgG2/IgG4" isotypes highlights a POSA's uncertainty in treating humans with a little-studied, clinically untested, non-natural isotype. (ALXN2022, ¶¶81-82, 86; ALXN2092, 172:6-173:2.)

Dr. Balthasar points to Tacken and Mueller II as evidence that "switching to an IgG2/IgG4 isotype" caused "no significant alteration" in antibody function. (AMG1081, ¶69.) But Tacken and Mueller II did not study the impact of isotype switching on anti-C5 activity, "fine specificity" or blocking cleavage – critical factors for an anti-C5 antibody. (ALXN2032, 92:21-93:1; ALXN2092, 156:17-164:7, 165:10-166:21; ALXN2022, ¶¶224-227.) Dr. Balthasar also cites Bell, Evans and Thomas to assert that 5G1.1 antibodies retain their function when changing isotype. (AMG1081, ¶¶67, 70.) But neither Evans nor Thomas studied any IgG2/IgG4 antibodies (ALXN2032, 90:8-22, 97:7-21, 163:25-164:8;

ALXN2092, 166:22-170:25); and Bell reported clinical data only for "eculizumab," identified as Thomas's IgG4 antibody (ALXN2092, 152:22-154:16; Section II.A *supra*).

C. Amgen Fails to Rebut the Strong Evidence of Objective Indicia of Non-Obviousness

Amgen cannot dispute the objective indicia of nonobviousness. On commercial success, nexus is presumed because the claims cover SOLIRIS®, and SOLIRIS® has significant sales in the relevant market. (ALXN2093, 69:4-72:4; ALXN2056, ¶¶1-9, App'x A; POR, 67-68.) SOLIRIS® sales cannot be due to elements in the prior art (AMG1088, ¶¶15, 24-27) because a POSA did ***not*** know of an antibody having SEQ ID NOs: 2 and 4 and its anti-C5 activity. (Section II.C *supra*.) Nor can SOLIRIS® sales be attributed to an "Orphan Drug Exclusivity" period that expired in 2014 (AMG1088, ¶¶37-41), rather than the remarkable clinical properties of the claimed antibody. (ALXN2022, ¶¶255-259.) SOLIRIS® had substantial sales, despite its very small patient population, because of the ***value*** it brought in successfully treating a rare condition that lacked adequate treatment. (ALXN2093, 131:25-133:24, 134:12-135:1, 135:11-136:24, 144:22-146:17, 147:16-148:18, 149:4-21, 151:21-153:5; AMG1092, 2-3, 5; AMG1095, 1; AMG1096, 1.)

Amgen's "blocking patent" theory is wrong on the facts and the law. As Mr. Hofmann conceded, the existence of an earlier patent is not *per se* evidence against commercial success. (ALXN2093, 49:21-50:11, 50:25-51:5.) Mr. Hofmann failed to consider whether another company might have been motivated to, *e.g.*, develop the claimed invention before March 12, 2002 (the start of the alleged "disincentive"); engage in research and development under the § 271(e)(1) safe harbor; or license innovations beyond Evans to Alexion. (ALXN2093, 51:23-52:5, 56:4-57:18, 117:10-12.) Amgen is presently developing its eculizumab product in the U.S. within the term of both Evans and the '149 patent. (ALXN2093, 11:25-13:1, 63:24-64:3, 64:19-65:16, 67:18-68:9; ALXN2096.) Amgen's theory that companies would have avoided developing products covered by Alexion's patents is belied by Amgen and others attempting exactly that.

Amgen also fails to rebut the evidence that the claimed invention fulfilled a long-felt but unmet need and received significant industry praise. (ALXN2092, 144:8-145:18, 147:13-148:5.) Amgen's position that PNH was suitably treated by frequent "blood transfusions" is not credible. (*Cf.* Reply, 23-24.) SOLIRIS® was a groundbreaking, life-saving therapy that substantially improved quality of life for PNH patients – including reducing frequent blood transfusions that were previously a necessary measure. (ALXN2022, ¶¶260-269.)

Amgen also cannot dispute that it, and others, are currently developing purported "biosimilar" products that ***exactly*** copy SEQ ID NOs: 2 and 4. (ALXN2092, 143:4-144:6.) They are doing so, rather than designing their own antibodies, because SEQ ID NOs: 2 and 4 is the anti-C5 antibody known to be safe and effective for multiple complement-mediated conditions. (POR, 68.)

VI. CONCLUSION

Alexion respectfully submits that the Board should confirm the patentability of claim 1.

Respectfully submitted,

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing **PATENT OWNER'S SURREPLY TO PETITIONER'S REPLY and EXHIBITS 2092-2096** were served via electronic mail April 27, 2020, in their entirety on the following:

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CERTIFICATION OF WORD COUNT

The undersigned hereby certifies that the portions of the above-captioned **PATENT OWNER'S SURREPLY TO PETITIONER'S REPLY** specified in 37 C.F.R. § 42.24 has 5,590 words, in compliance with the 5,600 word limit set forth in 37 C.F.R. § 42.24. This word count was prepared using Microsoft Word.

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COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https://www.coronavirus.gov.
Get the latest research information from NIH: https://www.nih.gov/coronavirus.

A Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Participants With PNH (DAHLIA)

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

ClinicalTrials.gov Identifier: NCT03818607

Recruitment Status : Recruiting
First Posted : January 28, 2019
Last Update Posted : April 17, 2020

See Contacts and Locations

Sponsor:
Amgen

Information provided by (Responsible Party):
Amgen

ALXN2096
IPR2019-00741
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Study Description

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Brief Summary:

This is a randomized, double-blind, active-controlled phase 3 study of ABP 959 in participants with paroxysmal nocturnal hemoglobinuria.

Condition or disease	Intervention/treatment	Phase
Paroxysmal Nocturnal Hemoglobinuria	Drug: ABP 959 Drug: Eculizumab	Phase 3

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	40 participants
Allocation:	Randomized
Intervention Model:	Crossover Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	double-blind
Primary Purpose:	Treatment
Official Title:	A Randomized, Double-Blind, Active-Controlled Phase 3 Study Evaluating the Efficacy and Safety of ABP 959 Compared With Eculizumab in Adult Subjects With Paroxysmal Nocturnal Hemoglobinuria (PNH)
Actual Study Start Date :	April 24, 2019
Estimated Primary Completion Date :	February 28, 2021
Estimated Study Completion Date :	August 29, 2021

Resource links provided by the National Library of Medicine NIH NLM

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Genetics Home Reference related topics:

Paroxysmal nocturnal hemoglobinuria

Drug Information available for: Eculizumab

Genetic and Rare Diseases Information Center resources:

Paroxysmal Nocturnal Hemoglobinuria Myelodysplastic Syndromes

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
T (ABP 959) / R (eculizumab) ABP 959 for 52 weeks in Period 1 followed by eculizumab for 26 weeks in Period 2	Drug: ABP 959 intravenous infusion Other Name: Treatment T Drug: Eculizumab intravenous infusion Other Names: • Soliris • Treatment R
R (eculizumab) / T (ABP 959) Eculizumab for 52 weeks in Period 1 followed by ABP 959 for 26 weeks in Period 2	Drug: ABP 959 intravenous infusion Other Name: Treatment T Drug: Eculizumab intravenous infusion Other Names: • Soliris • Treatment R

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Outcome Measures

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Primary Outcome Measures :

1. Hemolysis as measured by Lactate dehydrogenas (LDH) (Parallel Comparison) [Time Frame: 12 months]
2. Hemolysis as measured by LDH (Crossover Comparison) [Time Frame: 18 months]

Secondary Outcome Measures :

1. Total hemolytic complement (Total Complement) [Time Frame: 18 months]
2. Total hemoglobin [Time Frame: 18 months]
3. Serum-free hemoglobin [Time Frame: 18 months]
4. Haptoglobin [Time Frame: 18 months]
5. Bilirubin [Time Frame: 18 months]
6. Degree of hemoglobinuria [Time Frame: 18 months]
7. Type III erythrocytes [Time Frame: 18 months]
8. Crossover comparison of hemolysis as measured by LDH [Time Frame: 18 months]
9. Lactate dehydrogenase-time profile [Time Frame: 18 months]
10. Incidence of red blood cell transfusion [Time Frame: 18 months]
11. Pharmacokinetic area under the curve (AUC) of ABP 959 [Time Frame: 18 months]
12. Pharmacokinetic area under the curve (AUC) of eculizumab [Time Frame: 18 months]

Eligibility Criteria

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Information from the National Library of Medicine NIH NLM

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

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

Criteria

Inclusion Criteria:

- Men and women ≥ 18 years of age.
- Historical diagnosis of PNH.
- Administration of eculizumab for ≥ 6 months and currently receiving 900 mg of eculizumab.
- Hemoglobin ≥ 9.0 g/dL for at least 6 weeks before randomization.
- Lactate dehydrogenase < 1.5 × the upper limit of normal at screening.
- Platelet count ≥ 50 × 10^9/L.
- Absolute neutrophil count (ANC) > 0.5 x 10^9/L (500/µL).
- Participants must be vaccinated against Neisseria meningitidis.
- Participants must sign an IRB/IEC-approved ICF before participation in any procedures.

Exclusion Criteria:

- Known or suspected hereditary complement deficiency.
- Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure [New York Heart Association ≥ Class III], serious uncontrolled cardiac arrhythmia), peripheral vascular disease, cerebrovascular accident, or transient ischemic attack in the previous 6 months.
- Evidence of acute thrombosis (liver Doppler ultrasound of hepatic and portal veins).
- Known to be positive for human immunodeficiency virus.
- Woman who is pregnant or breastfeeding.

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- Participant is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s), or participant is receiving other investigational agent(s).
- Participant has known sensitivity to any of the products to be administered during the study, including mammalian cell-derived drug products.
- History of meningococcal infection.
- Presence or suspicion of active bacterial infection, or recurrent bacterial infection.
- History of bone marrow transplantation.
- Red blood cell transfusion required within 12 weeks before randomization.
- Participant experienced ≥ 2 breakthrough events, (ie, signs and symptoms of intravascular hemolysis, that require dose and/or schedule adjustments of eculizumab) in the previous 12 months before screening.

Contacts and Locations

Go to

Information from the National Library of Medicine NIH NLM

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

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT03818607***

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Sponsors and Collaborators

Amgen

Investigators

Study Director: MD Amgen

More Information

Go to

Additional Information:

AmgenTrials clinical trials website AmgenTrials clinical trials website

Responsible Party: Amgen

ClinicalTrials.gov Identifier: NCT03818607 History of Changes
Other Study ID Numbers: 20150168

First Posted: January 28, 2019 Key Record Dates
Last Update Posted: April 17, 2020
Last Verified: April 2020

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: Yes

Plan Description: De-identified individual patient data for variables necessary to address the specific research question in an approved data sharing request

Supporting Materials: Study Protocol
Statistical Analysis Plan (SAP)
Informed Consent Form (ICF)
Clinical Study Report (CSR)

Time Frame: Data sharing requests relating to this study will be considered beginning 18 months after the study has ended and either 1) the product and indication have been granted marketing authorization in both the US and Europe or 2) clinical development for the product and/or indication discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for this study.

Access Criteria: Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. Requests are reviewed by a committee of internal advisors. If not approved, a Data Sharing Independent Review Panel will arbitrate and make the final decision. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in

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analysis specifications. Further details are available at the link below.

URL: https://www.amgen.com/datasharing

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

Keywords provided by Amgen:
- Marchiafava-Micheli Syndrome
- Paroxysmal Cold Hemoglobinuria

Additional relevant MeSH terms:

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

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Page 952



Deposition of:

Ivan T. Hofmann

March 12, 2020

In the Matter of:

Amgen vs. Alexion

Veritext Legal Solutions
800-734-5292 | calendar-dmv@veritext.com |

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN, INC.
Petitioner

v.

ALEXION PHARMACEUTICALS, INC.
Patent Owner
U.S. Patent No. 9,725,504
U.S. Patent No. 9,732,149
U.S. Patent No. 9,718,880

IPR2019-00739
IPR2019-00740
IPR2019-00741

Video Deposition of IVAN T. HOFMANN, taken at the Law Offices of Sterne, Kessler, Goldstein & Fox, P.L.L.C., 1100 New York Avenue NW, Washington, DC, beginning at 9:04 a.m., before Ryan K. Black, a Registered Professional Reporter, Certified Livenote Reporter and Notary Public in and for the District of Columbia.

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I N D E X

TESTIMONY OF: IVAN T. HOFMANN PAGE

By Mr. Diamond.....4

E X H I B I T S

PREVIOUSLY MARKED EXHIBITS

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THE VIDEOGRAPHER: Good morning. We are going on the record at 9:04 a.m. on March 12th, 2020. Please note that the microphones are sensitive and may pick up whispering, private conversations and cellular interference. Please turn off all cell phones, or place them away from the microphones, as they can interfere with the deposition audio. Audio and video recording will continue to take place unless all parties agree to go off the record.

This is Media Unit 1 of the video-recorded deposition of Mr. Ivan Hofmann, taken in the matter of Amgen, Inc., Petitioner, versus Alexion Pharmaceuticals, Inc., Patent Owner, Case Number IPR2019-00741, filed in the United States Patent and Trademark Office before the Patent and Trial Appeal Board.

This deposition is being held at the Law Office of Sterne Kessler Goldstein & Fox PLLC, located at 1100 New York Avenue Northwest, Washington, DC.

My name is Solomon Francis, from the firm of Veritext Legal Solutions, and I'm the videographer. The court reporter is Ryan Black, with Veritext Legal Solutions.

At this time will counsel present please state their appearances and affiliations for the record?

MR. DIAMOND: This is Evan Diamond, of King & Spalding, on behalf of the patent owner Alexion.

DR. STERLING: Deborah Sterling, from Sterne Kessler Goldstein & Fox, on behalf of petitioner Amgen. I'm joined by David Holman, also from Sterne Kessler Goldstein & Fox, on behalf of petitioner Amgen.

THE VIDEOGRAPHER: At this time will the court reporter please swear in the witness and we can proceed?

* * *

Whereupon --

IVAN HOFMANN,

called to testify, having been first duly sworn or affirmed, was examined and testified as follows:

EXAMINATION

BY MR. DIAMOND:

Q. Good morning, Mr. Hofmann.

A. Good morning.

DR. STERLING: Excuse me, Evan, I

don't mean to interrupt, --

MR. DIAMOND: Oh.

DR. STERLING: -- this is for all three proceedings, so we should clarify that on the record.

MR. DIAMOND: Yeah. Yes. To -- to be clear, this deposition is for all three proceedings today.

DR. STERLING: Thank you.

BY MR. DIAMOND:

Q. Good morning, Mr. Hofmann, again.

A. Good morning.

Q. A little restart here.

Would you -- would you please tell us your full name for the record?

A. Yeah. It's Ivan T. Hofmann.

Q. And that's H-o-f-m-a-n-n?

A. It is.

Q. Okay. Where do you live?

A. My -- my personal residence?

Q. Sure.

A. 301 Serendipity Lane, Cranberry Township, Pennsylvania 16066.

Q. And where do you currently work?

A. I work for Gleason.

Q. Mm-hmm. What's Gleason?

A. Gleason is a consulting firm that focuses on economics, finance and accounting, and I'm the leader of the intellectual property practice.

Q. Okay. You've -- you've -- you've taken a lot of depositions, right?

A. I haven't taken any --

Q. Or --

A. -- but I've -- I've given --

Q. Let me -- let me -- let me rephrase that.

You've -- you've been a participant as a -- as a -- as a deponent in many depositions, right?

A. I have been deposed --

Q. Yeah.

A. -- many times, --

Q. Yeah.

A. -- yes.

Q. And -- and most of that's been in your capacity serving as an expert witness in pharmaceutical patent cases, right?

A. Correct.

Q. All right. So I know you know the

deal here. Let me ask you, have -- have some of those cases been before the Patent Trial and Appeal Board, like this one here?

A. They -- they have. And -- and -- and they -- they -- they're not limited to pharmaceutical patent cases, but other intellectual property issues and even just other general commercial litigation-type matters. But, yes, I've had a -- I've had several before the PTAB.

Q. Yeah. And a -- and a -- and a lot of those cases have been pharmaceutical patent cases, right?

A. They have, --

Q. Okay.

A. -- yes.

Q. So let me just give you some quick ground rules. You know, I -- I'll be asking you questions, and -- and you'll be giving me answers. You understand that, right?

A. I do.

Q. Okay. And you have the court reporter here taking a record of what we say, and we've got the videographer recording.

You understand that, right?

A. I do.

Q. We'll need verbal answers, so, you know, words, no head-nods, no mm-hmm.

You understand that, right?

A. I'll do my best.

Q. Okay. And if I -- if I tell you that you're not giving a verbal answer, you'll -- you'll un -- you'll understand and try to give me a verbal answer, right?

A. Of course.

Q. Okay. Great.

Now, your counsel may object at certain points during the deposition. That's just for the record, okay? You understand that you're to answer my questions unless your counsel's instructing you not to answer, right?

A. I do understand that.

Q. Okay. Now, if you don't understand any of my questions today or you need me to clarify, would -- would you please let me know?

A. I will do my best.

Q. Okay. If you -- if you answer, I'll understand that you understood the question. Is that fair?

A. I understand that understanding.

Q. Yeah. Great.

And you understand you took an oath to tell the truth today, right?

A. Of course.

Q. Yeah.

And you submitted three declarations in this proceeding, right?

A. In these proceedings.

Q. These -- these three proceedings, right?

A. Correct.

Q. And you understand that those were submitted under penalty of perjury, as well, right?

A. I do understand that.

Q. All right. And is there any reason you can't give me true and accurate testimony today?

A. No, sir.

Q. All right. Now, if you need a break at any point, please let me know. Okay?

Okay?

A. I will do so.

Q. Okay. But -- but if a question is pending, I'll ask that you answer the question

before we take a break. Is that fair?

A. Sure.

Q. Great.

So the -- we just were talking about these -- these three proceedings. What's your understanding of what these three proceedings are?

DR. STERLING: Objection; form.

THE WITNESS: You know, my understanding is that they relate to three challenges under Inter Partes Review with respect to three patents that Alexion has associated with the product Soliris.

BY MR. DIAMOND:

Q. Mm-hmm.

A. And they're challenging the validity of the patents that -- that Alexion claims cover the Soliris product.

Q. When you say they're -- "they're challenging the validity of the patents that Alexion covers [sic] the Soliris product," the -- the they is Amgen?

A. Yeah. The petitioner.

Q. Okay. All right.

And you understand that Amgen is

trying to make a biosimilar version of eculizumab, right?

DR. STERLING: Objection. Foundation. Form. Scope.

THE WITNESS: I mean, I -- I'd -- I'd defer to the lawyers. You know, from a -- from a commercial reasoning perspective, sure. That's, I think, part of the motivation to challenge the patents, but, you know, I haven't studied the biosimilar under development for Amgen.

BY MR. DIAMOND:

Q. I guess just in general, were you aware that Amgen is developing an eculizumab product?

DR. STERLING: Objection. Foundation. Form. Scope.

THE WITNESS: I think, yeah, generally, I'm aware of that. But, again, I don't know that that's all that germane to the opinions that I've formed here.

BY MR. DIAMOND:

Q. Fair enough.

You didn't discuss it in your declarations, right?

A. Correct.

Q. Okay. So let's -- I'm going to give you your -- your declarations.

So here's the three.

So --

A. Do these need to be marked or --

(Previously marked Exhibit No. AMG1088 was introduced.)

BY MR. DIAMOND:

Q. No. They're -- so these -- well, let's -- let's -- let's do it this way.

A. Okay.

Q. So we've been handed three documents, and you see that the three documents in front of you, each one is stamped AMG1088, but these are your -- your three declarations in -- in the three proceedings that you submitted in this case, right?

MR. DIAMOND: Sorry. I didn't collate.

THE WITNESS: I mean, I ha -- I haven't studied every page of what you've handed me, but they appear to be the declarations that I issued in the three parallel proceedings.

BY MR. DIAMOND:

Q. Now, you -- you didn't -- you didn't see anything in the three documents in front of you that made you think those are not your -- your declarations, right?

A. No. I didn't -- I mean, like I said, I didn't study every page. But doing a quick page-flip, it looks like the declarations that I issued.

Q. Okay. And if you see something today that makes you think otherwise, you'll let me know, right?

A. I will.

Q. Okay. Great.

And if you look at each of those declarations that you have in front of you, you have a signature page in each one with your signature. Why don't you -- why don't you find that in each one and then confirm that for me.

A. I do see that in each of the declarations.

Q. And I -- I should have asked you when you were looking for that last question, but did you see that each of those signatures are -- are dated February 14th?

A. Happy Valentine's Day.

Q. So yes?
A. Yes.
Q. Okay. Great. And thank you.
Is everything in your declarations true and correct?
A. Yes.
Q. Who drafted your declarations?
DR. STERLING: I'm going to object to the extent that gets to privilege. You can answer gen -- you can discuss generally, but not talk about any substance of any back and forth with you and/or any conversations with you and counsel.
MR. DIAMOND: And that's right. I'm not asking for the substance of any communications you had with counsel.
THE WITNESS: I dr -- I -- I drafted the declarations, and I relied upon and worked with my team at Gleason IP to draft the declarations.
BY MR. DIAMOND:
Q. Who -- who did the first draft of your declarations?
DR. STERLING: I'm going to give you the same instruction.

THE WITNESS: A combination of myself and -- and Ray Bummer, who's a managing director at my firm.

BY MR. DIAMOND:

Q. Mm-hmm.

Before you doing that draft, did you receive any drafts from counsel of your declaration?

A. No.

Q. Okay. Are there any portions of your declarations that were drafted by counsel and -- and not you?

DR. STERLING: I'm going to object again to the extent this gets to privilege.

You may answer generally.

THE WITNESS: No.

BY MR. DIAMOND:

Q. So in -- in -- again, I'm not asking for the substance of any communication with counsel, but after -- after you drafted your -- your first declaration, did you have your counsel review it and make revisions?

A. Of course.

Q. Okay. And how many rounds of revisions were there?

A. I mean, I -- I don't -- I don't remember exactly, but the -- you know, this -- this -- these declarations are entirely my work and were entirely done under my supervision. I did ask counsel for feedback prior to finalizing it, --

Q. Mm-hmm.

A. -- and they may have had some, you know, minor edits, but it's -- it's entirely my work and my opinions.

Q. And who was the -- I'm sorry. You had mentioned -- I'm trying to find it, but I'll ask you again, you mentioned some other fellow at -- at Gleason that was involved in the -- in the first draft?

A. Yes.

Q. Who was that?

A. Ray Bummer.

Q. Ray Bummer.

And who is a Ray Bummer?

A. He's a managing director at Gleason.

Q. Okay. And what is his educational background?

A. He went to the University of Pennsylvania, --

Q. Good school.
A. Yes.
-- and, I think, had a dual major in economics and accounting, --
Q. Uh-huh.
A. -- and, you know, spent time as a -- that -- that -- I mean, in terms -- in terms of his formal education, I think that's the extent of it.
Q. Yeah. I mean, do you know if he has any formal education as a -- you know, as a biologist or immunologist or someone with expertise in antibodies?
A. I wouldn't think so, no.
Q. And -- and neither do you, right?
A. Correct.
Q. Okay. And do you know if he has any -- any education or expertise in -- in FDA regulations?
DR. STERLING: Objection; form.
THE WITNESS: I mean, whether that was covered in his formal education, I don't know. He, certainly, has applied experience, as do I, in the regulatory scheme and how that applies to the economics of pharmaceuticals, and that's

something we study every day.

BY MR. DIAMOND:

Q. Yeah. But you wouldn't consider yourself an FDA regulatory expert, right?

DR. STERLING: Objection; form.

THE WITNESS: I -- I -- I -- I would not and have not held myself out as a FDA regulatory expert. But given my expertise in the economics of intellectual property, particularly as it relates to pharmaceuticals, I, necessarily, I think, have a pretty deep understanding and knowledge of the FDA regulatory scheme and how that applies to prescription pharmaceutical products, as well as other nutraceuticals, et cetera.

BY MR. DIAMOND:

Q. Let -- let's put it this way. You -- you've never worked in a -- you've never worked at the FDA, right?

A. No, sir.

Q. You've never worked at the regulatory department of a pharmaceutical company, right?

A. I haven't --

DR. STERLING: Objection; form.

THE WITNESS: I have not.

BY MR. DIAMOND:

Q. Or let's -- you haven't worked in the -- in the FDA regulatory department of any company, for that matter, right?

A. Well, yeah. I mean, certainly, never as a W2 employee. But, like I said, in the consulting work that I do, I study the regulatory scheme as it relates to life sciences products, medical devices, prescription pharmaceutical products, biologics, each and every day.

Q. Right. Just -- just to be clear, you've never -- you've never worked in or -- or consulted on FDA regulatory matters, per se, for a pharmaceutical company, right?

DR. STERLING: Objection; form.

THE WITNESS: I mean, I don't -- I don't know that that's a fair characterization. I mean, I think -- I certainly haven't expressed opinions that are limited or narrowed to FDA regulatory issues, but I've -- I've -- I've addressed the regulatory implications of FDA and how they apply to the economics of pharmaceutical products on -- on almost every matter that I'm involved in.

BY MR. DIAMOND:

Q. Let me -- let me -- let me put it this way: Have you ever advised a pharmaceutical company on the standards they need to get a product approved by the FDA?

DR. STERLING: Objection; form.

THE WITNESS: I mean, I -- I think that the work that I've done in terms of advising pharmaceutical companies prelaunch necessarily includes some aspects of the regulatory work that needs to be done to bring a product to commercial launch, but my focus is on economics and the economics of intellectual property and the economics of market formation and those types of things.

BY MR. DIAMOND:

Q. Mm-hmm. Mm-hmm.

And is the consulting you're talking about in the context of litigation?

A. Sometimes.

Q. Mm-hmm. Mm-hmm.

Have you ever attended an FDA Advisory Committee meeting with -- with a company?

A. I don't -- I don't believe so, no.

Q. Okay. Mm-hmm.

Have you ever advised a company on the contents of a Citizen's Petition?

DR. STERLING: Objection; form.

THE WITNESS: I mean, I've, over the years, had several cases, within a dispute setting, Citizens' Petitions were at issue, but that was after all the Citizens' Petition, kind of, stuff had happened.

BY MR. DIAMOND:

Q. You've never helped a company draft a Citizens' Petition, right?

A. No, sir.

Q. Okay. You ever help a company, in general, draft a communication to the FDA?

A. I mean, whether or not the work I've done in a consulting setting informs or shapes what's done with FDA, that's probably not where I'm involved at that -- at that end of the -- the work --

Q. Yeah. I -- I understand. I don't mean indirectly. I mean, like, directly, did you ever work with a company to help them draft a communication going to the FDA, that you can recall?

A. As I sit here now, I can't -- I can't

think of one, one way or the other.

Q. Okay. Going back to your declarations, did you do your best to include all the opinions that you had for these proceedings in those three declarations?

DR. STERLING: Objection; form.

THE WITNESS: Yes. Certainly.

BY MR. DIAMOND:

Q. You -- you didn't hold back any opinions for later, right?

A. No. I think they're -- they're my attempt to collect and -- and explain my opinions as of the date I issued the declarations.

Q. Okay. And in looking at your -- your declarations, I saw there's a lot of overlap. Would you agree with me that the -- you know, with -- with some differences, there's a lot of overlap between your three declarations?

A. Yeah. I -- I think it's fair to say that they're fairly consistent. There's just, primarily, differences with respect to the patents that are at issue --

Q. Mm-hmm.

A. -- and the implications therein.

Q. Mm-hmm.

And what -- what's your understanding of what the patents at issue here cover?

DR. STERLING: Objection; form, and to the extent it calls for a legal conclusion.

THE WITNESS: I -- I'm not a lawyer, and I'm not a technical expert, but my --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- understanding is that the patents relate to, generally, the -- well, each is -- each, you know, has its own specific scope and claims, --

Q. Mm-hmm.

A. -- and, again, I'm not weighing in, and I would defer to technical experts on the specific claim scope, but, you know, methods and views, composition of matter and formulations with respect to the use of eculizumab for the treatment of PNH, as well as other disorders.

Q. And I think in your declarations you -- you say you're not a medical doctor, right?

A. I am not.

Q. Okay. And -- and going back for a

second, you -- that understanding -- that general understanding that you have of the patents that you just described, where'd you get that understanding?

A. I would say, you know, I reviewed the Balthasar declaration, which framed things. I review the patents --

Q. Mm-hmm.

A. -- themselves. I reviewed Alexion documents, which, you know -- as well as Amgen documents with respect to the patent owner's -- you know, the petition and the patent owner's response, --

Q. Mm-hmm.

A. -- and -- and, I'm sure, had discussions with counsel along the way, as well.

Q. With respect to the -- you said you reviewed the declarations of Dr. Balthasar. Were those -- those were the declarations that Dr. Balthasar submitted last -- last year in connection with Amgen's petition?

A. I don't remember the dates, --

Q. Okay.

A. -- but I'm sure it was last year.

Q. Well, let -- let's do it this way.

You have -- why don't you take your -- your '504 declaration in front of you.

A. Okay.

Q. And I'm -- by '504 declaration, I'm referring to the -- the declaration that's in the proceeding ending in Number 739 with the U.S. Patent, the last three digits ending in -- ending in '504 -- Patent 9,725,504. You understand that?

A. Luckily, it was on the top of my stack.

Q. Okay. And if I refer to the other two patents as the '880 and '149 patents, will you understand that, as well?

A. I -- I will.

Q. Okay. And throughout the day today, I'll -- I'll probably, just for convenience, refer, primarily, to your '504 declaration, unless there's some difference between the declarations, we could refer to one of the other ones, okay?

A. Okay.

Q. Okay. So if you go to your '504 declaration, which has AMG1088 on the front, and please turn to Page 8, here you have a list

of -- of documents considered, or a section on documents considered.

Do you see that?

A. Correct. Yeah. And it carries over --

Q. Right. So --

A. -- to the next page.

Q. Yeah.

So you say here that, in formulating your opinions, you've considered the references and the documents cited herein, in -- including those listed below, right?

A. And it goes on, but, yes, --

Q. Yeah.

A. -- I do say that.

Q. So when -- when you say, "those listed below," you're referring to the documents in the -- in the table that starts at the bottom of Page 8 and bridges on to Page 9.

A. I am.

Q. Okay. And when you're -- you're talking about, you know, the references and documents cited herein, you're saying that in -- in add -- in addition to whatever's in this table on Page 8 and Page 9, if there's some

other document that's cited in the declarations but didn't happen to make it into this table, for some reason, that's also a document that you considered, right?

A. Yeah. I mean, I endeavored to include everything in this table.

Q. Yeah.

A. If -- if there was something I cited in -- in the text that is not in this table, that was just administrative error.

Q. Right. But the -- but the documents that are cited in this table, and otherwise cited in the, you know, 43 patents of this '504 declaration, that's the world of documents that you considered in formulating your opinions that are in this '504 declaration, right?

DR. STERLING: Objection; form.

THE WITNESS: I -- I didn't understand. The 43 patents?

BY MR. DIAMOND:

Q. Paragraphs. Sorry.

A. Oh. Oh.

Q. So I'm -- if I'm looking at your -- I'm looking at your declaration here, your '504 declaration here, it's 43 paragraphs long.

Can you -- if you can confirm that.

A. Okay. Sor -- I'm sorry. I don't --

Q. Yeah. We'll start over.

A. I don't know what the question is.

Q. Yeah. We'll start over. No worries.

A. Okay.

Q. I appreciate you letting me know.

All I was saying is, the world of documents that you considered in formulating the opinions in this '504 declaration are whatever's in this table on Page 8, bridging to Page 9, and then anything else that you cite within, as I said, the -- the 43 paragraphs of this declaration, right?

A. It -- it -- and I've done my best to make sure that is so.

Q. And sitting here right now, you're not aware of any documents you considered outside of that scope, right?

A. As I sit here now, nothing comes to mind one way or the other.

Q. Okay. And the same is true with respect to your '149 and '880 declarations, that the documents that you considered in formulating your opinions in those declarations would be the

documents in the documents-considered tables in -- in those two declarations, plus anything else that's cited within the -- the paragraphs of those declarations, right?

A. Yeah. Same answer. I did my best to -- to summarize those.

Q. And -- and -- and same answer, you're not aware of anything sitting here right now that you failed to include as a cited reference in those declarations that's something you considered, right?

A. I would --

DR. STERLING: Objection; form.

THE WITNESS: I would agree with that.

BY MR. DIAMOND:

Q. Okay. So going back to your '504 declaration, Page 8 -- oh, you're there? Great.

So one of the documents you cite here is Exhibit 1002?

A. It is.

Q. Do you see that?

A. It is, yes.

Q. And is that the declaration of -- of Dr. Balthasar you were referring to earlier, at least the one with respect to the '504 patent?

A. It is.

Q. All right.

And you considered Exhibit 1002, Doc -- the declaration of Dr. Balthasar, for the other two patents, for the '880 and '149, right? And you can flip to your tables there to confirm that.

A. I did.

Q. All right. And did you get those declarations of Dr. Balthasar from counsel?

A. I -- I don't -- I don't remember if I pulled them or had my team pull them directly from the -- the PTAB docket or if counsel sent them.

Q. Do you know Dr. Balthasar?

A. I don't.

Q. Have you met him?

A. No.

Q. Have you talked to him in the context of this case?

A. No.

Q. Or have you ever talked to him?

A. No.

Q. Okay. Do you know his reputation in the field?

DR. STERLING: Objection; relevance.

THE WITNESS: I -- I -- I mean, I've -- I've reviewed his report, or declaration, I should say, --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- which gives information regarding his background, and he seems eminently qualified in this space.

Q. Mm-hmm.

A. But I certainly would not be one to weigh in on a subjective thing like reputation in the field, --

Q. Mm-hmm.

A. -- given that his field is different than the field in which I studied.

Q. Right.

And when you say, "his field is different than the field in which you studied," what's your understanding of what his field is?

A. I -- I think it's probably best to just refer to his declaration and the background and qualifications that he lists. I don't have that in front of me.

Q. Right. Be -- beyond what's -- beyond

what he says about his qualifications listed in his declaration, did you have any understanding about what his field is?

A. Not beyond what's in his declaration --

Q. Fair enough.

A. -- and CV.

Q. Fair enough.

And then when you said -- when you referred to your field, what did you mean by that?

A. Well, I mean, I'm a -- I'm an economist --

Q. Mm-hmm.

A. -- and accountant. I study -- the economics of intellectual property is -- is -- is -- is the primary area of my focus, --

Q. Mm-hmm.

A. -- and with a particular focus on life sciences, but also doing work in other fields of intellectual -- or other industries.

Q. Mm-hmm.

A. Sometimes that's in a dispute setting, such as this, but it's also outside of a dispute setting. And so, you know, I think the broadest

way to explain it is I'm an expert and I am a consultant to companies, individuals and institutions with respect to the economics of intellectual property.

Q. And aside from working with counsel on your -- on your declarations, did you consult with anyone else in preparing your declarations, and -- and -- aside from the other individual you mentioned earlier from -- from Gleason, whose name is escaping me right now.

A. Well, I -- I mean, there were -- there were other people, in addition to Mr. Bummer --

Q. Uh-huh.

A. -- at Gleason --

Q. Mr. Bummer.

A. -- that -- that -- that helped me. And then I, obviously, reviewed signi -- you know, a long list of -- of documents --

Q. Mm-hmm.

A. -- and information and conducted independent research, and, you know, attempted to articulate the basis of what all I did in the -- in the declaration. I also bring to my declaration --

Q. Mm-hmm.

A. -- my deep knowledge and experience having consulted and studied many, many products, pharmaceutical products, biologic products, medical devices, et cetera, in the life sciences ind -- industry over many, many years, so my knowledge and experience is part of what I bring to my declaration.

Q. So may -- maybe it will be easier, why don't we start with Mr. Bummer, because I want to break this down a bit. What was Mr. Bummer's specific role in the draft -- in that first draft of your declaration? What did he do?

A. Well, I mean, you -- you know, essentially, when I had -- I get a project such as this, --

Q. Mm-hmm.

A. -- he and I will sit down and, you know, have -- someone have done some preliminary research and gained some preliminary understanding of the issues.

Q. Mm-hmm.

A. And then we formulate a plan on how to execute, either, in this case, a declaration; in District Court cases, you know, a report. And I -- I, basically, describe and direct him,

as well as the team underneath him, to do the things that I want us to do, in terms of review of documents, conducting independent research and developing and drafting, in this case, a declaration.

Q. So just to make sure I understand this, earlier you mentioned people, in -- in addition to Mr. Bummer at Gleason, that -- that helped you. Is that the -- the -- the team working under Mr. Bummer that you just referred to?

A. Well, they're all working under me, --

Q. Yeah.

A. -- but, yes, there are -- there are a couple additional layers.

Q. Okay. Do you know how many people were assisting you and Mr. Bummer in -- in the work that you did for this declaration?

A. I -- I don't know, specifically, but off the top of my head I would guess two.

Q. Okay. And do you know who any of those individuals were?

A. Sure. Erin Wheeler, --

Q. Uh-huh.

A. -- who is a senior manager at Gleason

IP.

Q. Mm-hmm.

A. And then I think there was more junior staff involved, I believe it was Megan George, in helping manage the documents and getting the citations, you know, cite-checked and things like that.

Q. And do they both have economics backgrounds, as well?

A. I think that Erin Wheeler's ex -- formal education, she went to Penn State, not U Penn, and, you know, graduated with high honors, I think, in accounting, --

Q. Okay.

A. -- but had, certainly, had applied experience in the area of economics and accounting in her time --

Q. Mm-hmm.

A. -- at Gleason.

And then Megan George is, I think, a -- a paralegal, officially, and, like I said, helped with a lot of the document management and cite-checking.

Q. And when you -- when you talked about independent research that was done by you or Ray

Bummer or -- or those other individuals, Erin Wheeler and Megan George, what was that independent research?

A. Well, I think that, you know, pretty much everything that's in here --

Q. Mm-hmm.

A. -- is information that was in the public domain. I think that some of the website references, --

Q. Mm-hmm.

A. -- or perhaps all the website references, are research that I and my team found. I -- you know, I don't -- I didn't inventory it to figure out which of these are things we found --

Q. Mm-hmm.

A. -- versus things that were already produced or part of the PTAB proceeding.

Q. Mm-hmm.

Do you know if there are any documents in this list, just sticking with your '504 declaration, the table on Pages 8 to 9, are there any documents in that list that were provided to you by counsel, initially, instead of you or your team finding them?

A. I -- I -- I -- I just don't remember, as I sit here right now, because the PTAB is very transparent and you can pull and harvest a lot of information from the -- the docket. I can't say whether the -- the counsel provided us with, you know, certain declarations or certain information or whether --

Q. Mm-hmm.

A. -- we just grabbed that on our own.

Q. Well, let's -- let's put it this way: If we just focus on Exhibits 1089 through 1096, do you see that -- that series of exhibits listed in your table on Page 9?

A. I do.

Q. Were any of those provided to you by counsel, initially, rather than found by you or your team first?

A. I haven't cataloged or inventoried them to give you a complete answer one way or the other --

Q. Mm-hmm.

A. -- as to that question. I mean, as I'm looking at them, my inclination is that most of them are things that I and my team found, --

Q. Mm-hmm.

A. -- as opposed to coming from counsel. But there could be one or two of the documents that came from counsel. I just don't know as I sit here right now.

Q. And when you talk about the independent research that was done by -- well, let -- let me phrase it as this: Was there any independent research that you personally did, as opposed to research done by Ray Bummer or the people working under you and Ray?

A. Well, sure. I mean, I've studied -- you know, a lot of the articles that you're specifically asking me to -- to address are articles related to orphan drugs, and, I mean, I've studied orphan drugs and consulted on orphan drugs and expressed opinions on orphan drugs many times. So I think over the -- over the time period I've done so, some of this may have come from me, some of it came from people on my team, or our cumulative knowledge, having studied orphan drugs many, many, many times.

Q. But, specifically, is there any search that you can recall that you did for purposes of this case?

A. I mean, I -- I'm --

Q. Any specific search?
A. Yeah. I'm -- I'm -- I'm sure I did.
Q. What was it?
A. You know, in terms of looking up Alexion, looking up the Soliris product and label and understanding a little bit of the, you know, market dynamics, but then I used all that to direct my team to, you know, again, conduct thorough research at my direction and -- and under my supervision to --
Q. Mm-hmm.
A. -- to pull together the information that -- that appears here.
Q. Did you do your searching on Google, or what -- what'd you use for your searching?
A. Typically, I use Google.
Q. Okay. And do you know what your team used to search?
A. Typically, we used Google --
Q. Mm-hmm.
A. -- or, you know, I mean, there may be some other searches that were done with other tools that are -- that are there.
Q. Do you know what terms they searched for?

A. Not off the top of my head, no.

Q. Okay. And you don't -- you don't say so in your declarations, right?

A. I -- I don't believe that I have a section that talks about the search terms that I and my team used.

Q. Okay. For the declarations of Dr. Balthasar that you reviewed, or that you considered in the context of this case, did you review the entire declarations?

A. I did, um, you know --

Q. Cover to cover?

A. Yeah. I -- I did review them cover to cover.

Q. Mm-hmm.

A. I'm, obviously, focused on my economic lens, and some of the technical information in there, you know, I -- I -- I read, --

Q. Mm-hmm.

A. -- but, you know, my focus is on the economic aspects of this case.

Q. Right. And you also reviewed the declarations of Dr. Arturo Casadevall in these three proceedings, right?

A. I did.

Q. You reviewed the deposition transcripts of Dr. Casadevall in these three proceedings, right?

A. I did.

Q. All right. And did you review those cover to cover, as well?

A. I did.

Q. Okay. Now, you didn't list the deposition transcript of Dr. Balthasar here in this table, and, confirm this for me, I -- I don't think you cited the deposition transcript of Dr. Balthasar at all in your -- in your declarations; is that right?

A. I think that's correct.

Q. All right. Why didn't you look at that?

A. I don't know when it took place, but I -- I don't believe that was something that I reviewed.

Q. Well, you said you -- you could have accessed documents from the PTAB website, right? You think you might have accessed some -- you weren't -- earlier you testified that you weren't sure, maybe you or your team pulled down some of these documents from the PTAB website

yourself, right?

A. Right. I -- I guess I'm just -- I just don't know temporally --

Q. Mm-hmm.

A. -- when that took place and whether that was even available.

Q. Sure. But you could have gone to the PTAB website to look at and see, right?

A. To the -- yeah. To -- to the extent that it was there, I guess that would be, certainly, accessible, --

Q. Okay.

A. -- if it was accessible as of February 14th. I just don't remember, as I sit here, whether that was something that -- that had occurred or whether it was available on the PTAB website at the time I issued my declaration.

Q. Okay. Fair enough.

And as far as -- as far as you could recall, that document wasn't -- or, yeah, let me rephrase that.

As far as you can recall, the deposition transcript of Dr. Balthasar in these proceedings was not provided to you by counsel,

right?

A. No. Had it been, it would be listed here.

Q. Okay. Would you be interested to hear what Dr. Balthasar had to say at his deposition?

A. I -- I mean, sure.

Q. How much time in total, and you could estimate if you don't have an actual number, that's fine, but how much time in total did you spend preparing your declarations for these proceedings, you -- you personally?

A. Me, personally, --

Q. Mm-hmm.

A. -- I certainly don't have any precise estimate. You know, I mean, 50 to 75 hours. I don't -- I -- that's just a total guess that --

Q. Mm-hmm.

A. -- I don't -- I -- I have no idea.

Q. Do you have any estimate of how much time Ray Bummer spent?

A. I would -- I would guess that he may have spent a little bit more.

Q. Mm-hmm. And what about Erin Wheeler and Megan George, what -- how much time do you think they spent on the declarations?

A. I would guess that Erin Wheeler, and, again, this is total guesses, --

Q. Mm-hmm.

A. -- but I would guess that Erin Wheeler spent about the same as Ray, or Mr. Bummer, --

Q. Mm-hmm.

A. -- and that Megan George spent less.

Q. Now, you -- you talk in your declarations about an Evans '245 patent, right?

A. Correct.

Q. Yeah. And in -- in your understanding, the -- the Evans '245 patent has certain claims that would cover Soliris and -- and eculizumab, right?

A. That's my understanding.

Q. Okay. And you understand that the Evans '245 patent expires on March 16th, 2021, inclusive of its patent term extension?

A. Correct.

DR. STERLING: Objection; form. Foundation.

BY MR. DIAMOND:

Q. And you consider the Evans '245 patent to be a -- a blocking patent with respect to eculizumab, right?

A. As explained in my declarations.

Q. Right.

So it -- it's your opinion that, in view of this Evans '245 patent, companies, other than Alexion, would be disincentivized from developing an eculizumab product within the claims of the three patents that are at issue here, the '149, '504 and '880, right?

A. I --

DR. STERLING: Objection to the extent it mischaracterizes testimony.

THE WITNESS: I would defer to the language and explanation that I include in my declarations --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- with respect to the '245 patent, --

Q. Mm-hmm.

A. -- but, generally, yes, --

Q. Mm-hmm.

A. -- the '245 patent created an economic disincentive for anyone other than Alexion --

Q. Mm-hmm.

A. -- to conceive of the alleged inventions contained in the patents at issue

in these three proceedings.

Q. And you -- you understand, in general, those inventions relate to eculizumab, right, --

A. Those inventions --

Q. -- of the -- of the patents at issue in this proceeding, these three proceedings?

A. They relate to eculizumab, but, as I understand it, --

Q. Mm-hmm.

A. -- the '245 patent, you know, also relates to eculizumab and would -- again, not weighing in in any technical --

Q. Mm-hmm.

A. -- or legal way, but based on the understandings as articulated in my three parallel declarations, --

Q. Mm-hmm.

A. -- they would have encompassed what is claimed in the, you know, later-issued patents.

Q. Mm-hmm.

Is it -- is it your understanding that the existence of a blocking patent necessarily detracts from evidence of commercial success?

DR. STERLING: Objection; form, and to the extent it calls for a legal conclusion.

THE WITNESS: So, I mean, I've -- I've -- I've studied the issue of blocking patents quite a bit, but I'm not a legal scholar, I'm not weighing in in any legal way. I think that the existence of a blocking patent, based on the studying that I've done, tells us that one should, at most, disregard claims of potential commercial success because it upsets and disturbs the framework that -- that was originally, you know, driving the reason why I'm here at all, at least the existence of a blocking patent, should counsel, the trier of fact, to, you know, put a week [sic] or limit any weight that they put on evidence of potential commercial success because of the existence of a blocking patent.

BY MR. DIAMOND:

Q. Yeah. But I just want to -- and I'm not asking you as a lawyer, I'm asking you as -- as an economist, okay, and the understanding as an economist to be applied, you know, here, is it your understanding that the existence of a blocking patent makes it so we should necessarily disregard the economic evidence of commercial success?

DR. STERLING: Objection; form.

THE WITNESS: Yeah. And I think that -- that, like any issue, it's highly facts-and-circumstances dependent. And in studying the issue, I -- I wouldn't say the superlative, as your question implies, that it's necessarily so that the existence of a blocking patent eliminates the ability to look at commercial success, but I think one has to study the aspects that exist both temporally and in terms of claim scope and things like that, --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- which I've done in this case. And based on the facts and circumstances here, as I've articulated in detail in my various declarations, the existence of the '245 patent undermines any weight that anyone should put on commercial success, if any. And -- and, again, it's not a necessarily-so standard, it's the facts and circumstances dictate that we don't put weight on commercial success in this case, because it's -- it's almost a gating issue based on the -- the situation that exists here.

Q. Right. So when you have a -- when you

have a blocking patent, in general, you don't say, oh, that, necessarily, means I disregard commercial success. You -- you look to the facts and circumstances in every case.

A. I think that's a fair statement.

Q. Okay. If you'll look at Paragraph 35 of your '504 declaration, please, in the middle of the page here you have graphic depicting the period of economic disincentives from the '504 patent, as --

A. '245.

Q. I'm sorry. Let me rephrase that.

You have a graphic here where you depict, and I quote, the period of economic disincentives from the '245 patent, end quote.

Do you see that?

A. I do.

Q. And you graphically depict this, quote, period of economic dis -- disincentives from the '245 patent, end quote, as a brick wall?

A. I do.

Q. All right. And the period of economic disincentives from the '245 patent that you depict here starts on March 12, 2002, which you

list as the date the '245 patent issues, and then extends to March 16th, 2021, which you list as the date the '245 patent expires with PTE; is that right?

A. I do.

Q. Okay. And looking at Paragraph 35 above there, so it's your opinion that during this -- this period of economic disincentives from the '245 patent, that you're depicting in this graphic, no company, other than Alexion, had the incentive to develop the alleged invention since such companies would be at risk of infringing the '245 patent; is that right?

A. Yeah. I mean, I'd defer to the -- the language not just of the specific sentence you've cited, but to the entirety of the -- the section and the entirety of the declaration. But, yeah, that's -- that's the -- the concept here, that this patent issued five years before the, in this case, '504 patent and -- or -- and the priority date of the '504 patent. And so it disturbs the -- the concept of commercial success as a term of art and an obviousness inquiry, because Alexion had telegraphed to the world that they, you know, had the rights to

this. And that's particularly so in the facts and circumstances here when you're dealing with an ultra orphan population.

Q. Let's do it this way: So in Paragraph 35 you say -- it starts off as saying, "as illustrated in the timeline below," do you see that?

A. Yes.

Q. And when you say "the timeline below," you're referring to the graphic with the brick wall?

A. I am.

Q. Okay. So you say, "as illustrated in the timeline below, at the time of the priority date of the '504 patent, March 15, 2007, from an economic perspective, no company other than Alexion had the incentive to develop the alleged invention since such companies would be at risk of the infringing the '245 patent."

You -- you say that, right?

A. Yeah. I'm -- I'm -- I'm saying that --

Q. Well, sir, that -- that's -- I just read that --

A. Yeah. You --

Q. -- correctly, right?

A. -- you read -- you read it correctly.

Q. Okay. That -- that was my only question.

A. Okay.

Q. So my next question is, you -- you say, "at the time of the priority date of the '504 patent," but would it be true, in your opinion, that this economic disincentive would exist throughout the period that you've depicted with the brick wall in the timeline?

DR. STERLING: Objection; form.

THE WITNESS: Well, I -- I think with respect to -- the -- the -- the period of time --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- is -- is expressed in the timeline. I mean, what -- what matters most is as of the priority date. Because this is the -- as I understand it, and I'm not a lawyer, but the -- the issues that are germane to obviousness with respect to commercial success, as a term of art and an obviousness inquiry is, as of the priority date, would others have had economic

incentive to have conceived of the alleged invention of the respective patents at issue.

Q. Okay. My -- my question's a little different, because I just want to understand -- I -- I understand you're talking about the priority date, but beyond the priority date, would it also be your opinion that the economic disincentive you're referring to would -- would exist at other dates, including the -- the -- the time range you depict here under the brick wall?

DR. STERLING: Objection; form.

THE WITNESS: Certainly -- certainly so, to some degree. I mean, we might see, closer to the, you know, later stages of the brick wall, ANDA filers or bio -- B -- BCPA filers, you know, coming into the fold, or even other brands coming into the fold, because the regulatory pathway takes many years, and so -- you know, and there are regulatory safe harbors and things like that and protections that allow people to start to, kind of, spend time in a particular therapeutic area. But, again, I'm not --

BY MR. DIAMOND:

Q. Right.
A. -- I'm -- I'm just applying my economic lens to this issue.
Q. You -- you under -- you understand -- you -- you've heard of the Section 271(e)(1) Safe Harbor in your work, right?
A. I have.
Q. And you understand that allows companies to do research on a -- in general. I know you're -- you're not a regulatory expert, right, but, in general, you understand that that allows companies to do research on a product without liability for infringement, right?
A. Yeah. And that's exactly what I was just saying, --
Q. Yeah. Okay.
A. -- is that -- is that we may see some activity --
Q. Mm-hmm.
A. -- along the way --
Q. Mm-hmm.
A. -- of people doing research because they're looking towards --
Q. Mm-hmm.
A. -- a lengthy regulatory --

Q. Right.

A. -- pathway. But the reality is commercialization, and that's really the central issue that is -- is -- is the focus of my declaration, is what are the economic implications --

Q. Mm-hmm.

A. -- and when can --

Q. Mm-hmm.

A. -- someone commercialize.

Q. Mm-hmm.

A. Really, the '245 patent blocks anyone from commercializing anything until after 2021. But in order to commercialize something after 2021, you need to -- you need to do some work long before --

Q. Mm-hmm.

A. -- 2021 to get approval.

Q. Sir, do you -- do you know when the -- the -- the three patents at issue in these proceedings, the '149, '504 and '880, when they expire?

DR. STERLING: Objection; form. Compound.

BY MR. DIAMOND:

Q. And if you haven't considered that for purposes of this case, you can tell me that, too.

A. No. I -- I'm trying to remember where I may have seen that or where that's addressed in my declaration. I mean, it would be -- obviously, these are -- I think the -- the -- the --

Q. Let's take it bit by bit.

The -- the -- you would assume they haven't expired yet because we're here in this proceeding, right?

A. Of course.

Q. And Amgen is challenging those patents, right?

A. Of course. Yeah.

Q. Okay. And correct me if I'm wrong, I don't believe you discussed the expiration dates of those patents in your declarations.

A. Yeah. That's -- that's --

Q. And you could look through it and -- and let me know if I'm -- I'm wrong, but I -- I didn't see any reference to that in there; --

A. What I'm --

Q. -- is that correct?

A. What I'm trying to remember is whether that's something that I observed in other, you know, expert reports or in the patent owners' --

Q. Let's --

A. -- response or --

Q. Let's do it this way: You don't discuss the expiration dates of the -- of the '149, '880 and '504 patents in your three declarations, right?

A. I -- I mean, as I sit here right now, I'm -- flipping through, I -- I don't -- I don't remember explicitly laying that out one way or the other, --

Q. Okay. And --

A. -- um --

Q. -- and you don't recall just sitting here today --

DR. STERLING: Sorry. Can you let the witness finish his answer?

MR. DIAMOND: Oh. So sorry.

THE WITNESS: But --

MR. DIAMOND: Go ahead.

THE WITNESS: -- but just because I'm not explicitly laying that out here doesn't mean that isn't something that I observed in, you

know, other the -- other materials that -- that I considered or things I analyzed. I mean, I would expect that, you know, like you said, the reason we're sitting here is, they haven't expired. I'm looking at a 2007 issuance date, you know, so I'm thinking 2024, but I just can't remember where I may have seen that or where I would have --

BY MR. DIAMOND:

Q. Okay. And -- and it's fine. Sitting here right now you don't recall what that date -- that expiration date for the three challenged patents here would be, right?

A. Not with specificity.

Q. Okay. All right.

If you look -- well, let me ask you this: Were -- were you aware that -- we -- we -- we talked earlier about -- generally, about Amgen's biosimilar. Were you aware that Amgen was in the process of recruiting PNH patients for a clinical study of Amgen's eculizumab product?

DR. STERLING: Objection; scope.

THE WITNESS: I'm not a clinician or research scientist. I think, if I saw that, I

probably saw it in the -- in the review of other technical experts.

BY MR. DIAMOND:

Q. Let -- let's put it this way: In the course of your research and work in this case, did you investigate what research Amgen is currently doing in the United States with respect to their eculizumab product?

Did you consider that?

A. Well, like -- like we talked about, I mean, --

Q. Did you consider it?

We didn't talk about that yet.

A. Well, no. We did talk about regulatory safe harbors we talked about other non-Amgen --

Q. Yeah. But I'm asking a specific question, sir. Do -- did you -- did you consider, specifically, what research is -- Amgen is currently doing with respect to its biosimilar eculizumab product? Did you look into that for this case?

DR. STERLING: Objection; relevance.

THE WITNESS: I mean, I -- I would defer to -- to lawyers and technical experts,

but I --
BY MR. DIAMOND:
Q. Well, I'm asking you -- ask -- you what you did.
A. Yeah.
Q. I'm not asking you what the lawyers did. What did you do? Did you --
DR. STERLING: Objection.
BY MR. DIAMOND:
Q. Did you look into that or not?
DR. STERLING: Objection; form. Relevance.
THE WITNESS: I -- I just -- to me, that's not germane to the issues that I'm studying be --
BY MR. DIAMOND:
Q. And so you didn't look at, right?
A. -- be -- beyond --
DR. STERLING: Can you let the witness answer the question, please?
MR. DIAMOND: He's -- he's being non-responsive. I'm asking him the question, did you look into that or not? I'm not asking if this is germane, okay? I'm asking you, did you look into the -- the clinical work that

Amgen is doing for its biosimilar eculizumab product. Did you look into that? Yes or no.

DR. STERLING: Objection; relevance. Form.

THE WITNESS: The -- the -- the -- the work -- you know, ob -- obviously, I understood and read pleadings and read infor --

BY MR. DIAMOND:

Q. Sir, that's not my question. Did you -- do you understand my question? I'm asking you whether you looked at something.

A. It -- it's hard to answer your questions when you repeatedly interrupt me.

Q. Okay. Well, you've gotta -- you know, your counsel has an opportunity later to ask you questions if there's additional things --

A. Well, I'm --

Q. -- that you want -- that you wanted to say that were not responsive to my questions. My question is really simple: I'm asking you whether you -- let's start with you personally, then we can go to your other folks, whether you personally -- and if you don't recall, say, I don't recall, whether you personally looked at the research, specifically, that Amgen is doing

with respect to its -- the development of its eculizumab product? Did you look at that in the context of this case?

DR. STERLING: Objection; relevance.

BY MR. DIAMOND:

Q. It's yes, no, or I don't recall.

DR. STERLING: Objection; relevance. Scope.

THE WITNESS: Yeah. And I'm -- I'm not sure that you can dictate, you know, the -- what my answer must be. What I'm saying is --

BY MR. DIAMOND:

Q. What's your -- wait. What's your answer to that question, sir?

A. Okay.

DR. STERLING: Same objections.

THE WITNESS: Let me finish.

You know, I'm saying that in -- in working on this project --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- I understood that Amgen had a biosimilar application --

Q. Mm-hmm.

A. -- pending.

A necessary part of that is going to be them doing all the regulatory stuff that they have to do. I did not undertake any sort of technical or clinical study of the work that they're doing, but it's -- it was, necessarily, part of what I understood is part of the normal process that happens when someone is bringing a biosimilar to market, not identical to when someone's bringing a ANDA to market, but the same concept in that there's work that's done and legwork that's done with clinical trials and work. But I did not study it with -- with specificity, it's not something that I would take on, because I'm focused on the economic issues here.

Q. And it's not something that you cited in your declarations, right?

A. I mean, whether it's part of --

Q. No. My -- it's not something that you cited in your declarations, right?

A. I don't --

DR. STERLING: Objection; form.

THE WITNESS: I don't know how we're going to get along here if you keep interrupting

me.

BY MR. DIAMOND:

Q. Well, I need you to answer my question, sir. This -- this is -- this is how it works: I ask you a question. You answer the question, okay? And if there's something else that you want to say that's not responsive to one of my questions, your counsel could ask you later, okay?

So I'm going to ask you one more time, do you, in your declarations, cite Amgen's clinical research regarding its biosimilar eculizumab product?

DR. STERLING: Objection; foundation.

MR. DIAMOND: And, if you do, show me where. And if you don't, say you don't.

DR. STERLING: Objection.

BY MR. DIAMOND:

Q. Okay?

DR. STERLING: Foundation. Form. Compound.

THE WITNESS: As I -- as I sit here right now, I know that I cite to a lot of information --

BY MR. DIAMOND:

Q. Mm-hmm --

A. -- from both technical experts, as well as the evidentiary record. Whether that specifically includes Amgen's clinical work, I -- I just don't remember as I sit here right now, --

Q. Okay.

A. -- but it's -- it's -- it's a -- it seems like a -- just a obvious aspect of -- of what's -- what's happening with respect to Amgen challenging the patent; that they're, necessarily, --

Q. Mm-hmm.

A. -- doing the things that a sophisticated pharmaceutical company would do in order to, potentially, bring a biosimilar product to market.

Q. And -- and, in general, you -- you -- you don't know -- or let me -- let me ask you this: I'm sorry. You don't know the specific timelines of Amgen's clinical development of that eculizumab product, right?

DR. STERLING: Objection; form. Relevance.

THE WITNESS: I mean, --

DR. STERLING: Scope.

THE WITNESS: -- I would defer to -- to others. As I sit here right now, --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- I do not --

Q. Mm-hmm.

A. -- I do not know the specific time lines.

Q. Mm-hmm. Um --

DR. STERLING: We've been going an hour -- over an hour, actually. Is it a good time for a break?

THE WITNESS: Yeah. Sure.

DR. STERLING: Okay. Thanks.

THE VIDEOGRAPHER: The time is 10:07 a.m. This completes Media Unit Number 1. We're now off the record.

(Recess taken.)

THE VIDEOGRAPHER: The time is 10:25 a.m. This begins Media Unit Number 2. We're now on the record.

Please proceed, Counsel.

BY MR. DIAMOND:

Q. Mr. Hofmann, did you talk with your

counsel about the substance of your deposition during the break?

A. No, sir.

Q. You reviewed -- in the context of your work on your three declarations in this case, you -- you reviewed the three declarations of Dan Bazarko submitted in these proceedings, right?

A. I did.

Q. Okay. And you saw in those declarations that he reported sales figures for Soliris from launch through Q3 2019?

DR. STERLING: Objection; foundation.

THE WITNESS: I mean, I -- I don't have the declarations in front of me, but I -- I think, essentially, that's -- that's -- that's all he did, was identify sales figures --

BY MR. DIAMOND:

Q. And --

A. -- from public filings.

Q. Fair enough.

And -- and you -- you don't have any opinions that you put in your declarations disputing the sales figures that he -- that were in the Bazarko declarations, the -- the -- the

actual numbers, right?

A. I didn't identify any errors in his summarization of those figures. Of course, I express a number of opinions in my declarations about the folly of just focusing on sales figures when one doesn't identify whether there's a nexus to those sales figures and the claims of the patents at issue.

Q. Fair enough.

Your -- your -- your issue wasn't the figure them -- the sales figures themselves, but the interpretation of those sales figures and the use of those sales figures to support a commercial success claim, right?

A. He doesn't interpret them at all. He just says what's in the public filings.

Q. Right.

A. But my issues are that first you have to look at things like the blocking patent, the failure to demonstrate nexus, the failure to address what was known in the prior art, you know, all those issues as articulated in the entirety of my declaration.

Q. Okay. And you're not offering any opinions in -- in your declarations disputing

that the challenged claims of these three patents at issue here, that those claims cover Soliris and its method of use, right?

A. I mean, I -- I think that that's probably better question for lawyers and technical experts.

Q. Mm-hmm.

A. I think I would defer to the language in the entirety of my declaration. I think I do, and I point out that, yes, there's a -- there's a representation to -- in the form of the label that these patents do cover the Soliris product, but then there's also the '245 patent, which is a blocking patent, and the other things that were known in the prior art that also relate to the Soliris product.

Q. And I -- I understand, and I'm not asking you as a lawyer, and I'm not asking you about the '245 patent right now. We can talk about that later. But just with respect to the '149, '504 and '880 patents, those three patents, you're not disputing in your declarations that those three patents cover Soliris, right?

DR. STERLING: Object to the extent it

calls to the -- for a legal conclusion.

THE WITNESS: I -- I would say it differently. I would say that's not an issue that I'm addressing, one way or the other, in terms of I understand that, you know, lawyers and technical experts may address the -- those specific issues. The issues I have are articulated in the entirety of my declarations.

BY MR. DIAMOND:

Q. Fair -- fair enough.

You understand that, at the time of its approval, Soliris was -- was indicated for the treatment of patients with paroxysmal nocturnal hemoglobinuria, PNH, to reduce hemolysis, right?

A. It's so much easier to say PNH, yes.

Q. But you understand that, right?

A. Yes.

Q. Okay. You understand that the active ingredient in -- in Soliris is -- is eculizumab, right?

A. That's what's indicated on the label, yes.

Q. Yeah.

A. I mean, I'm not a clinician or

technical expert, but that's my understanding.

Q. But you're not offering a different opinion, right?

A. I'm not.

Q. Okay. And you understand that Soliris is available in the 300 -- in a 300 milligrams -- let me rephrase that.

You understand that Soliris is available in a 30 milliliter single-dose vial for intravenous infusion containing 300 milligrams of -- of eculizumab, right?

DR. STERLING: Objection; foundation.

THE WITNESS: I mean, I -- I would defer to whatever's in the label.

BY MR. DIAMOND:

Q. Well, I mean, you -- you offer an opinion about that in your declaration, don't you?

A. Yeah. I mean, I -- I -- I think citing to the label, --

Q. Correct.

A. -- so it's not an opinion. It's -- it's background information that's explaining my understanding, again, not as a medical doctor or clinician, but what's -- what -- what one can

read on the label.

Q. Well, let's -- if you could look at your Paragraph 19.

A. I'm there.

Q. The very -- the very first sentence in your wri -- written testimony in this paragraph is, "Soliris is available in a 300 milligram and 30 milliliter single-dose vial for intravenous infusion," right?

A. Right. And I believe that's citing to the label, --

Q. All right.

A. -- which is what I just said.

Q. And you -- you believe the label, right?

A. Of course.

Q. Okay. Now, if you go to your Paragraph 25 of your '504 declaration, you see in the -- in the first sentence it begins, "For example, I understand," and then it -- and then it goes on. Do you see that?

A. I do.

Q. And then the third sentence, again, says, "For example, I understand from Dr. Balthasar's declaration," do you see that?

A. And it goes on.

Q. Yeah. And -- and the next sentence it says, "I further understand that this study concluded," and -- and it goes on. Do you see that?

A. It does, yes.

Q. And the next sentence says, "I understand that the eculizumab antibody used in these clinical trials," and -- and it goes on. Do you see that?

A. It does.

Q. In each one of those instances, you cite Dr. Balthasar's declaration, AMG1002, right?

A. Yes. That's correct.

Q. And if we go back to the second sentence of Paragraph 25, it says, "Moreover, several of these clinical trials had evaluated the use of eculizumab as a treatment for PNH."

You see that, right?

A. Yes.

Q. And, again, you -- you cite Dr. Balthasar's declaration for that, as well, right?

A. I do.

Q. All right. And Dr. Balthasar's declaration was the basis for the understanding that you put here in your Paragraph 25?

A. Yeah. I think as I -- as I go through it, the citations, in each instance, are to Dr. Balthasar's declaration.

Q. All right. And the last sentence says, "I further understand that an antibody with the amino acid sequence of SEQ ID Numbers 2 and 4 was disclosed in the prior art."

Do you see that?

A. I do.

Q. And you cite Dr. Balthasar's declaration for that understanding, as well, right?

A. I do.

Q. Okay. So regarding this issue of whether an antibody with the amino acid sequence of Sequence ID Numbers 2 and 4 was disclosed in the prior art, did you investigate that yourself, aside from reading Paragraphs 50 to 60 of Dr. Balthasar's declaration you cite here?

A. I'm not -- I'm not a technical expert. You know, I'm -- I'm applying the technical

issues and relying on technical experts such as Bal -- Dr. Balthasar. I didn't independently form a view on that.

Q. Did you consider what Dr. Casadevall had to say in his declarations that you reviewed from cover to cover, or his deposition transcript that you reviewed cover to cover, regarding whether an antibody with the amino acid sequence of Sequence ID Numbers 2 and 4 was disclosed in the prior art?

A. That's --

DR. STERLING: Objection to form.

THE WITNESS: That's part of the information I reviewed and considered, yes.

BY MR. DIAMOND:

Q. But -- but you don't discuss what Dr. Casadevall had to say about that issue here, right?

A. I -- I relied -- I -- I considered it, and, you know, again, I'm not weighing in. It's really up to the PTAB on what they interpret. It's -- it's my economic lens being applied to what I saw in the record, as I've articulated it in my declarations.

Q. But you -- with respect to the issue

of whether an antibody with an amino acid sequence of Sequence ID Numbers 2 and 4 was disclosed in the prior art, with respect to that issue, you understand that Dr. Balthasar's view is, yes, an antibody with the amino acid sequence of Sequence ID Numbers 2 and 4 was disclosed in the prior art, right?

DR. STERLING: Objection to the extent it mischaracterizes witness's testimony.

THE WITNESS: I -- I would defer to the -- the declaration and testimony of -- of Dr. Balthasar, but I -- that's, generally, the understanding that I have based on the citation that -- that is here.

BY MR. DIAMOND:

Q. Mm-hmm. And -- and you understand what Dr. -- that Dr. Casadevall disagrees with Dr. Balthasar on that issue, right?

A. I do understand that Alexion and Dr. Casadevall disagree with that.

Q. All right. You don't offer any opinions in your declarations under the assumption that Dr. Balthasar is wrong about this point regarding an antibody with the amino acid sequence of Sequence ID Numbers 2 and 4

being disclosed in the prior art, right?

DR. STERLING: Objection; form.

THE WITNESS: I -- I think with respect to the discussion in this section as focused on what was known in the prior art, I do rely on Dr. Balthasar. I haven't independently assessed the -- that from a technical or clinical perspective.

BY MR. DIAMOND:

Q. And -- and just to work backwards here you -- what you're discussing in sec -- this section, if we go to Page 13 of your '504 declaration, the heading here is, "The marketplace performance of Soliris is driven by features that I understand were known in the prior art."

Did I read that right?

A. Yes.

Q. And when it -- when it says, "I understand were known in the prior art," the I, that -- that's you, Mr. -- Mr. Hofmann, right?

A. Yeah. And -- and I guess I should say it's not limited to the -- the findings of Dr. Balthasar. I also recite or cite to Paper 15 in Paragraph 24 which is the, you know,

PTAB's preliminary findings.

Q. Mm-hmm. Mm-hmm. Mm-hmm.

A. And that's where I had gotten my understanding from, was that the PTAB found this, that Dr. Balthasar found this.

Q. Now, you understand the PTAB's decision was a preliminary one, right?

A. I do.

Q. Okay.

A. But, I mean, I'm not a lawyer, --

Q. All right.

A. -- but, yeah.

Q. And -- and, again, if -- if -- if the PTAB changes its mind, right, and -- and finds that an antibody with an amino acid sequence of Sequence ID Numbers 2 and 4 was dis -- was -- was not disclosed in the prior art, you haven't offered any opinion regarding nexus under this Section 7 in your declaration, right?

DR. STERLING: Objection; form.

THE WITNESS: There -- there are a lot of ifs in there. What I'm citing to is what they preliminarily found --

BY MR. DIAMOND:

Q. Yeah.

A. -- and what Dr. Balthasar believes.

Q. Now, in -- let me put it this way: The second-to-last sentence in Paragraph 25 you say, "I understand that the eculizumab antibody used in these clinical trials had the amino acid sequences recited in challenge claims of the '504 Patent, Sequence ID Numbers 2 and 4." Do you see that?

A. I do.

Q. And the next sentence we read says, "I further understand that an antibody with the amino acid sequence of Sequence ID Numbers 2 and 4 was disclosed in the prior art.

Do you see that?

A. I do see that.

Q. Do you have any understanding as to whether, prior to March 15th, 2007, the antibody described in the clinical literature as eculizumab was known at that time to be an antibody with Sequence ID Numbers 2 and 4?

DR. STERLING: Objection; form.

THE WITNESS: I mean, I -- I think that that's a better question for technical experts, but my declaration explains that it's my understanding that Alexion themselves had

said that the '245 patent, in their patent term extension application, explained that eculizumab was -- was covered by the '245 patent.

BY MR. DIAMOND:

Q. Mm-hmm.

A. You know, getting into the details or specifics of the specific sequence is a better question for technical experts.

Q. Well, I want to -- I want to be clear here. You -- you -- you looked at the -- the '149, '504 and '880 patents, right?

A. I did.

Q. You looked at the claims of those patents?

A. Again, I'm not a lawyer, not a technical expert, but, yes, I read those patents.

Q. Right. And in -- if we go just in your '504 declaration just to Page 12, Paragraph 20, you say you understand -- I'm looking at the second sentence there, you understand that the '504 patent generally claims a method of treating a patient suffering from, I'll just say PNH, comprising administering to the patient a pharmaceutical composition comprising an

antibody that binds C5 wherein the antibody comprises a heavy chain consisting of sequence ID Number 2 and a light chain consisting of sequence ID Number 4. Do you see that?

A. I do.

Q. All right. And -- and the word -- the word eculizumab doesn't appear in that claim, right?

A. No. I don't -- I don't see that word in that sentence.

Q. Okay. And as -- as far as you're aware, the word eculizumab doesn't appear in -- in any of the claims of the -- of the '504 patent.

DR. STERLING: Objection; foundation. Form.

THE WITNESS: I don't have the '504 patent in front of me, --

BY MR. DIAMOND:

Q. No.

A. -- so I just don't remember one way or the other.

Q. Yeah. Well, let's do it this way: So in Paragraph 24 -- not Paragraph 24.

In the -- in the section that begins

on the bottom, Page 13, Section 7, in general, is it -- is it your opinion here that there's not a nexus between the commercial success of the claimed invention -- or let me rephrase that.

Is it your opinion that there's not a nexus between the commercial success of the -- of the Soliris product, right, the one that we have sales figures for, and the patented invention of the '504 patent, because it's your understanding that the invention of the '504 patent was disclosed in the prior art?

DR. STERLING: Objection to the extent it misstates testimony.

THE WITNESS: I think that, you know, my opinions are articulated in the entirety of my declaration. I think in the first instance, as I point out, there's a complete and utter failure by Alexion to address the question of nexus and the question of what was known in the prior art --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- versus what is claimed in the alleged inventions of the patents in suit.

And when you look at that --

Q. Mm-hmm.

A. -- and then you look at what I understand from reliance on what the PTAB preliminarily found and what Dr. Balthasar found, that further undermines any potential reason to look at commercial success.

And then when you further look at the existence of a blocking patent that Alexion themselves said covered the eculizumab product, and the framework -- work being an orphan drug, you know, that -- those are my opinions as detailed in my -- my declarations.

Q. Let's do -- let's do this: You -- you -- you just said that -- you referred to the, let me get it right, the complete and utter -- I'm using your words here, the complete and utter failure by Alexion to address the question -- the nexus and the question of what was known in the prior art.

You -- you -- you read Alexion's patent owner responses, right?

A. I did.

Q. You read the declarations of Dr. Casadevall, right?

A. I did.

Q. And you read -- you read Dr. Casadevall's deposition -- deposition transcripts, right?

A. I did.

Q. And after reading those three documents, it's your understanding that Alexion failed to address the question of whether the patented invention of the '504 patent was known in the prior art?

A. Yeah. I think --

DR. STERLING: Objection to the extent it misstates testimony.

THE WITNESS: I -- I think that, as I explained in my declarations, --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- first off, there's no economics expert that addresses the issue of commercial success --

Q. That wasn't my question. My question was, did Al -- did Al -- did Alexion fail -- in those documents, in your view, did Alexion fail to address the question of whether the patented invention of these three challenged patents was

known in the prior art? Is that your testimony here today?

A. I -- I --

DR. STERLING: Objection; form.

THE WITNESS: I would defer to the specific way in which I articulated in my testimony and my declarations, but, yes, that's the ultimate conclusion. There's a -- there's a failure by Alexion to properly address the existence of what was known in the prior art versus what the alleged novelty is of the claimed invention.

BY MR. DIAMOND:

Q. Mm-hmm.

A. There's a failure to address the existence of the blocking patent, the '245 patent, which, by their own words, covered ec -- ec -- eculizumab --

Q. Well, we'll -- we'll get to the -- we'll get to the blocking patent, but I -- I would --

DR. STERLING: Let the witness finish.

MR. DIAMOND: Well, he's -- he's -- he's being non-responsive.

DR. STERLING: Let the witness finish.

BY MR. DIAMOND:

Q. Are -- are you -- are you -- do you have more to say to my question?

A. Well, and -- and there's a failure to address the -- the impact of orphan drug exclusivity on the market dynamics.

Q. Yeah. And so I -- I do want to talk to you about the orphan drug, we've talked a bit about the blocking patent, so I -- we will talk about that more, okay? But right now I'm trying to focus you on -- on this nexus opinion that's in your Section 7, and I -- I want to go back to Paragraph 25 and -- and this last sentence there.

You -- you -- is it -- is it your understanding that Alexion and -- and -- and its experts have no opinion on the issue of whether an antibody with the amino acid sequence of Sequence ID Numbers 2 and 4 are disclosed in the prior art?

DR. STERLING: Objection. Misstates the testimony.

THE WITNESS: You know, that's -- that's not really in my domain of expertise in that I'm relying on, you know, what the

PTAB preliminarily found and I'm relying on Dr. Balthasar, I -- I understand that that's in dispute, that's why we're all here, and, certainly, Alexion has some differing theories or views, but I would defer to the technical experts on that.

BY MR. DIAMOND:

Q. Well, that's what I'm -- I just want to understand what you're talking about, because you're telling me, just before, and I want to get your words here -- my realtime is a little bit wonky.

You told me just before that "there's a failure by Alexion to properly address the existence of what was known in the prior art versus the alleged novelty of the claimed invention," but tell me -- tell me -- and that was your testimony there. Tell me -- tell me if I'm wrong, but you do understand that Alexion disputes whether this antibody, Sequence ID Numbers 2 and 4, was disclosed in the prior art, right?

DR. STERLING: Objection. Misstates witness's prior testimony, and form.

THE WITNESS: Yeah. You're -- you're

not, I think, fairly characterizing what I said.
BY MR. DIAMOND:
Q. Well, why don't you explain.
A. I think that, in the context of commercial success, you know, all -- all that Alexion has put forward is a declaration from Bazarko that has some numbers in it, and there's some passing reference in Casadevall with respect to conclusory statements regarding purported commercial success. There's nothing that I think properly addresses, in the context of commercial success, what the marketplace performance of eculizumab has been relative to the alleged novelty of the claimed inventions. There's no -- there's no discussion of that specifically.
I -- I don't disagree with you. Like, I understand --
Q. Mm-hmm.
A. -- that there's -- that -- that Amgen is challenging validity and Alexion is disputing validity. But the point is is, in terms of nexus in the context of commercial success, what can we attribute the marketplace performance --
Q. Mm-hmm.

A. -- of eculizumab to the specific alleged novelty of the claimed inventions, --

Q. Mm-hmm.

A. -- that's not -- that's not existent. And -- and the -- the issue is that there are things that were known in the prior art that -- that are based on Balthasar, based on what the PTAB preliminarily found. And then there's the '245 patent, which, using Alexion's own words, essentially, attribute eculizumab to the '245 patent, which I understand, again, I'm not a lawyer, I'm not a technical expert, but I understand there are things that were known in the prior art.

So that's what I'm saying is, through my economic lens, there is an entirely lacking discussion addressing or witness that properly looks at the very basics of how and why we may want to look at commercial success in an obviousness inquiry that -- that's not -- it's not here.

Q. Let's do it this way: Going back to the top of -- or the top of the section on Page 13, the Heading 7 in your '504 declaration, it's your opinion that the marketplace performance of

Soliris is driven by features that you understand were known in the prior art, right?

A. Yeah. I -- I don't think you can just take a heading and -- and cast that as the entirety of my opinions. I mean, my opinions are outlined in the entirety of my declaration. And as I explain there, certainly, from what I saw in what the PTAB preliminarily concluded and what I saw in -- in Balthasar, suggests that there were clinical trials being conducted, that -- that eculizumab was found to be, you know, safe and efficacious for the treatment of PNH and all that was known long before the priority date of these patents.

Q. Go to Paragraph 27.

You say, "From an economic perspective, because the claimed antibody Alexion alleges is, quote, responsible for the remarkable clinical properties of Soliris and, consequently, its commercial success, end quote, was known in the prior art, the claimed features lack a nexus between the claimed marketplace performance of Soliris and the '504 patent."

Do you see that?

A. I do.

Q. Okay. When you say, "the claimed antibody Alexion alleges is responsible for the remarkable clinical properties of Soliris, and, consequently, its commercial success," you understand that claimed antibody is Sequence ID Numbers 2 and 4, right?

A. I -- I'm not a technical expert, but I think that's consistent with my read of some of the technical expert reports, but I'd defer to them.

Q. And let's see.

Well, you -- you cite a document here, right, --

A. I did.

Q. -- Paper 22 at -- at 64, right?

You -- you cite -- you cite that?

A. I -- I do.

Q. Okay. So you -- you would have looked at that in preparing your declaration, right?

A. Yes.

Q. So I'll hand you -- this is Paper 22 for the '504 patent, which is the -- the patent owner response. And if you want to confirm that, as well, you can see it's in your -- in your table on Page 8, you'll see Paper 22 is the

patent owner response.

Actually, could I have one of those back?

Thanks.

So you -- first of all, just to be on the same page, you understand this is Paper 22 that you cite as the reference for -- for Paragraph 27 of your '504 declaration, right?

A. I believe so.

Q. Okay. And if you look at Page 64, you see, in the middle of the page it says, "Further, the '504 patent claims recite pharmaceutical compositions --

A. Hold on.

Q. Yeah. Further --

A. When you say the --

Q. -- in -- sort of -- sort of two-thirds of the way down.

"Further, the '504 patent," do you see that sentence?

A. Oh, I do. I do.

Q. Yeah. It says, "Further, the '504 patent claims recite pharmaceutical compositions of the sole active ingredient in Soliris, the uniquely engineered, non-naturally occurring

antibody, comprising sequence ID Numbers 2 and 4, which is responsible for the remarkable clinical properties of Soliris, and, consequently, its commercial success as a treatment for PNH."

Do you see that?

A. I -- I do see that.

Q. So going back to your Paragraph 27 of your '504 declaration, you see that you -- you partially quote from that sentence, right?

You start the quote at the words, "responsible for the remarkable clinical properties," right?

A. Yeah. I think that's right.

Q. And you leave out the first part?

You leave out the first part, right?

DR. STERLING: Objection; form.

THE WITNESS: Yeah. I think I was just highlighting the germane aspects of it, but --

BY MR. DIAMOND:

Q. The germane aspect is the claimed antibody, right?

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. That's what you say here, "The claimed antibody Alexion alleges is," and then you go on to quote the rest of the sentence, right?

A. Correct.

Q. And the claimed antibody that Alexion is referring to here is, and I'm quoting from Alexion, "the uniquely engineered, non-naturally occurring antibody, comprising sequence ID Numbers 2 and 4," and they say, "that is responsible for the remarkable properties of Soliris," right?

A. Well, you know, again, this is --

Q. Sir, did I read that?

A. That -- that is the words that appear here, but I think that --

Q. And you left those words out of your declaration, right?

DR. STERLING: Let the witness finish his answer, please.

THE WITNESS: I'd defer -- I'd defer to the technical experts, and I cite to technical experts with respect to the -- you know, this -- this information and what was known in the prior art. And then, of course, there's the other issues I've identified in the

entirety of my declaration regarding the blocking patent, et cetera.

BY MR. DIAMOND:

Q. But this -- this is the element that you're pointing to is that Alexion's alleging is responsible for the remark -- remarkable clinical properties of Soliris, this antibody with Sequence ID Numbers 2 and 4 that's clearly in the patent, right?

A. Well, this -- this isn't a witness -- I mean, again, I'm not a lawyer, but this is just the patent owner's response. It's not a -- a witness statement. It's a lawyer's statement. And I -- I think what I'm saying is is, in this section, and you have to take my declaration in the entirety of its content, that, you know, you have both what the PTAB preliminarily found and what Balthasar found that are forming the basis for my opinion. And then I'm saying -- and when I look at what the PTAB found and what Balthasar found, what Alexion is claiming is responsible for the purported commercial success was known in the prior art. That's what I'm doing here.

Q. But you don't personally know whether Sequence 2 and 4 was known in the prior art or

not, right?

DR. STERLING: Objection; relevance.

THE WITNESS: In -- in -- in any, you know, technical way, I mean, I'm not a formulator, I'm not -- I'm not weighing in on those technical issues.

BY MR. DIAMOND:

Q. Does the citation here to ALXN -- well, let me read your specific.

On Page 64 of Paper 22, the -- the -- in the sentence that you quote from in your Paragraph 27, there's the citation on Page 64 of the patent owner response in that sentence to ALXN20022, Paragraphs 265 and 268, you see that?

A. I do.

Q. And you understand ALXN2022 is Dr. Casadevall's declaration, right?

A. I do.

Q. He's -- he's an expert on -- it's whose opinion as being cited on this issue in -- in that sentence that you quote from, right?

A. It -- it -- yeah. It looks like that.

Q. And you don't discuss or respond to those paragraphs of Dr. Casadevall's declaration in your declarations, do you?

A. I think that's a better domain for technical experts.

Q. Okay. So you didn't, right?

A. Again, I'm not -- I'm not weighing in from a technical perspective. I'm saying that, from what I saw in what the PTAB preliminarily found and what Dr. Balthasar found, that what they're alleging is responsible for the purported commercial success of Soliris is things that were known in the prior art, and I cite it as -- as articulated and outlined in the entirety of my declaration.

Q. But you don't discuss those paragraphs with Dr. Casadevall's declaration that are cited for that sentence you quote in Paragraph 27, right?

DR. STERLING: Objection; form.

THE WITNESS: Well, I -- I mean, I think that --

BY MR. DIAMOND:

Q. If you do, show me where.

A. Well, what I'm -- I -- I, certainly, cite Dr. Casadevall's declaration in the table of information I considered.

Q. Mm-hmm.

A. I am looking at what the PTAB preliminarily found, which looked to the -- the -- the landscape and the issues that were before them --

Q. And Dr. Casadevall submitted the declaration after the PTAB's decision, right?

DR. STERLING: Objection; foundation.

THE WITNESS: I think temporally that might be right.

BY MR. DIAMOND:

Q. Okay. And you don't discuss those paragraphs of Dr. Casadevall's declaration. The ones that are cited in the sentence you quote from in Paragraph 27 of your '504 declaration, you don't cite those or discuss those in your declarations, right?

DR. STERLING: Objection; form.

THE WITNESS: I -- I mean, I think they're indirectly part of the record in that I'm citing this paper, which, you know, includes those references, but I don't disagree with you that I don't explicitly cite his declaration in that paragraph.

BY MR. DIAMOND:

Q. Okay. Or you don't cite that -- that

-- that -- that declaration elsewhere, for that matter, in this Section 7, right?

A. I don't remember whether I have an explicit cite or if it's in underlying citations that I have here.

Q. I'm happy to let you look through at least Paragraphs 24 that -- to 28 of your '504 declaration in Section 7 just to confirm that you have no citations to Dr. Casadevall's declarations here.

A. I -- I don't -- I mean, just having skimmed through it, I don't see any explicit references to his declaration, no, but it's, obviously, part of the information I looked at and considered.

Q. And you don't see any implicit references either, right?

A. Well, I mean, we just did the Paper 22 reference. I mean, it's in that specific page and area that I'm referencing, so it's --

Q. But sitting here right now, you don't know what Dr. Casadevall says in those three paragraphs, right -- or -- is that -- four paragraphs, 265 through 268?

A. Well, that's a crazy question.

Q. I -- maybe you think so, but just if you could answer it.

A. Well, --

Q. Sitting here right now, you don't know what --

A. -- of course, --

Q. -- you don't know what Dr. Casadevall discusses in those four paragraphs, 265 to 268, of his -- of his '504 declaration?

A. You're --

DR. STERLING: Objection; relevance.

THE WITNESS: You're switching sentences, because we were talking about Paragraph 267, but 267 is within 265 to 268.

BY MR. DIAMOND:

Q. Oh, sorry. I was talking about the sentence that you -- that you quoted from on Page 64, which is the sentence beginning, "Further, the '504 patent claims," and you see that cites to Paragraphs 265 and 268 of Dr. Casadevall's --

A. Oh, okay.

Q. -- declaration.

A. All right.

Q. Do you see that?

A. Okay. Yeah. I mean, I certainly did not memorize however many hundreds of paragraphs are in Casadevall's declaration and don't have them at my command right now.

Q. Okay. And you -- and I think we talked about it earlier, but you don't know what -- and I'll represent to you ALXN2032 is Dr. Balthasar's depo -- deposition transcript. You don't know what he says at Page 262, Lines 2 to 19, right?

DR. STERLING: Objection; form.

THE WITNESS: I don't believe that's something that I've reviewed.

BY MR. DIAMOND:

Q. In general, in a -- in -- in assessing whether a patented invention is commercially successful, would you agree that if -- if a -- if there's a product disclosed and claimed in -- in a patent that we have, the patent at hand, right, and that product is commercially successful, with significant sales in the relevant market, we can presume that the commercial success is -- is due to the patented invention?

DR. STERLING: Objection; form,

incomplete hypothetical, and to the extent it calls for a legal conclusion.

THE WITNESS: I -- I'm not a lawyer.

BY MR. DIAMOND:

Q. Mm-hmm.

A. I've -- I've certainly studied this issue, and, from an economic perspective, when you have multiple patents and you have things that were known in the prior art, it doesn't make good or sound economic sense to presume there's nexus. It seems to me that there's situations where, you know, that has to be shown, and there has -- it has to be shown that there is, in fact, a nexus between the alleged novelty of the claimed invention and that the marketplace performance is due to the alleged novelty and not to things that were known in the prior art. I also understand that patent validity is determined on a claim-by-claim, patent-by-patent basis, such that you -- you -- you have a hazard in terms of not properly attributing the marketplace performance to the particular patents that you're studying the validity question for, so --

Q. Sure. And I just want to understand,

in -- in forming your opinions in this case and the issues that you considered, right, did -- did you, in forming those opinions, do so with the understanding that, if a product is claimed in a patent, right, and if the product is, from an economic perspective, commercially successful and has significant sales in the relevant market, that it's presumed that there's a nexus between the patent and the commercial success of that product? Did -- did you form your opinions in this case with that understanding or -- or -- or not?

DR. STERLING: Objection; form, and to the extent it calls for a legal conclusion.

THE WITNESS: Again, I -- I'm -- I'm not a lawyer. I'm -- I'm -- I would defer to the -- to the language in my declaration, which lays out the opinions that I have and the basis for those opinions.

I think that, from a -- from an economic perspective, particularly in situations where you have multiple patents and things that existed in the prior art, presumption of a nexus is economically unsound.

BY MR. DIAMOND:

Q. Well, let's do it this way: If -- if -- if you go to Page 12 of your '504 declaration, you have a section on the -- Section 6 on the definitions of commercial success and nexus relative to objective indicia of non-obviousness.

A. Correct.

Q. Do you see that?

A. Mm-hmm.

Q. And you have three paragraphs, 21 to 23 where, you know, 21 begins, "it is my understanding that," 22 says, "I further understand that," and then 23 says, "I also understand that."

You -- you see those three paragraphs?

A. I do.

Q. Where did your understanding from these three paragraphs come from?

A. The decades' long work I've done on the economics of intellectual property.

Q. Mm-hmm.

Are these legal standards?

DR. STERLING: Objection; form.

THE WITNESS: I -- I mean, --

DR. STERLING: Relevance.

THE WITNESS: -- the -- the -- the point of -- and I guess why I'm saying these are my understandings is I'm not -- I'm not weighing in from any legal perspective, but this is my understanding of the framework --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- and why I'm here at all, to weigh in on the economic issues associated with objective indicia of nonobviousness.

Q. Sure. And -- and I'm not asking for the substance of any communications with counsel, but did you rely on your counsel at all to provide you with any legal standards that are applicable to the issue of commercial success in -- in -- in patent cases?

A. I -- I mean, obviously, there would be some level of that that's inherent in -- in the project, but, you know, most of this I brought to the -- to the project before I was ever contacted by counsel.

Q. Okay. Are there -- are there any legal standards that you apply in your declarations in this case that you did receive

from counsel here?

DR. STERLING: Objection; form.

Also, --

BY MR. DIAMOND:

Q. And, again, not --

DR. STERLING: -- you can answer yes or no without getting into any substance.

BY MR. DIAMOND:

Q. We'll start with yes or no.

A. It's a really broad question, I mean, obviously -- and I know you said start with yes or no, but, you know, the -- the --

Q. Let me -- let me try to narrow it a bit for you.

A. Okay.

Q. I'll just go to -- we'll focus on -- let's stick -- stick with your '504 declaration, okay, and I'm just going to talk about the -- not, generally, what you thought about, but, actually, the text that's in your -- your '504 declaration and the -- and the 43 paragraphs of it. Are there any legal standards that you state in this '504 declaration that you obtained from -- from counsel versus some that you brought yourself?

DR. STERLING: Objection; form.

THE WITNESS: I mean, --

BY MR. DIAMOND:

Q. And I guess you could also answer, I don't recall or I don't know, if that's the answer, verse yes or no.

A. Yeah. I --

DR. STERLING: Same objection.

THE WITNESS: -- I mean, it -- it seems to me that, obviously, I brought a deep knowledge and experience in the issues of economics of intellectual property, including my understanding of the legal framework, and -- and counsel reviewed my understanding of the legal framework. So I don't know that it was obtained from counsel, necessarily, in this matter, but, you know, tacit approval or agreement or, you know, whatever you want to call it, this is -- this is the understanding that I applied, --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- and I have applied, --

Q. Mm-hmm.

A. -- and has been accepted by PTAB and many courts in many, many cases that I've --

Q. Mm-hmm.

A. -- studied these issues on.

Q. Mm-hmm.

Going back to -- well, just let me ask, generally, what's your understanding of what aspects of eculizumab or Soliris are covered by the Evans patent?

DR. STERLING: Objection; form. Relevance. Scope.

THE WITNESS: Evans being the 245?

BY MR. DIAMOND:

Q. Yeah. Earlier I think you were talking about how there's multiple patents that -- that you understand covered the Soliris product, and you said there's the -- the three patents at issue in this case, but there's also the -- the Evans patent, right?

A. Yeah.

DR. STERLING: Objection to the extent that it mischaracterizes testimony.

BY MR. DIAMOND:

Q. And -- and you were -- and you were critiquing Alexion -- Alexion's positions, I believe, because you said they didn't consider, you know, the contribution of -- let me rephrase

that.

Well, you know what, let's go to Paragraph 32 of your '504 declaration.

You got that?

A. Okay.

Q. All right. So here in this paragraph you're talking about the -- the Evans '245 patent, right?

A. Yes.

Q. All right. And you -- you say in the second sentence, you understand that the '245 patent claims an anti-C5 antibody, e.g., and then it goes on. You see that?

A. I do.

Q. Now, do you understand -- when you say, "claimed an anti-C5 antibody," do you -- do you understand what that means?

A. Not in any scientific or technical way.

Q. Is it your understanding that this Evans patent covers all anti-C5 antibodies?

DR. STERLING: Objection; scope. Relevance. Form.

THE WITNESS: I -- I think --

DR. STERLING: And to the extent it

calls for a legal conclusion.

THE WITNESS: I think that's a better question for technical experts and -- and lawyers, and I'm not -- I'm not interpreting claim scope. I'm saying what my understanding is.

BY MR. DIAMOND:

Q. Well, where'd you get that understanding that the Evans '245 patent claims an anti-C5 antibody?

A. Well, I think that, you know, I -- I did read the patent and -- and then -- as a nonscientist, so, again, I would defer to technical experts, and then I cite to AMG1007 and AMG1002, as noted at the bottom of Paragraph 32.

Q. Okay. And AMG1007 is the Evans patent, right?

A. It is.

Q. And -- and just to be clear, you know, when we're looking at the bottom on Page 16 at this claim from Evans that you -- you -- you paste the text of here, when this claim uses phrases like "specific binding being targeted to the alpha chain of human complement Component

C5," or on the next page the phrase, "does not specifically bind to the human complement activation product free C5a," you -- you personally don't have an understanding of what those phrases mean, right, --

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. -- either -- either legally or -- or scientifically, for that matter, right?

DR. STERLING: Same objection.

THE WITNESS: Yeah. I -- I mean, I'm not -- I'm not a technical expert. You know, to the extent I have any understanding of those things, it's from my review of the record and the patents, but I'm not weighing in affirmatively on what those -- what the meaning of those --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- phrases are --

Q. Mm-hmm.

A. -- and how they technically apply in this case. That's a better question for technical experts.

Q. Okay. So you're not offering any

opinion on that?

A. I'm not.

Q. Okay.

A. But I -- but I am offering the opinions, as I articulated in my declaration, that, you know, based on my understanding of what that covers, it would have created economic disincentives to anyone other than Alexion to pursue the alleged novelty of the claimed inventions that are at issue in these IPRs.

Q. Right. That's the -- the blocking patent issue that we were discussing earlier?

A. Correct.

Q. Okay. Got it.

Let me just ask you a quick question about that. If you go to Paragraph 37 in your declaration, your '504 declaration, and in the -- in the second-to-last sentence when you say, "other -- other companies would have been discouraged from developing and commercializing the alleged invention disclosed in the '504 patent as of March 15th, 2007," do you see that?

A. I do.

Q. When you're talking about "other companies," do you have any understanding or

opinion as to how much it would have cost another company, as of March 15th, 2007, to independently develop the inventions of the '504 patent?

DR. STERLING: Objection; form. Scope.

THE WITNESS: I mean, I -- I don't know that I've -- I've studied that issue --

BY MR. DIAMOND:

Q. Mm-hmm.

A. -- in the way that your question asks. The -- the point is, from an economic perspective, the existence of the, you know, '245 patent being out there for many years, the clinical trials that were being undertaken, the very narrow ultra orphan, you know, population that -- that was, potentially, going to be addressed by this product, other companies wouldn't have -- you know, they would have divert -- you know, spent their resources elsewhere, which is, in fact, what we see will happening in how the market has formed.

Q. Well, that's what I want to understand, when you're talking about spending their resources, do you have any opinion

-- other -- when you're talking about other companies spending their resources, do you have any opinion as to the magnitude of what the resource spend would be to -- to de -- for other companies to develop the invention of any of these three patents, the '149, '880 or '504 patent as of -- as of March 15th, 2007? Do you have any opinion on that?

DR. STERLING: Objection; form.

THE WITNESS: I mean, there's a -- there's a lot you have to unpack in that question to make it cogent. You know, there's a difference between conceiving of the alleged invention and commercializing a fully FDA-approved product, you know, with the expense of a regulatory pathway of an NDA at the time and everything else, so I'm not sure what you're exactly asking.

BY MR. DIAMOND:

Q. That -- that -- that's fair enough. You could -- you could invent and -- conceive and invent and -- and get a patent on a product without commercializing it, right?

DR. STERLING: Objection; form.

THE WITNESS: Theoretically, yeah.

BY MR. DIAMOND:

Q. Right.

A. But -- but -- but, you know, typically, there's either an eye towards doing that to, hopefully, make some money some day.

Q. Right. And money could be made -- make -- made by commercializing a product, right?

A. Sure.

Q. Money could be made by licensing IP, right?

A. Well, it -- it -- it can, but, --

Q. Okay.

A. -- again, you have to also recognize that if someone else has already put up a wall around a particular product for a particular indication or therapeutic area that's especially ultra orphan, you know, it's -- again, it's a highly facts and circumstances-based inquiry, --

Q. Okay.

A. -- but, you know, I -- I -- you have to be careful on using platitudes, like your question suggests.

Q. I'm -- does the -- let's talk about the Orphan Drug Act for a minute. Does -- does

-- ex -- so you understand that the Orphan Drug Act has an orphan drug exclusivity period of seven years, and we're talking about in the U.S., right?

A. Yes.

Q. And you understand that that period excludes -- during that exclusivity period, it excludes other companies from making the same drug for the same indication as was granted orphan designation, right?

A. Right. Said differently, I mean, if you can demonstrate an improvement over and existing orphan drug, it's -- you're not barred. But, again, when you're looking at ultra orphan, and, again, I -- I should defer to lawyers and regulatory experts, but I -- I think that the -- the practical reality, especially for something that's ultra orphan, is, you've got -- you've got the -- the only game in town.

Q. Is -- is PNH ultra orphan?

A. I believe so.

Q. What does ultra orphan mean?

A. Well, I mean, I guess the way I understand it is that an orphan drug is a drug that is meant to serve a patient population of

less than 200,000 people in the United States.

Q. Mm-hmm.

A. I don't know that there's a bright line of what gets you to ultra orphan, but I understand that, you know, based on the numbers and based on the documents I've reviewed, that we're talking about, you know, only thousands of -- of patients, not approaching 2,000 -- 200,000 patients.

Q. Okay. So just to -- to make sure I understand, you -- it's your understanding that the -- the prevalence of PNH in the U.S. is on the order of thousands of patients?

A. Correct.

Q. Okay. And going back to my earlier question, there's nothing in the orphan drug exclusivity period that precludes a company from making a different drug for the same indication as granted orphan drug exclusivity, right?

A. So --

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. In other words, like, you know, if one company has a small-molecule drug that is granted orphan exclusivity for a rare disease,

another company could make an antibody of a totally different drug for that indication, and the orphan drug exclusivity period would not block them from doing so, right?

DR. STERLING: Objection; form, and to the extent it calls for a legal conclusion.

THE WITNESS: So I would defer to regulatory experts and lawyers specifically, but from an economic perspective, the granting of orphan drug exclusivity has certain economic implications --

BY MR. DIAMOND:

Q. Well, I'm -- I'm asking you about the -- the -- the -- the exclusivity, sir, because you do offer opinions about exclusivity, right?

A. Right. And --

Q. Okay.

A. -- my -- my point is, I'm saying that the exclusivities have economic implications. And those exclusivities, essentially, --

Q. Sir, I'm not asking you about the economic implications of exclusivities. I'm asking you about the exclusivities themselves. If you feel like you're not qualified to answer my question about the exclusivity, then just

say so and we can move on. But my quest -- my question is, focusing on the FDA regulations and rules, whether they will or will not approve a product during the orphan drug exclusivity period, okay? With that in mind, do you understand that the FDA could approve a different drug during the orphan drug exclusivity period -- let me rephrase that.

Do you understand that, under those rules and regulations that apply for orphan drug exclusivity, if there's Drug A, that has an orphan drug designation for -- for -- for a particular indication, the FDA still can approve a different drug, a different molecule, for that same indication during the seven-year period?

DR. STERLING: Objection.

BY MR. DIAMOND:

Q. Is that your -- is that your understanding of the -- of the -- what the FDA can do under its approval rules?

DR. STERLING: Objection; form.

THE WITNESS: That was a really long question, and I was trying to answer it before you interrupted me.

BY MR. DIAMOND:

Q. You weren't -- you weren't answering it.

A. No.

Q. I think you got confused. My --

A. No.

Q. My question is about the FDA regu -- do you un -- do you, sir, understand the FDA's rules and regulations regarding what they can and can't approve during the orphan drug exclusivity period?

A. So I -- I think my opinions are explained in my report, and --

Q. Do you, sir, understand --

A. -- I think that the -- you know, I would defer to lawyers and regulatory experts, in terms of the specific what is possible or capable of happening. But having studied orphan drugs --

Q. Sir -- sir -- sir --

A. -- in many instances, I believe that the -- the -- the rules or the -- the --

Q. Mm-hmm.

A. -- way that it works is that, if an entity is granted orphan drug exclusivity, it is, theoretically, possible that another company

could, theoretically, pursue and get approval for a product that they can demonstrate shows an improvement over the existing orphan drug exclusive product.

Q. Well, that -- sir, that's for -- that's for -- that's for -- that's for when it's the same drug, right? The rules regarding clinical superiority are for when a second company seeks approval of the same drug for the orphan indication, right?

A. Correct.

Q. I'm talking about a different scenario. I'm talking about two totally different molecules, okay?

A. Oh, okay.

Q. Okay. And so -- so -- so with that in mind, do you understand that --

A. Okay.

Q. -- a comp -- that the FDA, during the orphan drug exclusivity period for Molecule A, and we have -- let's make PNH the disease, okay, for this hypothetical. If you have Molecule A orphan drug exclusivity for PNH; Molecule B, totally different molecule, the FDA can approve Molecule B during the orphan drug exclusivity

period for Molecule A even if B is asking for a PNH indication, --

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. -- right?

A. I -- I think that, setting aside the -- the economic implications and disincentives that are created by the fact that --

Q. I'm only asking you, sir, about the regulatory -- the regulatory -- F -- what FDA can do.

A. As I understand it, and it's not fair to Mr. Black for us to talk over each other, and I'm trying not to do that, but I think that, theoretically, yes, it's my understanding that another Molecule B, if Molecule A had orphan drug exclusivity, it is not barred from being approved for that particular indication or therapeutic area. The -- the practical reality is --

Q. No, sir. That's -- that's all I was asking you, okay?

Again, your -- your counsel --

DR. STERLING: Can you let -- let the witness finish his answer?

MR. DIAMOND: No. He's -- he's -- you know, your -- your -- so your counsel can ask you questions later, all right, that are beyond the scope of what I'm asking, if there's something your counsel wants to ask you. But I need -- I need you to be responsive to my questions.

DR. STERLING: And I'd like you to let the witness to finish his answer.

MR. DIAMOND: The witness was finishing his answer, and he was starting to answer a different question I didn't ask him, and he's wasting our time.

DR. STERLING: Please finish your answer.

MR. DIAMOND: No.

So you could -- your counsel can ask you on -- on -- on -- on redirect.

BY MR. DIAMOND:

Q. Let me -- let's look at -- I just want to show you some documents here.

So you discussed the orphan drug exclusivity issues in your '504 declaration, starting at Page 19, Paragraph 38; is that right?

DR. STERLING: Actually, we've been going for a while.

MR. DIAMOND: Yeah.

DR. STERLING: I don't know if you're about to start into a new section.

MR. DIAMOND: We can -- we can take a break now.

DR. STERLING: Okay.

THE VIDEOGRAPHER: Time is 11:28 a.m. This completes Media Unit Number 2. We are off the record.

(Recess taken.)

THE VIDEOGRAPHER: Time is 11:49 a.m. This begins Media Unit Number 3. We're now on the record.

Please proceed, Counsel.

BY MR. DIAMOND:

Q. Mr. Hofmann, did you speak with your counsel during any of the breaks today about the substance of your testimony?

A. No.

MR. DIAMOND: I've Purelled.

I'm going to hand you a document that's been marked in this case as Exhibit 1089.

///

(Previously marked Exhibit No. AMG1089 was introduced.)

BY MR. DIAMOND:

Q. And -- and you recognize this document as one of the -- the documents you considered and you discussed in forming your opinions in this case?

A. I do.

Q. All right. It's titled Evaluate Pharma Orphan Drug Report 2019?

A. Correct.

Q. All right. Who wrote this report?

A. It's an entity called Evaluate Pharma that I think we can look at the back -- very back page, and it gives you, kind of, a description of the role that they play, the information that they gather and disseminate and is used and regularly relied upon by pharmaceutical companies with respect to emerging issues.

Q. Yeah. But who -- who wrote it? Do you know, like, the -- the -- the -- which people wrote it?

A. The author?

Q. The authors. Yeah. Who wrote it?

DR. STERLING: Objection; relevance.

THE WITNESS: I mean, I think this is a -- this is, like, a company report. I don't know that they articulate the specific authors, unless I'm missing it.

BY MR. DIAMOND:

Q. Okay. But you -- at least sitting here today, you don't know who the authors are of -- of this report?

A. Sitting here today, I do not know the specific authors.

Q. And this document isn't -- isn't a peer-reviewed document, right?

DR. STERLING: Objection; form.

THE WITNESS: I -- I think, yeah, it's not like the Journal of New England Medicine or something like that. It's a -- again, a relied-upon source of information that's used by --

BY MR. DIAMOND:

Q. Well, that wasn't what I was asking, sir. I was asking if this is -- if this document is a peer-reviewed publication?

A. Yeah. I -- I -- I don't believe it is peer-reviewed, but it is --

Q. Okay.
A. -- regularly relied upon.
Q. Sir, I'm not -- sir, I -- I understand that's your testimony. I was just asking you if it was peer-reviewed.
A. Okay. And I'm -- but --
DR. STERLING: You can finish your answer.
THE WITNESS: -- it -- it's a regularly relied-upon source of information that's used by --
BY MR. DIAMOND:
Q. Do you think that's what I asked you? When I asked you whether it was peer-reviewed, is that what I asked you?
A. I -- I think that it's important to explain and give context to --
Q. Well, sir, if -- if you think something's important to say, your counsel could ask you later, okay? I'm just asking you whether this document was peer-reviewed.
A. I -- I don't believe this is a peer-reviewed journal, --
Q. Okay. Thank you.
A. -- but I think it is something that --

MR. DIAMOND: All right. Sir -- sir, now you're not answering my question anymore.

Let me give you another document. This is previously marked in this case as Exhibit 1092.

(Previously marked Exhibit No. AMG1092 was introduced.)

BY MR. DIAMOND:

Q. And do you have -- do you have that in front of you, Exhibit 10 -- 1092?

A. I do.

Q. This is one of the documents that you considered in forming your opinions in this case, right?

A. One of the many documents, yes.

Q. And this document has the title Orphan Drug Pricing and Reimbursement Challenges to Patient Access?

A. It does.

Q. And it -- it says, Analysis by -- by Joshua Cohen. Do you see that?

A. I do see that.

Q. Do you know Joshua Cohen?

A. No.

Q. If you look at the, I guess, Page 5,

the very bottom, you see it says, Josh -- Joshua Cohen is -- is a -- is a healthcare analyst?

A. Yes.

Q. You do.

A. And it goes on.

Q. And it goes on, yes.

And as we saw on Page 1, it says that this document is his analysis, right?

A. Correct.

Q. So these -- these are Joshua Cohen's opinions?

DR. STERLING: Objection; relevance. Form.

THE WITNESS: Yeah. I think that this is, you know, the -- the opinions that he's expressing, which are consistent with what I've found in numerous other publications, but, yes, these are his opinions, --

BY MR. DIAMOND:

Q. Okay.

A. -- having been someone, as you point out, that, you know, studies such issues on a regular basis.

Q. Mm-hmm.

This isn't a peer-reviewed document,

right, AMG1092?

DR. STERLING: Objection; form.

THE WITNESS: You know, I -- I -- I don't believe it's peer-reviewed, but it's, certainly, the types of things that people would reasonably review and rely upon.

BY MR. DIAMOND:

Q. Okay. If you go to Page 2 -- well, let me -- I mean, do you -- do you -- do you consider this a reliable reference?

A. Obviously so. I cite to it in my declaration.

Q. Okay. If you go to Page 2 of this document, AMG1092, and go to the second paragraph "In the decade prior," do you see that paragraph?

A. Yes.

Q. So he says, "In the decade prior to 1983, only 34 orphan drugs were licensed, whereas in 1983 the Food & Drug Administration, FDA -- I'm sorry. I -- I -- let me start at the beginning because I -- I misquoted that.

You see it says in that paragraph, "In the decade prior to 1983 only 34 orphan drugs were licensed, whereas since 1983 the Food &

Drug Administration, FDA, has approved over 500 orphan products."

Do you see that?

A. I do.

Q. He goes on to say, "These have been developed and launched across numerous rare diseases, particularly in therapeutic areas, with considerable unmet need, in parentheses, few or no treatment alternatives, closed parentheses."

Do you see that?

A. I do see that.

Q. On Page 3 -- go to Page 3 of this document, AMG1092, in the third full paragraph you see it begins, "Asking whether there is," do you see that paragraph?

A. I do.

Q. So in the -- in the second sentence there he says, "Surely the decision to reimburse a million dollar drug will depend on the drug's value and not its price alone," right?

A. Yeah. I mean, you're --

Q. You see he says that, right?

A. You -- have read it correctly, but --

Q. O -- okay.

A. -- you're --
Q. That's all I'm asking, sir.
A. -- but you're --
Q. Sir, I'm asking -- sir, I'm asking you read I whether that read that sentence correctly. Did I?
A. You did read that correctly, --
Q. Okay. Great.
A. -- but --
Q. So the -- in the next -- I'm -- I'll -- we'll read more, okay?
He goes on to say, right, "that value could be measured in different ways," you see -- you see that next sentence beginning, "that," right?
A. That's how it begins.
Q. Right. And -- and he says, "Including cost-effectiveness," right? He says that?
A. He does.
Q. He says, "including treatment of an unmet need," right?
A. Yes.
Q. He says, "inc -- including burden of illness and the degree of rarity of the condition being treated," right?

A. Correct.

Q. And then, not the next sentence, but the sentence after, he says that "the budget impact of many of the prices of orphan drugs tends to be limited given the very small numbers of patients who are prescribed the drugs," right?

A. And -- and he goes on.

Q. And -- and then he -- and then he goes on. I understand.

If you go to Page 5 of this document, you see the -- the second full paragraph beginning, "moreover?"

A. I do.

Q. And in the third sentence of that paragraph you see it begins, "specifically, when payers," do you see that?

A. Yes.

Q. So Joshua Cohen says here, "Specifically, when payers examine orphan product characteristics to support reimbursement decisions, the criteria ought to go well beyond cost-effectiveness given that orphan drugs offer distinctive value."

Do you see that?

A. And -- and it goes on.

Q. And it goes on to say that -- that "distinctive value, measured in terms of their targeting rare and relatively severe diseases, in parentheses, e.g., high burden of illness," you see that, right?

A. I do.

Q. And he also says, "For -- for distinctive value, measured in terms of their addressing unmet need, parentheses, e.g., or relative lack of availability of treatment alternatives for most orphan products," right?

A. I think you've read that as it appears there, --

Q. Okay. Okay.

A. -- without reading many, many other sentences in here.

Q. That -- that -- that's -- that's fine. And -- and -- and you -- just to be clear, in your declarations, you don't -- you don't quote all the sentences in this document, right?

A. Fair -- fair enough.

Q. All right.

A. I'll agree with you on that.

Q. Okay. Good.

And in the next paragraph, you see the -- the sentence beginning, "While more intensive orphan drug formulary management," do you see that?

A. I do.

Q. So he says, "While -- while more intensive orphan drug formulary management may appear to be a rational means towards cost containment, one must not ignore that availability and access to certain orphan medicines are important to reduce morbility [sic] and mortality of many rare diseases, right?

DR. STERLING: Objection; form.

THE WITNESS: Yeah. I think you -- you misread it.

BY MR. DIAMOND:

Q. Well, I'll --

A. I think it says should, and I -- I think you said morbility, --

Q. Let me -- let me try --

A. -- instead of morbidity, but --

Q. Let me try it -- try it again. So I'm just -- I want to make sure we're -- we're -- we're right for the record. In -- in that --

in that third full paragraph on Page 5 of this document, AMG1092, he says, "While more intensive orphan drug formulary management may appear to be a rational means towards cost containment, one should not ignore that availability and access to certain orphan medicines are important to reduce morbidity and mortality of many rare diseases," right?

A. That's what that says in that sentence.

Q. Okay. I'm going to give you another document.

I'll give you two documents, actually.

A. Lucky me.

MR. DIAMOND: Okay. So this is two documents previously marked in this case as AMG1095 and AMG1096.

(Previously marked Exhibit No. AMG1095 was introduced.)

(Previously marked Exhibit No. AMG1096 was introduced.)

BY MR. DIAMOND:

Q. And these are two documents that -- that you relied on in your -- in your declarations in these proceedings, right?

A. They are.

Q. Okay. And these are market analyst reports; is that right?

A. Correct. From Piper Jaffray.

Q. Okay. The two analysts listed on both of these documents 1095 and 1096 are Rachel L. McMinn and Hongbo B. Lu, right?

A. That's correct.

Q. Do you know either of them?

A. No.

Q. And if you go to the last page, --

A. Which -- which one?

Q. Sorry. Not -- not the last page. The second-to-last page of -- of -- of 1095 is Page 4. You see there's an analyst certification of Rachel L. McMinn, Ph.D, Senior Research Analyst, at the top of the page?

A. I do.

Q. And she says, "The views expressed in this report accurately reflect my personal views about the subject company and subject security."

Do you see that?

A. And it goes on, but, yeah.

Q. Right. It goes on to say that her compensation isn't -- isn't affected by this

report, right?

A. Correct.

Q. Okay. So you understand this report reflects the -- the analysts' personal views, right?

A. Sure. But analyst's reports are regularly reviewed and relied upon by people --

Q. I know that. I understand. You can tell your counsel that if they ask you later, but my question is sim -- simply my question. And you see that same certification on Page 7 of AMG1096, right?

A. Yeah. I mean, I haven't compared it word for word, but it seems to be consistent.

Q. All right.

So if we look at Paragraph 42 of your '504 declaration, you cite AMG1095 in this paragraph, right?

A. I do.

Q. In the second sentence of this Paragraph 42 you say, "Indeed, according to a market analyst, Alexion believes there is little wiggle room -- and wiggle room is in quotes -- for payers to opt out of paying for Soliris."

Do you see that?

A. I do see that.

Q. All right. And the market analyst you're referring to is -- is Rachel McMinn?

A. It -- well, I mean, coauthored with Hongbo Lu.

Q. Okay. And you're relying on this document authored by Rachel McMinn and Hongbo Lu for your understanding of what Alexion believed?

DR. STERLING: Objection; form.

THE WITNESS: Well, I -- I think that the way I would characterize it is analysts do provide their view and understanding of a company's perspective in writing their analyst reports. But, yes, it's -- it's what the -- the analysts believe are Alexion's views, they interview them on a quarterly basis, Alexion's a public company, they're reviewing their public filings, they're doing due diligence, and these are the things that they've concluded based on their review of the body of evidence that they've studied.

BY MR. DIAMOND:

Q. Sure. And just to -- I want to be specific, with -- with respect to this specific sentence, the last sentence in your Paragraph 42

of your '504 declaration, you're relying on what these -- what this analyst Rachel McMinn and her coauthor, Hongbo Lu, what they believe Alexion, the company, believed a -- about the -- the -- the subject matter of this statement, right?

A. As --

DR. STERLING: Objection; form. Asked and answered.

THE WITNESS: It -- it's -- it's what I said before. I mean, they -- they're, basically, reviewing public filings, they're participating in quarterly earnings calls, they're studying the market. And subject to their, you -- you know, requirements and qualifications, you know, putting out what they believe to be reasonable and reliable opinions that the investing public typically looks at. You know, sure, everybody may have a differing view on which analyst they think is right and which analyst has got the most thorough analysis, but these are the types of things that are regularly relied upon in analyzing a company's performance.

BY MR. DIAMOND:

Q. But in this case the only analysts

that you relied on with respect to what Alexion believed regarding its pricing in 2007 are these two coauthors from Piper Jaffray, right?

A. Well, I don't think that fairly characterizes -- you know, I have a whole section of this report where --

Q. Sir, focus on my question.

A. I --

Q. It's -- I'm talking -- talking about the -- the analysts that you rely on. Okay?

A. Okay. If --

Q. Are there any other analysts you can name for me that you rely on, aside from these two?

A. In --

DR. STERLING: Objection; form.

THE WITNESS: In terms of --

DR. STERLING: Relevance.

THE WITNESS: -- analysts, I believe these are the exemplary analysts that I've cited. I, obviously, cite to other documents and trade publications and articles and information throughout the section on the report, but I don't disagree with you that, in terms of analysts, these are the two exemplary

analysts' reports that I cite specifically in my declaration.

BY MR. DIAMOND:

Q. Are there any other analysts' reports that you considered regarding what Alexion believed about pricing 2007 that you failed to cite in your report?

A. I -- I -- I don't remember seeing --

Q. Okay.

A. A -- a -- again, narrowing it to analysts' reports --

Q. Analysts, yes.

A. -- and setting aside trade publications and independent non-profits like Kaiser, no, I -- I -- I don't -- I don't remember looking at other analysts' reports, specifically.

Q. O -- okay. So looking now at the -- the 1095 analyst report, do you have that in front of you, sir?

A. I do.

Q. All right. Now, the -- the sentence that I believe you're referring to -- well, let me -- let me put it this way: You -- you -- your second sentence in your Paragraph 42 of

your '504 declaration, you -- you refer to "little wiggle room."

You see that language?

A. I do.

Q. And if we look at the first -- the first bold -- bold bullet under -- on the right-hand side, under key points, you see it says, "ALXN confident reimbursement expertise will provide broad access."

Do you see that?

A. I do see that.

Q. All right. And the next sentence you see is -- and you understand ALXN, that's Alexion, right?

A. I do.

Q. So it says, "Alexion believes there is little wiggle room for payers to opt out of paying for Soliris."

You -- that's the -- that's the language that you quote, right?

A. Correct.

Q. But there's a comma, and -- and that -- that statement goes on, right?

A. That's true.

Q. And you don't include the -- the rest

of that language in your declaration, right?

A. Right. I mean, I'm not going to include the entire analyst's report.

Q. I -- I understand.

And the -- the part of the sentence that goes on says -- well, I'll read the whole thing. The entire sentence says, "Alexion believes there is little, quote, riggle [sic] wig -- wiggle room, end quote, for payers to opt out of paying for Soliris," and then it goes on to say, "Thanks to the drug's robust clinical trial results, open paren, e.g., every patient achieves an objective response, closed paren, and unambiguously broad label for all PNH patients."

You -- you see that?

A. Right. Which are things that I understand were known in the prior art.

Q. Sir -- sir, did I ask you that, or did I ask you whether you saw that sentence?

A. You -- you read it --

Q. Okay.

A. -- as the words appear there.

Q. Great. Okay. Thank you.

In this statement in the analyst's

report, AMG1095, where it says, "Alexion believes there is little, quote, wiggle room," and it goes on, this -- this -- this sentence, it's not a -- it's not a direct quote of -- of someone from Alexion, right?

DR. STERLING: Objection; form. Foundation.

THE WITNESS: I -- I mean, I don't know --

BY MR. DIAMOND:

Q. Or you don't know -- you don't know --

A. I don't know.

Q. Fair enough.

A. It may be. Like I said, --

Q. Yeah.

A. -- these analysts are doing, hopefully, adequate research to, you know, explain it. And -- and the way they're expressing it, it seems like that is something that they believe that Alexion believes, based on the research and interviews and earnings calls, et cetera, that -- that are the normal course for analysts.

Q. Right. And at -- at the -- at the end of that paragraph, we see, "The analysts also

believed that Alexion is committed to providing free drug to those who cannot receive coverage through other means, and management expects this will be a very small percentage of the overall commercial base," right?

A. You -- you read that correctly.

Q. Okay. And if you go on in the bottom bullet, "initial demand appears strong, sales working to increase PNH diagnosis," you see that bullet, sir?

A. I do.

Q. Okay. You -- you see the analysts also believe that, "Although Alexion did not provide specific numbers or patients requesting Soliris, several metrics management provided give us comfort in our 2007 projections."

Do you see that?

A. And then -- yeah. And then --

Q. Yeah.

A. -- it goes on.

Q. And then it goes on.

And it -- and the -- what I -- when they say us, they're referring to the -- the -- these two analysts, right?

DR. STERLING: Objection; foundation.

THE WITNESS: I -- you know, I guess, speaking on behalf of Piper Jaffray, sure.

BY MR. DIAMOND:

Q. Okay. And what -- what gave these analysts in Piper Jaffray comfort were, one, requests for free drug access through the Compassionate Use Program significantly exceed the current numbers of patients receiving drug in clinical trial program. Do you see that?

A. I do see that.

Q. And that the drug being referred to there you understand is Soliris, right?

A. Yes.

Q. And they were also given comfort by, two, demand from potential prescribers has significantly -- has -- I'm sorry. Demand from potential prescribers has increased significantly since FDA approval was announced less than two weeks ago.

Do you see that?

A. You read that as it appears.

Q. Okay. And at the bottom of the page on 1095, the first page, you see, "risks to achievement of target price."

Do you see that?

A. Okay. Yeah. Skipping over some more, sure.

Q. And one of -- the third risk they list there is "smaller-than-expected addressable PNH population."

Do you see that?

A. Yeah. I think -- I think you read that as it appears.

Q. Why would that be a risk?

DR. STERLING: Objection; foundation. Form.

THE WITNESS: I -- I'm not a clinician. That's a -- that's a better question for a clinician or --

BY MR. DIAMOND:

Q. Isn't this a question for an analyst?

A. Or -- or an analyst, who probably is consulting with a -- you know, well, I -- I don't know. I think it's a better question for a clinician and/or analysts.

Q. So you don't know?

DR. STERLING: Same objection.

THE WITNESS: Well, I mean, from an economic perspective, it's, obviously, the fewer patients that are actually prescribed, that's

going to have a revenue impact, so that's what they're talking about.

BY MR. DIAMOND:

Q. What do you -- what do you mean by that?

A. Well, I mean, so this is an analyst's report that gives a target price for the stock, and it's talking about, as is standard in an analyst report, the risk to achieving that target price; that they're representing to the public of what they think the stock price could be. And so, you know, I -- I think a natural risk to achieve that target price, particularly with pricing at $500,000 a patient a year, is smaller-than-expected PNH patient population. You know, each and every patient means a lot --

Q. Mm-hmm. Okay.

A. -- to the revenue objectives and assumptions that they're making in forming their opinions.

Q. Okay. If you have -- you have AMG1096 in front of you still?

A. I do.

Q. And you -- you cite this document in, where's your declaration, Paragraph 41 of

your '504 declaration, regarding the -- the WAC, or Wholesale Acquisition Costs, for Soliris that Alexion announced after receiving FDA approval, right?

A. I do.

Q. And the -- the information that you're citing is -- is what appears un -- under the bullet towards the top, significant Soliris pricing update -- upside. You -- you see that the -- the WAC price you -- you quote is in that paragraph?

A. I do.

Q. All right. And in the -- in the sentence following where the -- where the WAC price is -- is quoted, you see it says, "Alexion believes this pricing will be supported by the strength of the clinical data and label for Soliris, the rarity and severity of the disease and the funds required to maintain Alexion's commitment to the PNH community."

Do you see that?

A. You -- you -- you read that accurately.

Q. And, again, that's what the analysts believed, right?

A. Well, I'm not speaking for the analysts, and, obviously, what they're reporting is in the entirety of the report, but that -- that is a comment that appeared within the report.

MR. DIAMOND: Okay. If -- let's get out this document here.

(Previously marked Exhibit No. AMG1090 was introduced.)

BY MR. DIAMOND:

Q. Okay. So this is a document previously designated as Exhibit 1090 in this case. And this is one of the documents that you consider and -- and cite in your -- in your declarations, right?

A. It is.

Q. And you understand this is a -- this is a document from the FDA, right?

A. It is.

Q. It's entitled Orphan Drug -- Orphan Product -- sorry. Let me start again.

It's entitled, Orphan Products: Hope For People With Rare Diseases.

Do you see that?

A. That is the title.

Q. All right. Now, if you look at the second paragraph -- full paragraph on Page 1, beginning, "An Orphan Disease" do you see that paragraph there?

A. The second paragraph?

Q. Yeah.

A. Yeah. I see that.

Q. So you see the FDA says here, "An orphan disease is -- is defined as a condition that affects fewer than 200,000 people nationwide."

Do you see that?

A. I do.

Q. And that's consistent with your understanding, right?

A. Mm-hmm.

Q. Yes?

A. Yes.

Q. Okay.

A. Sorry.

Q. No worries.

And then if you go to the last sentence of that paragraph it says, "Collectively, however, they affect as many as 25 million Americans, according to the

National Institutes of Health, and that makes the diseases, hyphen, and -- and finding treatments for them -- I should say dash, not hyphen, dash, a serious public health concern."

Do you see that?

A. I do see that.

Q. If you go to Page 2, and the first full paragraph, second sentence, beginning, "for example," do you see that?

A. Okay. At the top of the page?

Q. Yeah. You see that?

A. Uh-huh. Yes.

Q. You see it says this: "For example, for one-third of people with a rare disease, getting an accurate diagnosis can take one to five years."

Do you see that?

A. That is what it says.

Q. And is -- is it your understanding that -- that, for some rare diseases, it can be difficult to even identify and diagnose patients with the rare disease in the first place?

DR. STERLING: Objection; relevance. Scope.

THE WITNESS: That -- that's a better

question for a clinician or a technical expert.
BY MR. DIAMOND:
Q. All right. Okay. So you don't -- you don't have a view on that?
DR. STERLING: Same objections: Relevance. Scope.
THE WITNESS: I mean, it's facts and circumstances depending on the disease, but I would, again, defer to technical experts --
BY MR. DIAMOND:
Q. Okay.
A. -- and clinicians.
For PNH, do you -- do you know anything about the difficulty of identifying and -- and diagnosing PNH patients?
DR. STERLING: Objection; relevance. Scope.
THE WITNESS: I mean, I -- that's really not a good question for me. It's a question for technical experts, --
BY MR. DIAMOND:
Q. Okay.
A. -- you know.
Q. Well, let me -- let me ask you this: If you go to the bottom of Page 2, or

towards the -- or towards the bottom, you see the heading, "Adopting The Orphans." Do you see that?

A. I do see that.

Q. All right. And in this -- in this document, again, we're in AMG1090, the first sentence of that paragraph under that heading you say -- you see they say, "Before the passage of rare disease laws in the United States, patients diagnosed with a rare disease were dia -- denied access to effective medicines because prescription drug manufacturers rarely can make a profit from marketing drugs to such small groups."

Do you see that?

A. I do see that.

Q. And the FDA then says, "Consequently, the prescription drug industry did not adequately fund research for orphan product development," right?

A. Yes.

Q. And then in the next paragraph they say, "This changed in 1983 when Congress passed the Orphan Drug Act," right?

A. Yeah. You skipped over a few

sentences, but --

Q. Yeah. Sure.

And -- and the next sentence after the one we just read was, "The ODA created financial incentives for drugs and -- drug and biologic manufacturers, including tax credits for costs of clinical research, government grant funding, assistance for clinical research and a seven-year period exclusive marketing given to the first sponsor of an orphan-designated product who obtains market approval from the Food & Drug Administration for the same indication," right?

A. You -- you've read that as the words appear there.

Q. And that's consistent with your understanding, right?

A. Well, I -- I mean, yeah, I -- that -- that's, certainly, the spirit of why the Act was passed.

Q. Okay. And in the next paragraph it says, "Since 1983 the ODA has resulted in the development of more than 250 orphan drugs, which are now available to treat a potential patient population of more than 13 million Americans,"

right?

A. That's -- you've read those words as they appear there.

Q. And -- and they -- they go on to say, "In contrast, the decade before 1983 saw fewer than 10 such products' development without government assistance," right?

A. Tho -- those are the words that appear there.

I mean, obviously, there's been a gajillion changes to the healthcare system and prescription drugs since then, but, yes, those -- those are the words that appear there.

Q. Well, this is -- this is -- this is from 2012, right, this document, FDA Rare Disease Patient Advocacy Day 2012 is on the cover?

A. Yes. It appears so.

Q. All right. Okay. And if you go to Page 3, again, where we were reading, after the last sentence we read, the -- the FDA says, "As a result of the ODA, treatments are available for people with rare diseases who once had no --

A. I -- I don't know where you are.

Q. Sure. And this is the first full paragraph on Page 3 that begins, "since 1983." Are you with me on that paragraph?

A. Oh, okay.

Q. So it's the last sentence where -- where they say, "As a result of the ODA, treatments are available for people with rare diseases who once had no hope for survival," right?

DR. STERLING: Objection; form.

THE WITNESS: You read that as the words appear there.

BY MR. DIAMOND:

Q. Okay. And the -- the last sentence in this section just above the header for Patient Support Groups, it says, "Despite the success of the ODA, however, rare disease advocacy groups argue that the plight of people with orphan diseases deserves even more attention."

Do you see that?

A. You -- you read those words as they appear there.

Q. And you understand those to be -- those rare disease advocacy groups to be groups

that advocate on behalf of rare disease patients?

DR. STERLING: Objection; relevance.

THE WITNESS: I mean, I'm not a clinician or practitioner, but that certainly contextually makes sense.

BY MR. DIAMOND:

Q. And, for example, in the -- in the next section under Patient Support Groups, the second paragraph, they refer to a group called National Organization for Rare Disorders, or NORD. Do you see that?

A. I do.

Q. And they say, paramount -- in the second sentence -- second sentence of that paragraph they say, "Paramount to NORD's ongoing cause are efforts to promote legislation, such as the ODA, that encourages further research and continuing development of products that are necessary, dash, and often lifesaving, dash, and to provide easier access to such treatments."

Do you see that?

A. You read those words as they appear there.

Q. Okay. Now, you mentioned, I think

-- earlier you mentioned something about, I think you said KHN and -- and not nonprofits. What -- what -- what is KHN?

A. Kaiser Health Network.

Q. Okay. And what are they?

A. I mean, I don't -- I don't profess to know everything about them, but they're a -- I believe a -- they have many arms.

Q. Mm-hmm.

A. One -- one of the arms is, you know, kind of, focused on public health issues --

Q. Uh-huh.

A. -- from a not-for-profit, you know, foundational funding perspective.

Q. Well, let me -- let's do it this way. And you've heard of -- of NPR, right?

A. Of course.

Q. And what's NPR?

A. National Public Radio. I'm assuming that's what you're referring to.

MR. DIAMOND: Yeah. Yeah.

Here. So these are for you guys.

I'm going to give you two documents previously marked AMG1093 and 1094.

///

(Previously marked Exhibit No. AMG1093 was introduced.)

(Previously marked Exhibit No. AMG1094 was introduced.)

BY MR. DIAMOND:

Q. And these are two documents that you considered in connection with your opinions in this case, right?

A. They are.

Q. Okay. Do you know who -- who found these documents for -- for use in this case?

A. It was the independent research of my team.

Q. Do you know how they found them?

A. I think Google.

Q. Do you know what they were looking for?

A. I think just, you know, one of the areas I directed them to study and identify documents for was the section related to the role that orphan drugs and the Orphan Drug Act plays with respect to pricing and the sales that we see with respect to Soliris.

Q. Okay. And what would you call these, like, new -- news articles or news reports?

A. I -- I would call them, you know, articles, I guess, written by Kaiser Health and from their not-for-profit arm that are -- are providing, you know, their -- their views with respect to the issues that are addressed within the respective articles.

Q. Well, they're -- they're written by Sarah Jane Tribble and Sydney Lup -- Lupkin, right, --

A. They are.

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. -- or Lupkin?

A. They are.

Q. And do you -- do you know who Sarah Jane Tribble and Sydney Lupkin are?

A. Not personally, no.

Q. Do you know if they have any economic expertise?

A. I mean, obviously, they're reporters or, you know, working in some capacity within Kaiser Health.

Q. You don't -- you don't know anything --

A. I don't know. I don't know what

economic training they may or may not have.

Q. Okay. And the same thing with -- with respect to, you know, FDA regulations and FDA regulatory matters, you don't know what -- what training they may have in that, right?

DR. STERLING: Objection; form. Relevance.

THE WITNESS: Yeah. I -- I don't -- I don't know their CV or bios. I think that, --

BY MR. DIAMOND:

Q. Okay.

A. -- you know, Kaiser is someone that is regularly looked at and considered by people, and they, obviously, also refer to other contributors and sources.

Q. Sure.

If you go to Page 21 of AMG1093, do you see the list of other contributors there?

Do you see that?

A. Yes.

Q. So we have contributors John Hillkirk, Scott Hensley at NPR; Diane Webber, Marilyn Thompson, in parentheses, editors. Elizabeth Lucas, in parentheses, data editing. And Joe

Neel at NPR, in parentheses, radio editing.

Do you see that?

A. I do.

Q. So you understand some of those are -- are -- are, perhaps, people at Kaiser Health and some of them are people at NPR, National Public Radio?

A. That would stand to reason.

Q. And -- and -- and, I guess, same question, do you know anything about the economic expertise or education or credentials of -- of any of these folks listed as contributors in AMG1093?

A. I mean, not -- not specifically, but, again, --

Q. Or even generally, with these particular individuals?

A. Not specifically, but the -- or generally, but the -- you know, again, these are the types of information and articles that provide information and provide context to the opinions that I've formed.

Q. Certainly, you've never heard of these -- these names of these individuals before, --

DR. STERLING: Objection; foundation.

BY MR. DIAMOND:

Q. -- as far as you can recall, right, from all of your work in the field?

A. I -- I don't remember one way or the other. I didn't --

Q. And -- and the same goes for Sarah Jane Tribble and Sydney Lupkin, do you have any recollection of -- of -- of hearing about those particular individuals before from your work in the field?

DR. STERLING: Objection; relevance.

THE WITNESS: As individuals, no, --

BY MR. DIAMOND:

Q. Okay.

A. -- but, certainly, Kaiser Health is --

Q. Sure. I -- I understand.

And there's -- if you look at Page 15 of AMG1094, we see --

A. I'm not there yet, so --

Q. Oh, sure. Let me know when you're there.

You see the contributors there include John Hillkirk, Scott Hensley, NPR, Diane Webber, as editors; Elizabeth Lucas, data editing, and Joe Neel, NPR radio editing. Do you see that?

A. I do.

Q. And those are -- I guess all those folks were -- were -- we already saw listed as contributors in AMG1093, right?

A. It appears so.

Q. All right. These aren't peer-reviewed publications, 1093 and 1094, right?

A. They aren't peer-reviewed, --

Q. Okay.

A. -- but, like I said, they're the types of things that are reasonably relied upon.

Q. That wasn't my question.

So the -- the -- let's take 1093. You see the title of 1093 is Drug Makers Manipulate Orphan Drug Rules to Create Prized Monopolies?

A. I do see that.

Q. You see that?

Now, you're not saying that Alexion manipulated the orphan drug rules with respect to Soliris, right?

DR. STERLING: Objection. Misstates testimony.

THE WITNESS: I mean, I think that the opinions I have with respect to Orphan Drug Act and orphan drug exclusivity are articulated in

my declaration. What I'm saying is is that, certainly, Alexion has taken advantage of, I'm not accusing them of manipulation or fraud. I'm just saying that, you know, in the framework that exists in 2007 and beyond, when they launched the product, they've been able to harvest a lot of value because of the framework that was established by the Orphan Drug Act, as explained in detail in my declaration.

BY MR. DIAMOND:

Q. Let me -- let me ask this: At the bottom of Page 1 on 1093, you see this report says, "And many drugs that now have orphan status aren't entirely new. More than 70 were drugs first approved by the Food & Drug Administration for mass market use."

Do you see that?

A. Yes.

Q. Now, So -- Soliris wasn't one of these drugs that was first approved by the FDA for mass market use, right?

A. So, I mean, these articles aren't -- aren't solely directed to Soliris. Soliris does get mentioned, but, no, it was not like Humira has some orphan drug designations, which is the

top-selling drug in the world. Soliris wouldn't fall in that category.

Q. Okay. And on Page 3 of 1093, under -- under the -- the graphic with the -- with the gift box and a fistful of money saying "Designated Orphan Drug Incentives," you -- you see -- well, first of all, you see that graphic?

A. I do.

Q. Okay. And then below that graphic it says, "When a drug maker wins approval of a medicine for an orphan disease, the company gets seven years of exclusive rights to the marketplace, which means that the FDA won't approve another version to treat that rare disease for seven years even if the brand's -- the brand name company's patent has run out," right?

A. I see that.

Q. Okay. But Alexion's patents hadn't run out as of 2014 when the orphan drug exclusivity for PNH expired, right?

A. No, they had not.

Q. Okay. So Soliris doesn't fall in -- in this category they're referring to in that -- that last phrase there, right?

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. Actually, let me ask a different question.

If you go to Page 17, --

Are you there?

A. I am.

Q. -- you see at the very bottom of the page the paragraph that bridges Page 17 to 18, "Breaking down larger," do you see that?

A. I do see that.

Q. Okay. It says, "Breaking down larger, broader diseases into smaller groups is still allowed under certain conditions, and companies can still win multiple orphan drug approvals for a single drug, even if the total population served rises above the 200,000 mark."

Do you see that?

A. I do.

Q. Now, Soliris isn't one of the drugs being referred to here where larger, broader diseases were broken down into smaller groups, right?

DR. STERLING: Objection; form.

THE WITNESS: I mean, I'd defer to

clinicians and technical experts, but from what I understand, this is more so directed to products other than Soliris.

BY MR. DIAMOND:

Q. Mm-hmm. Mm-hmm.

A. Said differently, as I understand it, all the labeled indications fall under the $200,000 threshold -- or, excuse me, not $200,000, 200,000-patient population threshold.

Q. Right. Right.

How did you prepare for your deposition today?

DR. STERLING: I'm going to object to the extent it gets to privilege. You may talk, generally, about, you know, when, who, how much, time, but please do not discuss any substance of conversations, and I'm going to presume that is not the point of Mr. Diamond's questions.

BY MR. DIAMOND:

Q. Yeah. Yeah. I'm not -- you're -- you're right. I'm not asking for the substance of any communications with counsel. I'm just asking how you prepared for your deposition.

A. So, I mean, having -- having done work and done PTAB declarations before, --

Q. Mm-hmm.

A. -- you know, everything I did, the work I did in drafting the declaration and reviewing documents had an eye towards the chance that I would get deposed.

Q. Mm-hmm.

A. In the immediately preceding last few weeks, I -- I -- I re-reviewed my declarations, I re-reviewed all the documents and exhibits that I cite in my declaration, --

Q. Mm-hmm.

A. -- I spent some time with my team at Gleason IP and then yesterday I met with counsel for a few hours.

Q. So in terms of re-reviewing your declarations and re-reviewing the documents and exhibit -- exhibits that you cite in your declaration to prepare for -- talking about preparing for your -- your deposition today, did you re-review all the documents that you cited in your declarations to prepare for your deposition today?

A. I did.

Q. And did -- and, again, did you -- did you re-review them all front to back to prepare

for your deposition?

A. I mean, I wouldn't say front to back. Some are lengthier than others, --

Q. Mm-hmm.

A. -- but I -- I studied them and the citations, in particular. And if I cited to particular paragraphs or particular --

Q. Mm-hmm.

A. -- aspects of it, that -- that's where I focused.

Q. Okay. And how much time did you spend preparing with your Gleason IP team for your deposition today?

A. So, I mean, I did some things independently.

Q. Mm-hmm.

A. Like, are you asking, like, my specific live meetings with my Gleason IP team.

Q. Well, okay. So did -- did you have specific live meetings with your Gleason IP team to prepare for your deposition?

A. Maybe -- maybe a hour or two --

Q. Mm-hmm.

A. -- I did so.

Q. Okay. And aside from the live

meetings, did you have any other types of meetings, phone meetings, video conference meetings with the Gleason IP team to prepare for your -- your deposition.

A. Mr. Bummer was in attendance on my meeting with counsel yesterday --

Q. Okay.

A. -- by phone.

Q. Sure.

And you -- you appeared in person with your counsel yesterday to prepare for the deposition?

A. I did.

Q. And Mr. Bummer was on the phone?

A. Correct.

Q. Was there anyone else on the phone in your -- your dep prep meeting yesterday with counsel?

A. On the phone, I don't believe so.

Q. Mm-hmm.

A. There was one -- one -- you know, I mean -- well, I'll leave it at that. That's the answer to your question.

Q. And so who were the counsel that were present in the room during your meeting

yesterday?

A. The counsel that's present here, as well as Ms. Rebecca Lindhorst, --

Q. Mm-hmm.

A. -- and then in-house counsel from Amgen.

Q. Okay. And you said -- how -- how long did you say that meeting was?

A. I didn't say.

Q. Okay. How long was the meeting?

I -- I -- I wasn't sure whether you did or not.

A. Yeah. No.

I think we started at 9, and then maybe we were done around 3 or 4. I can't remember exactly.

Q. Mm-hmm. And then prior to that, did you have any other meetings with your Am -- with your counsel for Amgen to prepare for your deposition?

A. No, sir.

Q. Okay. And did you spend time -- apart from the meetings with your Gleason IP team and the meeting yesterday with counsel, did you spend time on your own preparing for your

deposition?

A. I did.

Q. That's the time that you spent reviewing the documents that we've discussed?

A. Yeah. Essentially, going through the documents cited and the information reflected in the declarations.

Q. Mm-hmm. And how long did you spend doing that?

A. I mean, it wasn't all at once, so, you know, maybe a day or two over the course of two weeks. I'm just guessing. I don't know off the top of my head.

Q. Were there any documents that you reviewed to prepare for your deposition beyond the ones that are cited and discussed in your declaration?

A. Not -- nothing comes to mind as I sit here right now.

Q. All right. I want to take a break just to see -- I think I'm pretty close to wrapping up. I just want to see if there's anything else, so --

DR. STERLING: Okay.

MR. DIAMOND: I guess it's close to or

past lunchtime, but I think I'm probably going to be done pretty soon after. So if you guys are good to hold out, we can just do that.

DR. STERLING: We can hold out.

MR. DIAMOND: All right.

THE VIDEOGRAPHER: The time is 12:43 p.m. We are going off the record.

(Recess taken.)

THE VIDEOGRAPHER: The time is 12:59 p.m. We're back on record.

Please proceed, Counsel.

BY MR. DIAMOND:

Q. Mr. Hofmann, you have your '504 declaration in front of you?

A. I do.

Q. And you go to Paragraph 10.

A. Okay.

Q. You say in Paragraph 10, "In -- in the course of my work in providing consulting and expert services, I regularly analyze and review data for the pharmaceutical and life sciences, industry, including data from IQVIA, formerly known as Quintiles IMS and IMS Health Services, Inc.; Symphony Health Services; Truven --

A. Solutions.

Q. I'm sorry. Symphony Health Solutions.

-- Truven Health Analytics and -- and other service providers."

Do you see that?

A. I do.

Q. And you -- you didn't -- you didn't analyze or review any data from -- from those services here in these proceedings, right?

A. I -- I don't recall seeing data sets from those service providers in this case.

Q. Okay. And you go on to say, "I am knowledgeable regarding the role of pharmaceutical databases, such as First Databank, Medi-Span, Gold -- Gold Standard and other information sources in the fulfillment of prescriptions."

Do you see that?

A. I do.

Q. And you didn't review data from those pharmaceutical databases in this case, right?

A. I -- I don't recall seeing data or documents from them in this case, no.

Q. All right. Did -- have you talked with your counsel during the course of any of the breaks today about the substance of your

testimony?

A. No, sir.

MR. DIAMOND: All right. No further questions for you at this time. Thank you very much.

THE WITNESS: Thank you.

DR. STERLING: And we, actually, also have no questions for you today, so this would conclude your deposition.

THE WITNESS: Okay. Great. Thank you.

MR. DIAMOND: Everyone get home safe.

THE WITNESS: Everybody stay safe.

THE VIDEOGRAPHER: The time is 1:01 p.m. This conclude today's testimony by Ivan Hofmann. We are now off the record.

(Deposition concluded -- 1:01 p.m.)

Ivan T. Hofmann

C E R T I F I C A T E

I do hereby certify that the aforesaid testimony was taken before me, pursuant to notice, at the time and place indicated; that said deponent was by me duly sworn to tell the truth, the whole truth, and nothing but the truth; that the testimony of said deponent was correctly recorded in machine shorthand by me and thereafter transcribed under my supervision with computer-aided transcription; that the deposition is a true and correct record of the testimony given by the witness; and that I am neither of counsel nor kin to any party in said action, nor interested in the outcome thereof.

WITNESS my hand this 19th day of March 2020.



Ryan K. Black

Andrew M.. Wilber, Esquire

awilber@kslaw.com

March 19, 2020

RE: Amgen Inc. v. Alexion Pharmaceuticals, Inc.
3/12/2020, Ivan T. Hofmann (#4021383)

The above-referenced transcript is available for review.

Within the applicable timeframe, the witness should read the testimony to verify its accuracy. If there are any changes, the witness should note those with the reason, on the attached Errata Sheet.

The witness should sign the Acknowledgment of Deponent and Errata and return to the deposing attorney. Copies should be sent to all counsel, and to Veritext at cs-midatlantic@veritext.com

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Amgen Inc. v. Alexion Pharmaceuticals, Inc.

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Ivan T. Hofmann Date

Amgen Inc. v. Alexion Pharmaceuticals, Inc.

Ivan T. Hofmann (#4021383)

ACKNOWLEDGEMENT OF DEPONENT

I, Ivan T. Hofmann, do hereby declare that I have read the foregoing transcript, I have made any corrections, additions, or changes I deemed necessary as noted above to be appended hereto, and that the same is a true, correct and complete transcript of the testimony given by me.

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Ivan T. Hofmann Date

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Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

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Deposition of:

Joseph P. Balthasar , PhD

April 22, 2020

In the Matter of:

Amgen vs. Alexion

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN, INC.,
Petitioner

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner
U.S. Patent No. 9,725,504
U.S. Patent No. 9,732,149
U.S. Patent No. 9,718,880

IPR2019-00739
IPR2019-00740
IPR2019-00741

Wednesday, April 22, 2020

Video deposition of JOSEPH P. BALTHASAR, PH.D., taken virtually via Zoom, at the home of Joseph P. Balthasar, Ph.D., 5630 William Street, Lancaster, New York, beginning at 9:08 a.m., before Ryan K. Black, a Registered Professional Reporter, Certified Livenote Reporter and Notary Public in and for the Commonwealth of Pennsylvania.

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Tara Rahemba - Alexion - Via Zoom
Nolan Church - Legal Videographer - Via Zoom

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THE VIDEOGRAPHER: We are now on the record. The time is 9:08 a.m. eastern. The date is April 22nd, 2020. This is the video-recorded deposition of Joseph Balthasar, Ph.D., in the matter of Amgen, Incorporated, versus Alexion Pharmaceuticals, Incorporated.

My name is Nolan Church. I'm the videographer. The court reporter is Ryan Black. We both are from the firm Veritext.

Will the attorneys please identify themselves and the parties they represent, and their location?

MR. DIAMOND: You have Evan Diamond here, from King & Spalding, representing the patent owner, Alexion Pharmaceuticals. And with me on the -- on the call -- deposition call today is Gerald Flattmann, also of King & Spalding, and Tara Rahemba of -- of Alexion.

That -- that's who I believe is on the line now.

DR. STERLING: Good morning. This is Deborah Sterling from the Sterne -- from the Law Firm of Sterne Kessler Goldstein & Fox, representing Amgen in this case. With me on the video deposition today are David Holman, also

from Sterne Kessler, as well as Paula Fritsch and Angie Mah, both from Amgen.

THE VIDEOGRAPHER: Please administer the oath.

* * *

Whereupon --

JOSEPH P. BALTHASAR, PH.D., called to testify, having been first duly sworn via Zoom videoconference, was examined and testified as follows:

EXAMINATION

BY MR. DIAMOND:

Q. Good morning, Dr. Balthasar.

A. Good morning.

MR. DIAMOND: And so, Counsel, before we start the deposition, just want to make sure we're -- I -- I believe we agree with this, but that we -- we all agree on the admissibility of -- of -- of this -- this -- this video deposition as if it were, you know, taken in person under the ordinary circumstances?

DR. STERLING: We do.

MR. DIAMOND: Okay. Great.

BY MR. DIAMOND:

Q. So, again, good morning, Dr.

Balthasar. You know, you -- you understand that, of course, we're -- we're taking this deposition today remotely by video, not -- not in the way that we did your previous deposition in person. So at any point today, if you can't hear me or can't see me or have any issues with technology, please -- please do speak up and let us know. Okay?

A. I -- I understand that, and I will.

Q. Great.

But as -- as -- as of right now, do you hear me well enough, do you hear, you know, what I'm saying and can you see me well enough?

A. Yes. It's absolutely fine.

Q. Great. Great.

And, you know, just for the record, you're the same Dr. Joseph P. Balthasar who gave a deposition earlier in these proceedings back in October of last year, right?

A. Yep. The same person as then, correct.

Q. Yeah. You were -- you were under oath when you gave that testimony, right?

A. That's right.

Q. And you understand that you're under

oath again today, right?

A. I do.

Q. And you understand we're here today to talk about your -- your reply declarations that you submitted in these proceedings that you -- you signed in February of 2020?

A. Yes. I understand.

Q. All right. Now, you understand I'll be asking you questions, and you'll be giving me answers, right?

A. Yes. I understand.

Q. Now, we -- you know, we -- as with last time, we have limited time to discuss your -- your three declarations that you've submitted in these proceedings, the three reply declarations. So if I ask a question, I do need you to answer the specific question that I ask.

Will -- will you do your best to answer my questions as I ask them?

A. Yes, I will.

Q. All right. And if there's something you -- else you want to add, do you understand that after I'm finished with my questions today, Amgen's counsel has the opportunity to ask you additional questions so long as it covers the

scope of the questions that I ask you today? Do you understand that?

A. I do understand. And just so that I'm clear, my understanding, as well, is that, after addressing your question, you know, hopefully, with a clear, maybe, yes or a no, that I could explain my answer as part of my response.

Is that correct?

Q. Well, I don't know. We'll have to take it question by question, but I do need you to focus on my questions today. Okay?

A. Sure.

Q. All right. Now, as I said, if there's any point at all today where you can't see me, you can't hear me, you can't see one of the exhibits that we're talking about, you'll let me know, right?

A. Yes.

Q. And if you don't understand any of my questions today, please let me know and -- and I'll try to rephrase it, or -- or -- or say it again, if you need to hear it again, okay?

A. Yes. Sure. That will be fine.

Q. Great.

And if you do answer a question, I'll

assume that you heard it and -- and understood it. Okay?

A. That's understood.

Q. Okay. As we talked about a little bit before the deposition, I'll be sharing exhibits with you electronically today. So, again, if you have any issues viewing an exhibit that I'm showing to you, just please -- please let me know. Okay?

A. Yes. That's -- I will.

Q. All right. Is there any reason you can't give truthful and accurate testimony today?

A. No.

Q. And just for the record, where -- where are you presently sitting for this video remote deposition?

A. I'm in the basement of my house, which is located in Lancaster, New York.

Q. All right. So you -- you -- prior to the start of this deposition, you were able to access the -- the -- the -- the -- the Exhibit Share website that -- that the court reporting company, Veritext, set up, right?

A. That's correct.

Q. Okay. And you were able to download your three reply declarations in this case, right?

A. That's correct. I've downloaded the three documents.

I -- I have to say that I haven't looked at them carefully, but I did download those three files that were in the Exhibit Share folder.

(Exhibit No. AMG1081, Dr. Balthasar's reply declarations, was introduced electronically.)

BY MR. DIAMOND:

Q. Okay. Well, why don't you just take a look at those and op -- open those PDFs now. Each one of them should be designated AMG1081, but they're the -- the three reply declarations in -- in these three IPR proceedings, right?

A. Right. I did open each file, and -- and I looked at the face page and a few pages that follow, and they all -- they all look appropriate as the declarations that I submitted.

Q. And you could also confirm in each of them that they have your -- your -- your

signature that you -- you -- you signed on -- on February 14th, 2020, right?

A. I -- I didn't look at that, but I'd be happy to do that if you'd -- if you'd like me to.

Q. Yeah. Could you please just check it and make sure that these are the declarations you signed on February 14th, 2020?

A. Yes. I can verify these are the documents that I signed on February 14, 2020.

Q. Great.

And you'll understand if I refer to these three documents altogether as -- as your reply declarations?

A. Yes. I'll understand that.

Q. And you'll understand if I refer to them individually as your -- your '504 reply declaration, your '880 reply declaration and your -- your '149 reply declaration, respectively?

A. Yes. I will -- I'll understand.

Q. Okay. How did you go about putting your reply declarations together?

DR. STERLING: I'm going to object to the extent this gets to privileged information.

Dr. Balthasar, you may answer generally about timing and logistics, but please don't discuss any substance of any discussions with your attorneys.

THE WITNESS: Yeah.

Sometime before February 14th, I don't remember exactly one -- when, maybe a month or two months before, Sterne Kessler contacted me to see if I would be into agreeing to submit declarations again. And we went through the process of looking at the arguments that were raised by Dr. Casadevall and Dr. Trout, and then discussed those arguments in the context of developing a reply declaration.

The first draft of the reply declaration was prepared by counsel, provided to me, and we went back and forth and eventually finalized it as the documents that were signed.

BY MR. DIAMOND:

Q. Okay. How many rounds of revisions were there?

A. I, honestly, don't know. I mean, we had discussions about the -- the declarations back in -- it's not like I re -- I don't recall, you know, specific iterations. Rather, just a

-- a discussion that was more fluid.

Q. Mm-hmm.

Do you recall when you received the first draft of your reply declaration from your counsel?

A. I don't recall exactly. I -- I think it was probably in January of this year, 2020, but I -- I don't recall exactly.

Q. Okay. And -- and how -- how much time did -- did you spend on your reply declarations?

A. Yeah. I -- I haven't reviewed that exactly, but my guess would be around 20 hours.

Q. Okay. Is -- are there any sections of your reply declarations that were drafted solely by counsel; for example, I think maybe in -- in your -- your prior declarations, you -- you might have said that the legal sections were -- were -- were drafted by counsel. But I'm wondering if there are any sections of these declarations that were drafted by -- you know, particularly by counsel and you relied on them?

DR. STERLING: Objection; form.

THE WITNESS: Yeah. It's tough for me to give a simple answer to that, because we had discussions about the material and about the

reply declaration before I saw the draft. And so I -- I don't know how much of those discussions were incorporated into the first draft, is -- is what I'm trying to say. So the entirety of the first draft was provided by counsel.

BY MR. DIAMOND:

Q. Yeah. Well, let -- let me ask -- ask it this way: As of the -- the first round of declarations, and -- and I'll -- I'll refer to those as your initial declarations, the ones you submitted back in October of 2019. Will -- will you understand that?

A. Yes.

Q. All right.

So as of your initial declarations, in -- in your reply declarations you relied on your counsel to supply you with the legal standards, right?

A. That's correct.

Q. All right. Who -- who -- who selected the documents that you cite in your reply declarations?

DR. STERLING: I'm going to object to the extent it gets to privileged information.

Please remember, do not disclose any discussions with your attorneys, or the substance of any discussions with your attorneys.

THE WITNESS: Yeah. So I think the documents cited within the reply declaration are a combination of documents from the initial declarations, and then also documents that were added in the reply. The documents that were added in the reply were all brought to me from counsel, if those are the ones, specifically, that you're asking about.

BY MR. DIAMOND:

Q. Yeah. Sorry. My -- sorry. Just -- I want to make sure I under -- understood, because you didn't come through so clear in the audio for your last answer.

Did you -- did you say that the -- the doc -- the additional documents -- well, let's step back.

I understand that your reply declaration discussed a number of documents that were discussed previously in your initial declarations, right?

A. That's correct.

Q. Okay. And there are -- there are

some additional documents included in your reply declarations, or cited in your reply declarations, that weren't cited in your initial declarations, right?

A. That's right. But then also I guess what I was trying to say is that there are citations within the reply declaration that are not referred directly within the reply declaration, but are referred to in the initial declaration. And those are also present within this cited list.

Q. Okay. Fair enough.

And then there -- but there -- there are some -- some documents, some exhibits, for example, that are -- that are cited for the first time in your reply declaration, right?

A. That's correct.

Q. And -- and all of those documents were provided to you by -- by counsel, right?

DR. STERLING: Objection; form. Foundation.

THE WITNESS: Yeah. That's correct.

BY MR. DIAMOND:

Q. Okay.

A. That is --

Q. Okay. So let's look at your -- actually, I'm going to do -- use a little technology here.

Can -- can you see your -- your reply declaration for the '504 patent on the screen?

A. I -- I can.

Can I ask a question about the materials before we go too far?

Q. Well, I -- I -- no, I don't -- I think -- is the question about the logistics, like, can you see the -- this exhibit?

A. No. It's more about materials that I have here.

Q. The materials that you have -- what -- what materials are you talking about, sir?

A. So I have the reply declarations with me here at my house, and so I just wanted to, virtuously, let you know that I have these reply declarations, and then also maybe to ask if it's okay if I refer to them?

Q. You're -- you're certainly free to refer to the paper copies, if that's easier for you.

A. Okay.

Q. You know, I'm putting this one up

on the screen so you could kind of look at the screen and we could see each other --

A. Sure.

Q. -- so you don't have to keep looking down, but -- and it -- it may be easier just to move along and show you some stuff. But please feel free to look at the hard copy, electronic copy, the copy you downloaded, whatever is convenient for you.

That -- that being said, are you able to see your '504 reply declaration on the screen right now?

A. Yes, I am.

Q. Okay. And if you can't -- if you can't see it or it's not clear to you at any time while I'm talking about what's on the screen, just let me know. Okay?

A. Sure.

Q. Great.

So I'm going to -- and -- and just to make sure, you -- you don't see any other documents from my -- from my screen on -- on your screen, right?

A. No. I don't see anything.

Q. Okay. I think I would have gotten

more of a reaction if -- if you did.

So let's go to and flip forward to your paragraph -- sorry. I moved things around here now. So let me go back to where I -- where we were.

Bear with me one moment. I'm still getting a little bit used to this technology.

All right. Here we go. I'm going to direct you to your Paragraph 12, and do you see that here, Paragraph 12 in your reply declaration?

A. Yes, I do see that.

Q. Okay. So you -- you -- you say that, in formulating your opinions, you -- you considered all the references and documents cited herein, including those listed in -- in attached Appendix B, right?

A. Yes, I do see that. Yes.

Q. And there -- there's an Appendix B attached to -- to each of your three reply declarations, right?

A. That's correct.

Q. So a -- apart from the documents cited in your reply declarations and the documents included in the Appendix B attached to each of

your three reply declarations, are there any other documents that you considered in formulating the opinions in your reply declarations, or --

A. No.

Q. -- or is that the universe?

A. Yeah. That's, you know, my best recollection. I think I can say, with great confidence, that that's the entire list of the documents that I, you know, included in forming the opinions that are listed within the declarations.

Q. Mm-hmm.

Are -- are there any documents that you reviewed in preparation for your deposition today that go beyond the documents that you cited in your reply declarations and -- and the documents in Appendix B as appended to them?

A. I -- I guess in between the submission of the declarations and today, I looked at some additional documents. And I think, in some cases, some of them are relevant to opinions that I hold with respect to this case. So I -- I mean, I would think that it's, you know, definitely a possibility that I've seen doc --

documents in between that are -- are relevant to opinions that I hold. It's not -- I'm not presenting or wouldn't have any new opinions. All of my opinions that are -- that -- that are relevant are contained within this declaration.

Q. Right. You're -- you're not -- you're not going to introduce any new documents today that you didn't already cite in your declarations, right?

A. No. I don't have any plans to.

Q. Okay. All right.

And you understand that these three declarations, your reply declarations, those are your last declarations in these proceedings, right?

A. Yes, I do under --

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. All right. Have -- have you reviewed the -- the -- the patent owner's responses that were filed in -- in -- November 22nd? Did you review those?

A. Yes, I did, at -- at least to a -- to a limited extent, yes.

Q. Okay.

A. I -- I maybe spent more time on the declarations of Casadevall and Trout than the -- the patent owner's response.
Q. Okay. So you reviewed the patent owner responses, you re -- your reviewed the -- the declarations of Casadevall and -- and the declarations of Dr. Trout, right?
A. Yes. That's -- that's correct.
Q. And you -- you can confirm this, but I -- I didn't see the declarations of Dr. Nussenzweig cited in your -- in your declarations or -- or in the Appendix B.
Could you please confirm that?
A. Sure. I'm going to look at the paper copy.
Q. Yes. Look at -- look at however is best from the programs.
A. So I -- I don't believe it's there, but if it is there, is there a number that would help me to find it?
Q. Yeah. Let me get you that -- that number.
So it would be -- it would be ALXN2026, or Exhibit 2026. You -- you don't cite that in your -- in your declarations or

include that -- in your reply declarations or include that in your Appendix B appended to them, right, --
A. Yeah, that would be --
Q. -- 202 --
A. I can confirm that.
Q. All right. And I'll -- just to close the loop there, you -- you also don't cite to, or include in your Appendix B of your reply declarations, Exhibit 2056, the -- the -- the Bazarko declaration?
A. No. I can confirm that that also is not present within Appendix B and wasn't used in preparing my declara -- reply declaration.
Q. All right. When did -- when did you first review the -- the patent owner responses and -- and the -- the -- the Casadevall and Trout declaration?
A. Yeah. I don't remember the date that --
DR. STERLING: Again, I'm going to object to the extent it gets to privilege. Please just talk about timing, but remember to not to discuss any substantive conversations with your attorneys.

THE WITNESS: I -- I would guess in January of 2020. That's my best guess.
BY MR. DIAMOND:
Q. Okay. Was -- was that -- well, did you see the patent owner responses, the Casadevall and -- and -- and Trout declarations, you know, before or after you received that -- that first draft?
A. Before. I'm sure it'd be before.
Q. Okay. In -- in preparing your -- your reply declarations, you also reviewed the deposition transcript of -- of Drs. Casadevall and -- and -- and Trout, right?
A. Yeah. I did review them and looked at them to some extent, yes.
Q. Yeah. Do you know when you reviewed them?
A. I reviewed them, you know, shortly after they were re -- received, probably in January of 2020.
Q. Okay. And was that before or after you got your -- your first draft of your declaration?
A. Before.
Q. Now, you -- you -- you --

A. And --
Q. Yeah. And you said -- you said, I believe, that -- that -- well -- well, I won't -- let me just ask you: Did you read those deposition transcripts in their entirety or -- or just certain portions?
A. Yeah. I -- I haven't read them in their entirety.
Q. All right. And who identified the -- the -- the deposition testimony in those -- in those transcripts for -- for you to review and -- and cite in your declaration?
A. It was done collaborative -- collaboratively with counsel. We talked about arguments that were presented, you know, and discussed about, within the declarations and depositions of the other experts that, you know, would -- would be part of the reply. It's something that we discussed as we moved forward.
Q. How did you decide which parts of Dr. Casadevall's and Dr. Trout's deposition transcripts to review and which ones not to review?
DR. STERLING: I'm going to object, because this gets to privilege. I'm going to

instruct you to not answer the question.
BY MR. DIAMOND:
Q. So would -- would -- would -- let me ask you this: Would answering that question require you to reveal communications with counsel?
A. I -- I don't -- I -- not that I know of. I don't know.
MR. DIAMOND: Well, Coun -- Counsel, I -- I -- it seems like maybe -- maybe there's not a privilege issue here.
DR. STERLING: Dr. Balthasar, do you think you can dis -- you can answer this question without revealing any substance of the conversations you had with counsel at Sterne Kessler?
THE WITNESS: I -- I think it's possible.
Maybe if you could just repeat the question so I'm sure I understand it.
BY MR. DIAMOND:
Q. Yeah. I was just asking you how you determined which portions of Dr. Casadevall's and Dr. Trout's deposition transcripts you -- you reviewed and which ones you didn't. And

then your counsel objected on the basis of privilege, and I'm trying to understand whether you could answer that question without revealing the substance of communications that you had with your attorney?
A. Yeah. I --
DR. STERLING: Dr. Balthasar, can you answer that question without revealing the substance of discussions that you had with your counsel?
THE WITNESS: I guess I -- I wouldn't be able to. I mean, we discussed all elements of it as we, you know, were trying to decide what to -- what to address. So I -- I guess I wouldn't be able to. It's -- it's something I came to through our discussion.
MR. DIAMOND: O -- o -- okay. Then --
DR. STERLING: Well, then, in that instance, I'm going to instruct you to not answer it. I think that explains the privilege issue to you, Mr. Diamond.
MR. DIAMOND: Yeah. No, I -- I think I -- I think I understand Dr. Balthasar's answer about that question.
BY MR. DIAMOND:

Q. You -- you didn't cite to Dr. Casadevall and Dr. Trout's deposition testimony in the places where they disagreed with your opinions, right?
DR. STERLING: Objection; form. Relevance.
THE WITNESS: Not that I can recall. I -- I don't recall.
I think that we did -- through the course of discussing the declaration, I think in parts of my reply declaration, we -- we made statements about areas of disagreement; for example, I recall that Dr. Casadevall made statements about what a POSA would think about references to Thomas that I disagreed with and they're just --
BY MR. DIAMOND:
Q. So let me -- let me -- let me -- let me -- let me stop you there, because I -- I'm asking -- I'm specifically asking about the deposition transcript. I know --
A. Oh.
Q. -- that you discussed Dr. Casadevall's and Dr. Trout's declarations, and we'll talk about that.

A. Okay.
Q. But with respect to the deposition testimony that they gave, you -- you didn't cite their deposition testimony where they disagreed with you, right?
DR. STERLING: Objection; foundation. Form.
THE WITNESS: I -- I can't think to a specific area. I think that, in many cases, the deposition testimony of Dr. Casadevall and Dr. Trout is consistent with their declarations in areas where we disagree within my reply declaration. So I --
BY MR. DIAMOND:
Q. Okay.
A. -- I don't know that I can separate them easily.
Q. Okay. Fair enough.
I'm going to, and you could look at your hard copy if you want, but let's look at -- back at your '504 declaration. And let's look at, sorry, Paragraph 60, which is on page -- we'll work from there -- be -- begins on Page 35, but then goes on to -- to Page 36. So I'm going to focus you on -- on Page 36.

A. Okay.
Q. Are you there with me?
A. Yes.
Q. Let me move things around. It's just the way it's oriented.
Okay. So you see, starting about four lines down you say -- you say, "Dr. -- Dr. Casadevall agrees that Bell's eculizumab is the -- is the same as the claimed antibody."
Do you see that?
A. I do see that, yes.
Q. Is -- is -- is that your -- your truthful understanding of the opinions that Dr. Casadevall offered in this case regarding Bell?
DR. STERLING: Objection; form.
THE WITNESS: My -- I guess my opinion is, in part, to the extent Dr. Casadevall's testimony that eculizumab refers to one antibody with one sequence, and --
BY MR. DIAMOND:
Q. Let -- let me ask you this: Do you --
A. -- I carry that --
Q. Do you understand that that --

A. -- understanding through to the --
DR. STERLING: I'm sorry. Can you let the -- can you please let the witness finish his answer?
BY MR. DIAMOND:
Q. Well, let me -- I'm going to actually --
A. So I was trying to tell you --
Q. I'll withdraw that question. I -- I have a different question.
A. Go ahead.
Q. Do you -- do you -- do you understand it to be Dr. Casadevall's opinion that when Bell used the word eculizumab, a -- a POSA, prior to March 15th, 2007, would have understood that to refer to the claimed antibody with Sequence ID Numbers 2 and 4? Is that your understanding of Dr. Casadevall's testimony?
DR. STERLING: Objection; form.
THE WITNESS: Yes. I believe that is a compound question in a way. So I -- my -- the point I was trying to make was --
BY MR. DIAMOND:
Q. Well, let me -- let me -- let me -- let me ask you that question again, because I --

I want you to understand my question. Okay?
A. Okay.
Q. And if you don't understand my question, just feel free to ask -- say, I don't understand that question, it's a compound question, and I'd be happy to clarify.
But do you understand it to be Dr. Casadevall's opinion that when Bell -- I'm talking about Bell, AMG1005. Do you follow me there?
A. Yes.
Q. Okay. Do you understand it to be Dr. Casadevall's opinion that when Bell used the word eculizumab, a POSA, prior to March 15th, 2007, would have understood that to refer to the claimed antibody with Sequence ID Numbers 2 and 4?
DR. STERLING: Objection; form.
THE WITNESS: Again, that's tough for me to answer, because there's two different things that are in that -- you know, it's two different issues in play. And I'd be happy to explain what's the reason why I'm thinking this or saying this, so --
BY MR. DIAMOND:

Q. Well, I'm just asking you --
A. -- I would say that I feel --
Q. -- whether you -- what you understand Dr. Casadevall's opinions to be, right?
A. Yep.
Q. And --
A. My understanding is that Dr. Casadevall's opinion is that a POSA wouldn't know the sequence of eculizumab, if that's what you're asking.
Q. Yeah. Right. And then -- and do you understand that Dr. -- do you understand that Dr. Casadevall does not agree with you that Bell -- that when Bell says the word eculizumab, that discloses the claimed antibody? You understand he doesn't agree with you on that, right?
A. That's --
DR. STERLING: Objection to form, to the extent it misstates witness's testimony, --
THE WITNESS: Yeah. That's not --
DR. STERLING: -- and foundation.
THE WITNESS: That's not -- sorry.
No, that's not my opinion. That's not what I was saying.

BY MR. DIAMOND:
Q. You -- you -- you don't -- you don't understand -- you think that Dr. Casadevall agrees with you that, when Bell says the word eculizumab, that discloses Sequence ID Numbers 2 and 4; you think he agrees with you on that?
A. I think when --
DR. STERLING: Objection; form.
THE WITNESS: I feel that when Dr. Casadevall indicates eculizumab, he agrees that eculizumab relates to one sequence, which is now known to be Sequence 2 and 4.
BY MR. DIAMOND:
Q. Well, I'm asking you, sir, about prior to March 15th, 2007. Remember March -- March 15th, 2007? Do you understand that -- is it your understanding that Dr. Casadevall agrees with you that Bell, from the perspective of a POSA prior to March 15th, 2007, disclosed Sequence ID Numbers 2 and 4 when it said the word eculizumab? Does he agree with you on that?
DR. STERLING: Objection; form.
THE WITNESS: So I'm trying to answer your question as best as I can, and my

statement is that I feel that it's very clear in Dr. Casadevall's declaration and testimony that he does not believe that a POSA would understand that eculizumab is comprised of Sequence 2 and 4 at the time of March 15th, 2007.
BY MR. DIAMOND:
Q. Okay. That's -- that's what I was asking.
So let's look at -- let me look, still in your reply declaration, we're going to skip back to Paragraph 6.
All right. You say here that your -- your -- your first declaration laid out the extensive prior art disclosures relating to eculizumab to -- to treat PNH, right?
DR. STERLING: Objection; form.
THE WITNESS: Yes.
BY MR. DIAMOND:
Q. All right. And then you say that -- that prior art publications from Alexion, such as Hillmen, Bell, Hill '05 and Hillmen 2006, described clinical trials in which doctors successfully administered eculizumab formulations to treat PNH, right?
A. Yes. That's correct.

Q. All right. Let's look at Paragraph 10 of your reply declaration -- your '504 declaration we're in. And I want to focus you on the last sentence here of that paragraph. You say, "A POSA would have understood that the goal was recreating an already-disclosed method of treating PNH with an already-disclosed anti-C5 antibody, eculizumab, which clinical trials had repeatedly demonstrated to be successful," right?
A. Yes. That's correct.
Q. And the successful clinical trials you're referring to here are the ones reported in the publications you mentioned earlier, Paragraph 6; for example, Hillmen, Bell, Hill '05, and Hillmen 2006, right?
A. That's correct.
Q. Let's go to Paragraph 68 of your reply declaration -- '504 reply declaration.
Now, the first sentence in Paragraph 68 of your '504 reply declaration you say, "Bell and other clinical trial publications disclosed that eculizumab is a safe and effective treatment for PNH before March 2007," right?
A. That's correct.

Q. And the -- the other clinical trial publications that you referred to in that sentence, again, we're talking about things like Hillmen, Hill, Hillmen 2006; is that right?
A. That's correct.
Q. All right. And you go on to say, "Dr. Casadevall does not dispute that these results would have provided a POSA with strong motivation to make and use eculizumab to treat PNH," right?
A. That's my understanding.
Q. And when you say, "these results" you mean the safety and efficacy results in Bell and the other PNH clinical trial publications you mentioned in -- in the -- in the prior sentence, right?
DR. STERLING: Objection; form.
THE WITNESS: I'm sorry. You're -- you're breaking up a little bit. Could you repeat the question?
BY MR. DIAMOND:
Q. Sure.
When -- when you say -- when you say, these re -- so -- so the -- the second sentence reads, "Dr. Casadevall does -- does not dispute

that these results would have provided a POSA with strong motivations that they could use eculizumab to treat PNH."

You see that, right?

A. Yes, I do.

Q. So in that sentence when you say, "these results," you're referring to the -- the safety and efficacy results in treating PNH from the -- the clinical trials you referred to in the -- the prior sentence, in Bell and those other clinical publications, right?

A. Yes. That's right.

Q. Right. And just to be clear, when you say, "Dr. Casadevall does not dispute that these results would have provided a POSA with a strong motivation make and use eculizumab to treat PNH," you -- you don't dispute that either, right?

A. That's correct. I -- I don't dispute that he --

Q. Okay.

A. -- would, you know, --

Q. Okay.

A. -- say that provides strong motivation. I -- I don't dispute that.

Q. Okay. Okay. Let's look at -- still staying in your '504 reply declaration, I'm going to take you to Page 8.

Sorry if I'm bothering anyone flipping back.

You know what, it's not Page 8. I must have meant Page 4.

Let's look at Page -- Page 4 of your -- your '504 reply declaration.

Are you there?

A. Yeah.

Q. It should be on your screen here, too.

And directing your attention to Figure 1, do you see Figure 1?

A. Yes, I do.

Q. All right. So you -- you -- this says it's a -- it's a timeline of eculizumab-related publications, right?

A. That's right. I'm -- I'm going to go to the written one, because it's -- the font is very small, so ...

Q. Oh, yeah. That -- that's fine. And I'm happy to try to make it bigger on the screen, as well, but please feel free to look at the --

A. Okay.

Q. -- the written one.

A. I -- I --

Q. Is that -- are you -- are you more able to see it on the screen, too, now?

A. Yeah. That definitely helps.

Q. Oh, great.

Who made this timeline?

A. Counsel made the -- the timeline. We discussed, you know, these documents, but this figure was put together by counsel.

Q. Okay. Now, do you know if this figure was based -- based on any other figures?

DR. STERLING: Objection to the extent it gets to privilege.

You can answer yes or no.

THE WITNESS: Yeah. I'm -- I mean, I'm not exactly sure what you mean. Do you -- are you asking if this relates to figures from Dr. Casadevall's timeline?

BY MR. DIAMOND:

Q. I'm just wondering if you're aware of any other timelines that your -- this figure was based off of?

A. No, I'm not aware of anything that

this was based off of that would be another timeline figure, no.

Q. Okay. Fair enough.

So you have publications on the -- I'll -- I'll refer to this as the top side of the timeline and the bottom side of the timeline. Will you understand what I'm -- what I'm talking about if I say that?

A. Yes.

Q. All right. On the -- on the top side of the timeline is Figure 1 of your '504 declaration. There's -- there's green boxes, right?

A. Yes.

Q. Bottom side of this timeline, there's -- there's gray boxes, right?

A. Yes.

Q. The green boxes are publications that you say relate to the structure and sequence of eculizumab, right?

A. That's right. The green ones you're -- you're saying, structure and --

Q. The -- the green -- sorry. I just didn't hear you.

Is the -- I have -- do you -- the

green boxes are -- are publications that you say relate -- they're -- well, you -- you say they're relating to the structure and sequence of eculizumab.

Do you see that?

A. Yes, I do.

Q. All right. And -- and the -- the gray boxes, you say those -- those relate to eculizumab clinical trials. Do you see that?

A. I do see that, yeah.

Q. All right. So the -- the green boxes at the top of the timeline, those include the -- the -- the Evans, Thomas, Mueller, Mueller II, Bowdish and Tacken documents, right?

A. They -- they do, yes.

Q. And I think this is a type -- it says "Bowdish AMG1240," but that should probably be AMG1006, right?

A. I think that's right, yes.

Q. Okay. On the -- on the bottom of the timeline in the gray boxes regarding "eculizumab clinical trials," you've got Hillmen, Hill 2004, Young, Hill -- Hill 2005, Hillmen 2006 and -- and you've got Bell, right?

A. Yeah. These here, again, are all --

all clinical trials that he used to -- to stand by eculizumab on behalf of his clients' sequence instruction, yes, I agree.

Q. Sorry. I -- I -- I -- your -- now your audio is not coming through super-clear, so I couldn't hear what you just said. I'll ask the question again, but, also, if you could just try to speak up a bit more, and speak a little bit slower, because it's not -- it's not coming through so clearly to me.

So my -- my -- my question was just that the -- in -- in the gray boxes regarding eculizumab clinical trials, on the bottom of the timeline of Figure 1, you've got Hillmen, Hill 2004, Bell, Young, Hillmen 2006 and then Hill 2005, right?

A. Yes. These are all clinical studies that relate to eculizumab --

Q. Okay.

A. -- that goes to the time, sequence and structure. That's exactly right.

Q. And I -- I think that this is a typo, where it says, "Hill 2005 AMG1013." Hill 2005 should be designated as A -- AMG1047. Is that what you meant to refer to there?

A. Yeah. Let me just check Appendix B. I'm sure you're -- you're right, but I just wanted to double-check that.

Q. Yeah. And I -- I see there's a doubling of 1013, but I believe you meant to refer to 1047, but please do confirm.

A. Yes. That's correct. It should be 1047, yes.

Q. So let's -- let's -- let's -- focusing now on the -- on the gray box reference in the bottom side of this timeline, so these -- these are the publications that disclose the results of clinical trials showing that eculizumab was an effective treatment for the condition PNH, right?

A. Yeah. They're -- they're all clinical trials of eculizumab. That's correct.

Q. In -- in PNH, right?

A. I -- I think that's -- they're all PNH, yes. That's right.

Q. You can see in each document, "treatment PNH," "treatment PNH," "treatment PNH." They all say "treatment PNH," right?

A. Yes. Yes.

Q. All right.

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. But the -- the eculizumab clinical trial references in the -- in the gray boxes, they didn't provide the -- the eculizumab sequence, Sequence ID Numbers 2 and 4, right?

DR. STERLING: Objection; foundation.

THE WITNESS: Yeah. So the -- not -- not in terms of providing sequence. My understanding is that there's an inherent description because eculizumab, as Dr. Casadevall agrees, is an antibody that has one sequence, one structure. So --

Q. Well, --

A. -- aside from the name eculizumab that implies sequence and structure, or provides them, there's no additional sequence information presented within these papers.

Q. Right. There's -- there's no -- there's no -- there's no -- there's no -- there's no sequences listed in those documents on the bottom of the timeline, the gray boxes, but they -- they include the word eculizumab, right?

A. Yes. That's correct.

DR. STERLING: Objection.
BY MR. DIAMOND:
Q. Okay. And the -- the documents that you -- you relied on for the -- the eculizumab sequence, those are the ones that are in the -- in the green boxes on the top of the timeline, the -- the Evans and -- and -- and Mueller and -- and Bowdish, those references, right?
DR. STERLING: Objection; form.
THE WITNESS: So when you say, "rely on," I'm not sure that I know what you mean. So to -- to be -- within the grounds for -- for making eculizumab, I guess?
BY MR. DIAMOND:
Q. Let me -- let me ask you a different question if you didn't understand mine. The -- the -- the -- the references in the green boxes on the top of the timeline, those are the ones that you cite as providing the eculizumab sequence in -- in this timeline, right?
DR. STERLING: Objection; form.
THE WITNESS: Yeah. So I -- I -- I guess, though, what I'm struggling with is, again, eculizumab is an antibody that has a defined sequence and a defined structure, and

that's agreed upon by the -- you know, the experts that -- that were enlisted to -- to be able to provide depositions from --
BY MR. DIAMOND:
Q. I -- I understand, but my -- my question's a little bit different, sir.
A. Okay.
Q. You cite these documents in the green boxes at the top of the timeline, and -- and I quote, publications related to the structure and sequence of eculizumab, right?
A. That's -- that is correct, yes.
Q. Okay. All right. I'm going to give you a -- a hypothetical, okay?
A. Sure.
Q. So imagine a POSA were -- were in a room, and it's -- it's prior to March 15th, 2007, and a POSA is in a room, okay? You follow me so far?
A. Yes.
Q. All right. And in this room, the only documents they have are Hillmen AMG1004 and -- and Hill AMG1047. Do you follow me?
A. Yes.
Q. And in this room, they aren't able

to look at or access any other -- any other documents. Do you follow me so far?
A. Yes. I understand.
Q. Would a POSA in that room, prior to March 15th, 2007, with only Hillmen and Hill, and -- and no other documents, be able to get to Sequence ID Numbers 2 and 4 while -- while sitting in that room?
DR. STERLING: Objection; form. Calls for speculation, incomplete hypothetical, and to the extent it calls for a legal conclusion.
THE WITNESS: So my answer, though, is, absolutely. That's my understanding of a POSA. So a POSA would have knowledge not only of the two documents that you said are in this room, but would have knowledge of all of the materials that were available in -- or up until March 15th, 2007.
Now, --
BY MR. DIAMOND:
Q. Well, now -- now, I --
A. -- my understand --
Q. But they're not --
A. So by having encyclopedic --
Q. Well, they're not refer -- they're not

allowed to refer to any other documents except for Hillmen and Hill, okay?
A. So I don't understand how that could be a POSA. That's --
Q. Okay. Well, if -- if a person with the level -- let's imagine a person with the level of skill as defined in this case for a POSA, okay? It's -- it's a person of -- it's a person that's that level of skill, okay?
A. So you -- you mean skill as having knowledge and some techniques, but not knowledge of any materials related to -- you know, to -- to -- to anything else, just knowledge -- I don't understand what you mean by skill.
Q. Let -- let's -- let's -- let's do -- let's do this: I'm going to go -- I'm going to pull up a document here for you, so just bear with me for a moment. Okay?
A. Sure.
(Exhibit 1002, Dr. Balthasar's Initial '504 Declaration, was introduced electronically.)
BY MR. DIAMOND:
Q. It's a little bit clunkier than the -- the usual system, but we'll -- we'll get by.

Okay. I'm going to deposit another document in the -- now in the -- the marked exhibits folder. And if you would go in there and refresh your window so you can -- well, it says it's 2 percent uploaded, so it's not done yet.

A. Okay. Just let me know when it's ready.

Q. Okay. I'll tell you what, it's hung up -- okay, it's kicking again. Good.

A. I'm sorry. Did you say that it was ready?

Q. I'll tell you. We're real close.

A hundred percent. All right.

You can -- you can go into the marked exhibit folder now. You'll have to refresh. You'll see Exhibit 1002, which is your initial '504 declaration?

A. Yes. I -- I do see that, and if I may download that?

Q. Yeah. And I'll -- you could download that. I'll -- when you download it, just open it and confirm that it is, indeed, your -- your initial '504 declaration.

A. Okay. So I was able to download it

and open it up. And I see the '504, you know, declaration. You know, I see the -- the name here. It -- it is a large document of 186 pages, but, you know, to -- to the extent of the face page, that verifies it's this document.

Q. All right. Fair enough. And if -- if you -- if you think -- if you question that, let me know, but I -- I believe this is the -- the right document.

So I'm going to also share this with you, and if you can go to Page 16, please.

A. You're going to navigate to that, or should I?

Q. I've navigated to it here. You're -- feel free to look at it either way, but --

A. Okay.

Q. -- I'm on Page 16 of your -- do you see this is your '504 declaration, AMG1002, right?

A. Yes, I do see that, and I --

Q. Yeah. So I'm referencing you to Page 16. And here on Page 16, if you look several lines down where I've highlighted, or selected, you say -- you said, "Typically, a POSA would have an M.D. and/or a Ph.D. in immunology,

biochemistry, cell biology, molecular biology pharmaceutics or a related discipline, with at least two years of experience in the field. Okay?

A. Yes. Yes.

Q. So I want you to keep that level of experience in mind, okay?

A. I have a quick question about that, because there is something I'm uncertain of with that.

Q. Well, let me -- let me ask you my question, and if you could tell me if you understand it. Okay?

A. Okay.

Q. So I -- I want you to keep that -- that level of experience in mind. And keeping that level of experience in mind, would a person, sitting in the hypothetical room we've talked about, prior to March 15th, 2007, having that level of experience, but only having access to the Hillmen and the Hill documents, and no other documents, would they be able to get to Sequence ID Numbers 2 and 4 from just those two documents, without referring to anything else?

DR. STERLING: Objection; form,

relevance, and to the extent it calls for a legal conclusion. Also incomplete hypothetical.

THE WITNESS: So the -- the question that I have with this is that, if we go back to the declaration -- the '504 declaration to the page that you looked at and the definition of POSA, are you asking me to exclude all of the other elements that relate to POSA?

BY MR. DIAMOND:

Q. What I'm -- I'm asking you to do is to -- to -- to simply confirm for me that -- whether -- one way or the other, whether a person with that level of skill would be able to get to Sequence ID Numbers 2 and 4 from just the information that's included in Hillmen and Hill?

A. Yeah. So --

DR. STERLING: Objection; form, relevance.

THE WITNESS: So --

DR. STERLING: And to the extent it calls for a legal conclusion, it's an incomplete hypothetical.

THE WITNESS: So my answer to that is that, yes, if you look at the definition that's included within the declaration -- the

'504 declaration that you just showed, that definition of POSA, that includes that sentence that you've highlighted. If that's your definition for POSA, I have absolute certainty that a POSA would be able to get to the sequence of 2 and 4 -- Sequence ID 2 and Sequence ID 4, from -- you know, from that position, from that certain point.

BY MR. DIAMOND:

Q. From -- from just Hillmen and Hill alone, no other documents?

A. Right. Because --

DR. STERLING: Objection to form.

THE WITNESS: -- they have knowledge from all acquired information.

BY MR. DIAMOND:

Q. You mean they'd have the other doc -- you mean have documents with -- with the sequence in their heads?

A. Yeah. They -- they -- my understanding of a POSA is they would have encyclopedic knowledge of all of the prior art.

Q. But -- but they'd have to refer to all other documents in their head, right?

DR. STERLING: Objection; form.

Relevance.

THE WITNESS: So I -- I don't know what you mean by "documents in their head," but the -- the knowledge that is associated with the prior art is something that a POSA knows, and, my understanding is, knows fully. So all of that information that a POSA has, and that includes the information that enables them to be able to generate eculizumab with Sequence ID Number 2 and Sequence ID Number 4, that's -- that's my -- that's my opinion on it.

BY MR. DIAMOND:

Q. They would have gotten that sequence information from other documents, right?

A. Well, it -- it --

DR. STERLING: Objection; form.

THE WITNESS: -- it is an element -- or those -- those would be from elements within the prior art. And my understanding of a POSA is that they have complete understanding of all of the prior art.

BY MR. DIAMOND:

Q. Within the prior art where? You mean within other documents in the prior art, right?

A. Again, --

DR. STERLING: Objection; form.

THE WITNESS: -- anything that exists within prior art.

I'm sorry. So, yes, my understanding is that they would have knowledge of anything that exists within the prior art, including information that comes from documents that were published before that time. But they -- they have that information, they understand that, they own that. And so my understanding is that a POSA has the ability, you know, to recall all of that information to be able to make judgments. That's my understanding.

BY MR. DIAMOND:

Q And -- and what information would a POSA have to recall to put together Sequence ID Numbers 2 and 4 from the disclosures of Hillmen and Hill?

DR. STERLING: Objection; form.

THE WITNESS: One -- one approach that one would take is to consider from the pri -- prior art, which includes Tacken, that Tacken defines that eculizumab, which is the antibody that is 5g1.1 humanized antibody, has the sequence of IgG2 and G4 and ref --

BY MR. DIAMOND:

Q. Okay. But doesn't Tacken have a number documents to do with it?

A. -- Mueller II, and they would know from Mueller II -- from Figure Number 9 of Mueller II, the sequence domains that relate to the G2/G4 heavy chains, for the hinge for CH1, for CH2, they would have those knowledge, they would have knowledge from Mueller II, that makes reference to Mueller I, with antibody 2A2 and 3F4, they would have knowledge of that, they would have knowledge that the sequence that is provided is -- in -- in Mueller II gives the entire sequence of the heavy chain domain. They would have knowledge -- Bowdish gives the entire sequence of eculizumab, which is 5G1.1, with the exception of CDR3 -- heavy chain CDR3. They would have knowledge that that information exists within Evans. They would have all of that knowledge available to them. And so from that knowledge, they could create the entire sequence, because they have knowledge of all that prior art, there's a direct chain that would lead them to that.

Q. Right. So a -- a POS -- a POSA with

just the Hillmen and Hill references, and no other references, would be able to put -- in your opinion, be able to put together Sequences 2 and 4 from their knowledge of what's in Tacken and Bowdish and -- and Mueller, right?

A. And Evans, that's correct.

DR. STERLING: Objection to the extent it misstates testimony.

BY MR. DIAMOND:

Q. Okay. Let me -- let me ask you this: In your -- okay. I'm going to go back to your -- your -- your '504 declaration -- reply declarations. Let's just go back and look at that. But I'm going to take you to -- let me just reduce the -- the size down here -- to Paragraph 38.

All right. So you -- I'm looking here at the -- the -- the second sentence. I mean, you -- you -- you understand that -- that it's improper to include the disclosure of other references when determining whether Hillmen or Hill discloses all of the elements of the claimed method, right?

DR. STERLING: Objection; form, and to the extent it calls for legal analysis.

THE WITNESS: Something --

BY MR. DIAMOND:

Q. Well, I -- I'm --

A. -- that I have from counsel is -- you know, as highlighted within my reply declaration, it's exactly as it's stated there, that -- the sentence says, "While it may be improper to include disclosure of other references in determining whether Hillmen discloses all elements of the claimed method, it's completely --

Q. Okay.

A. -- proper to consider, you know, the POSA and the disclosures of other references to determine whether Hillmen would have enabled a POSA to perform the method.

Q. Sir -- sir, we'll talk about enablement, but before we talk about enablement, you understand it's improper to include the disclosure of other references when determining whether Hillmen, or Hill for that matter, disclosed all elements of the claimed method, right?

DR. STERLING: Objection to the extent it calls for a legal analysis, and form.

THE WITNESS: So I -- I can give you my understanding of -- of this: My understanding is, again, --

BY MR. DIAMOND:

Q. Well -- well, sir, --

A. Go ahead.

Q. -- I -- I -- I'm just reading from your declaration. It says, "I understand from counsel," right?

You -- you -- this is your understanding from counsel, right?

A. Yes.

Q. And you say, "It is improper to include the disclosure of other references when determining whether Hill discloses all elements of the claimed method."

We -- we'll talk about enablement later, but right now I just want to focus you on this.

A. Okay.

Q. You understand from counsel that it's improper to include the disclosure of other references when determining whether Hillmen or -- or Hill discloses all elements of the claimed method; is that right?

DR. STERLING: Objection to the extent it calls for legal analysis.

THE WITNESS: I -- I see the -- the phrase portion of the sentence that you're referring to in the declaration, and I --

BY MR. DIAMOND:

Q. Okay.

A. -- agree with its accuracy. I -- I have no --

Q. Okay.

A. -- reason to disagree with that portion of the sentence.

Q. Okay. Is it your understanding that whether Hillmen or Hill are enabled is a separate question from whether they disclosed, expressly or inherently, the claim limitations at issue, including in Sequence ID Numbers 2 and 4?

A. Yeah. So maybe if you could restate that. So when you said that Hill and Hillmen are enabled, maybe if -- if you could explain that? I'm not exactly sure what you mean.

Q. Well, you -- you -- you talked about enablement. We -- we -- we -- you -- you were -- you were reading the remainder of the

sentence you looked at earlier, you talked about whether Hillmen would have enabled a POSA to perform the -- the method, right? You -- you talk about enablement.

A. Yeah. I -- I guess my misunderstanding is that, when you said that "Hill and Hillmen are enabled," do you -- do you mean that they're enabling?

Q. Well, I'm talking about whether the disclosure of a -- of a reference is enabled. Do you -- do you think that's a relevant consideration in assessing anticipation, sir?

DR. STERLING: Objection; form, and to the extent it calls for a legal conclusion.

THE WITNESS: Yeah. That's --

MR. DIAMOND: Well, we're just asking for his opinion here.

THE WITNESS: Definitely I must be not understanding this, and it must be an issue of, you know, legal -- you know, legal terminology. But I -- I imagine that what you're referring to is whether or not the information provided is enabling versus whether or not the authors have been enabled. I -- I -- that's -- I'm trying to understand what you're asking, but I think that

you're asking whether or not the information provided is enabling.

BY MR. DIAMOND:

Q. Well, I'll -- I'll ask you my -- I'll ask you my question, and -- and, you know, the lawyers can take up whether this is relevant or not under the legal standard, but my question to you is, do you understand that whether Hillmen or Hill are enabled is a separate question from whether they disclosed, expressly or inherently, the limitations at issue, including Sequence ID Numbers 2 and 4?

DR. STERLING: Objection; form, and to the extent it calls for a legal analysis.

THE WITNESS: I have to admit, I -- I don't really understand the question. I -- I don't understand what you would mean by Hill and Hillmen being enabled.

BY MR. DIAMOND:

Q. All right. Well, let -- let me -- let me ask it your way, although I'm not quite sure what you mean by it, but it -- it -- do you understand that whether Hillmen and Hill are enabling is a separate question from whether they disclosed, directly or inherently, the

claims limitations at issue, including Sequence ID Numbers 2 and 4?

DR. STERLING: Objection to form, and to the extent it calls for a legal analysis.

THE WITNESS: Yeah. So I guess I'm still -- maybe I'm confused about what you mean by that. It's -- it -- it is complex.

So my understanding is that Hill and Hillmen are enabling of the method because they show the use of eculizumab for the application for treatment of PNH, and inherently within eculizumab is information about the sequence. And so that's the way I understand that, through -- you know, through my understanding through counsel.

BY MR. DIAMOND:

Q. Yeah. So you -- you don't have an understanding from counsel one way or the other as to whether the issue of whether Hillmen or Hill are enabling, whether that's a separate question from whether they disclose, expressly or inherently, the same limitations at issue. You -- you don't have any understanding one way or the other about that, right?

DR. STERLING: Objection to form, and

to the extent it calls for legal analysis and conclusion.

THE WITNESS: I -- I would say my understanding is that they are enabling and that they provide information about the application --

BY MR. DIAMOND:

Q. Well, sir, that's not my question. That's not my question. I'm asking you about -- the question whether -- whether the -- whether the issue of whether they're enabling is a separate question from whether they disclose all the elements expressly or inherently. Do you understand that to be the case? Do you understand it to be the legal standard that you apply in this case or not?

DR. STERLING: Objection; form.

THE WITNESS: Keeping it to a legal argument that maybe I feel, you know, incompletely confident with what's -- what -- you're asking is enablement -- is -- is part of -- the tie to the sequence part of enabling. And I -- I -- I think that it is. That's my understanding, and I -- and I'm sorry if I'm not understanding your question correctly.

BY MR. DIAMOND:
Q. Well, let -- let me ask you a different way. Do you understand that it's not permissible to leap from enablement to disclosure in the context of discussing anticipation?
DR. STERLING: Objection; form. Objection; relevance. Objection to the extent it calls for legal analysis and conclusion.
THE WITNESS: So to -- to answer you -- you said, do I understand that it's not appropriate to leap from enablement to disclosure.
BY MR. DIAMOND:
Q. Yeah. Do you get that, in the context of anticipation?
DR. STERLING: Same objection.
THE WITNESS: So my understanding is that enablement in -- includes within it, in this context, inherent knowledge of the sequence. And so the -- the sequence is inherent, and so the disclosure -- if you're saying is the disclosure a separate issue, my understanding is the sequence information is inherent and it is not something that is

separate or combined with the enablement. The enablement refers to the application of eculizumab for the treatment of PNH. That's my understanding of enablement. And the relationship to disclosure of sequence is related to the -- the knowledge that exists about eculizumab.
DR. STERLING: We've been going for about an hour, Counsel. Would it be a good time for a break?
MR. DIAMOND: I have -- I have one more question.
DR. STERLING: Dr. Balthasar, would you like a break right now?
THE WITNESS: I'm -- I'm fine. I could take one more question.
DR. STERLING: One more question.
MR. DIAMOND: All right. We'll take a break right after that.
BY MR. DIAMOND:
Q. You -- you understand it's improper to look outside Hillmen or Hill to the specific disclosure of claim elements not found in those documents, right?
DR. STERLING: Objection; form, and to

the extent it calls for legal analysis and conclusion.
THE WITNESS: So my understanding, I think directly as stated within the declaration for this issue, which is this entire section that says, "I understand from counsel that while it is improper to include disclosure of other references when determining whether Hill discloses all elements of the claimed method, it is completely proper to consider the disclosures of other references to determine whether Hill would have enabled a POSA to perform that method.
That's my understanding. That's what makes up my --
BY MR. DIAMOND:
Q. That's -- that's -- that's the legal standard you got from counsel, right?
A. It's the --
DR. STERLING: Objection; form.
THE WITNESS: It was legal information that I got and discussed with counsel. And this --
BY MR. DIAMOND:
Q. Okay.

A. -- is in my declaration because it is what I understand about this issue. It's my understanding -- as I said, "I understand from counsel this definition." It includes --
Q. Okay. Okay.
A. -- my words in there that I understand it.
Q. I got it. All right. We can take a break. I'll go off video and I'll mute. You want to come back in 10 minutes or so?
DR. STERLING: Okay.
THE WITNESS: So -- so the time I should come back is 10:23?
MR. DIAMOND: If that works for you, Dr. Balthasar.
THE WITNESS: I'm -- I'm fine.
MR. DIAMOND: All right.
THE WITNESS: Okay.
MR. DIAMOND: See you all in 10.
(Recess taken.)
THE VIDEOGRAPHER: All right. We are back on the video record. The time is 10:24.
BY MR. DIAMOND:
Q. Dr. Balthasar, during the break that we just took, did you talk with or chat or text

or in any way communicate with your counsel regarding the substance of your testimony?
A. No, I did not.
Q. All right. Let's look at your -- your '504 declaration again, and I'm going to direct you to -- yeah, here we go, to -- to Paragraph 92, which is -- oh, shoot.
Okay. Nine -- Ninety-two. Are you there with me?
A. Yes.
Q. All right. Let me just make sure the window is open.
All right. So you say here in Paragraph 92 that -- that, "A POSA would have had reason to look to -- to Evans because Bell cites to Evans as providing, quote, methods for the preparation of h5G1.1-mAb, end quote, which is how Bell referred to eculizumab."
Do you see that?
A. Yes, I do see that.
Q. All right. And you have the citations to -- to Bell in Paragraph 12 and -- and Paragraph 52, right?
A. Yes. That's correct.
Q. All right. And we could look and see,

but I believe that the paragraph in -- in -- in Bell that refers to Evans is Paragraph 52. Is that your understanding?
A. I -- I -- I think -- I think so. Maybe it's best to look at it, but --
Q. All right. Well, let -- let's -- let's -- let's -- right now let's look at the declaration, and we could -- we could always look at that later. Let's break this down.
So when Bell states methods -- as you have quoted here, method for the preparation of h5G1.1-mAb, in quotes, you understand that h5G1.1-mAb is how Bell refers to eculizumab, right?
DR. STERLING: Objection; foundation. Form.
THE WITNESS: Yes.
BY MR. DIAMOND:
Q. Okay. And the statement in Bell, where it talks about methods for the preparation of h5G1.1-mAb, it cites to Evans, right?
A. So maybe I'm missing something that you're saying, so the -- the -- the sentence is there, Bell refers to eculizumab, it refers to the Paragraphs 12 and 52. And what you've asked

me, is Paragraph 52 referring to Evans, I'm not a hundred percent sure, but it -- it seems like it -- it could be. You know, I -- if you wanted to look at Bell, we -- we'd be -- I'd be happy to look at it, but --
MR. DIAMOND: Yeah. Let's do -- let's do that to make -- if that's -- if that's easier. So let me -- let me send the -- send Bell your way. And if you can go back into -- I'll tell you when it's -- when it's uploaded.
(Exhibit No. AMG1005, Bell, was introduced electronically.)
BY MR. DIAMOND:
Q. All right. It should be there. I'm going to refresh.
Yeah. So AMG1005, Bell, that should be in your -- in your marked exhibits folder, if you could download that.
A. Yes. I'm downloading it now.
Q. And I'll open it up here, as well, and we could see Bell. I'll have to increase the size here to make it visible.
Okay. So and we're going to take a look at Paragraph 52. I'll drag you there.

It is --
A. Do you mind if I ask a question just as we -- we get there? So is it necessary for me to download things if you're going to show them? I mean, do I have to go through the process of going into that if I'm just going to look at it on your screen?
Q. No. You -- you -- you certainly don't have to. It's an option for you to, and I'll -- and I'll upload them, but I'm happy to show you on the screen.
So if you --
DR. STERLING: Can -- can I -- sorry. Can I just interrupt?
I would recommend you do it, Joe, just in case, for some reason, there's a technical glitch. That way you can still follow along with Evan and answer Mr. Diamond's questions. That's the only reason I would ask you to do that, if there's a technical issue, because we're doing this remotely.
MR. DIAMOND: And I certainly have no issue with him doing it.
THE WITNESS: Okay.
MR. DIAMOND: But you -- you -- you

don't have to if it becomes an issue at some point.

THE WITNESS: Okay.

BY MR. DIAMOND:

Q. So are you with me in Bell on Paragraph 52?

A. Yes.

Q. All right. So we see at the bottom of -- of the left-hand column is where the sentence starts about methods for the preparation of h5G1.1-mAb. And that -- that's the -- going back to your -- your declaration, that's the language that you quote in Paragraph 92, your '504 reply declaration.

Do you see that?

A. Yes. I -- I do see that, yes.

Q. All right. And so just to -- to -- to refresh your memory here, let me go -- that language, "methods for the preparation of h5G1.1-mAb," and it goes on the top of the -- the right-hand column on that page it says, "are described in U.S. Patent Number 6,355,245."

Do you see that?

A. Yes, I do.

Q. And you understand that that's the

Evans reference, right?

A. That's correct.

Q. Right. And going back to your reply declaration, paragraph -- your '504 reply declaration, Paragraph 92, so just to go back to the question I was asking you earlier, you understand -- sorry, I'm a little lost here.

You understand that because Bell, in -- in that Paragraph 52 that we looked at, has a citation to Evans for -- for a method for the preparation of h5G1.1-mAb, or -- or eculizumab, you say that "a POSA would have had a -- a reason -- had reason to look to Evans," right?

A. Yes. That's correct.

Q. Okay. And that sentence we looked at in Bell, the other reference that is -- is -- moving back to Paragraph 52, after it mentions Evans, the next reference it cites is Thomas, right?

A. That's correct.

Q. Okay. Let's look at the -- another document. I'm going to show you -- well, first of all, let me just ask you, does the file history for the '504 patent, AMG1014, that's one of the documents you considered in formulating

your opinions, right?

A. So you're saying is File 1014 one of the documents, right?

Q. Yeah.

A. Okay. That's correct.

(Exhibit No. AMG1014, a document titled U.S. Patent No. 9,725,504 Part 2, was introduced electronically.)

MR. DIAMOND: All right. I'm going to show you that.

And I'll say now on record, so this is a large document. The -- the documents, as -- as your counsel provided this to us, is broken into several parts. So right now I'm just going to introduce Part 2, if that's okay? I'm -- I'm happy to introduce all of them, but then we'd have a few documents that I'm not going to refer to any -- any pages of. So I -- I did upload it to the -- the cite now, if you want to download it, but I'm also going to open it on my computer either way.

THE WITNESS: I'm trying to download it, so I'm waiting for it right now.

BY MR. DIAMOND:

Q. Yeah. And while you're doing that,

I'll open it up here.

And you could see -- at least the documents I've got -- I've got up on the screen, you could see in the lower right-hand corner AMG1014, Part -- Part 2, starting at Page 419?

A. Not quite yet. I'm still at the marked exhibits, and I'm waiting it -- for it to download.

Q. Sure.

A. It should be --

Q. But on the -- on the -- sorry.

On the -- on the screen -- are you able to see the documents that I'm sharing with you on the screen?

A. One second. I'm just still at the other one. So I -- I can't see both of them at the same time.

Q. Oh, okay. All right. Well, then let me know when you're ready.

A. Okay. So it -- it did -- it did download, and I'm able to open it. So I do have Part 2 saying -- so I do have that. And now I'll go back to Zoom, and I can see your screen, yes.

Q. Fine. Great.

So we're looking at AMG1014, Part 2, which begins on Page 419 of -- of the document, all right?

A. That's -- yes. I see that.

Q. And you understand this is a -- this is a portion of the -- of the file history for the '504 patent, right?

A. Yes. I understand.

Q. All right. And this -- this is one of the documents you considered in -- in formulating your opinions, right?

A. That's correct.

Q. All right. So I'm going to turn you to page, and I'll go ahead a bunch, to 555.

Do you see that?

A. Yeah. I -- I do -- do see that.

Q. All right. And you -- you see this is a -- a U.S. Patent Office communication that was sent on the date of December 22nd, 2016?

A. I -- I do see that. Is there any way you could make it a little bit bigger again?

Q. Yeah. Absolutely.

A. Thanks.

Q. So there the -- do you see that December 22nd, 2016, is the -- the date on which

it was sent electronically, the notification date?

A. I -- I do see that.

Q. All right. And if we turn to the next page, Page 556 in Exhibit 1014 Part 2, you see it says that "Claims 1 to 10 were pending in the application," right?

A. Yes. I see that.

Q. And it says, "Claims 1 to 10 were -- were rejected," right?

A. I see that notation, yes.

Q. Yeah. And if we go onto page now -- sorry, I have to shrink it down a little bit to see the page numbers, but you see we're at Page 557. At the top of that page you see it says, "detailed action?"

A. Yes, I do see that.

Q. And the -- this "detailed action" goes on, as we click through to Page 561, where you see it says, "signed by the examiner?"

A. Yes, I do see that.

Q. All right. It's also signed by the -- the supervisory examiner, right? Do you see that?

A. I -- I see that, yes.

Q. All right. You don't discuss this portion of the -- of the '504 patent file history on Pages 557 and 551, you -- you don't discuss that or cite that in your -- your reply declarations in this proceeding, right?

A. No, I don't -- I don't. So I don't believe that I do, no.

Q. Okay. Going back to -- well, going back to 557 of AMG1014, you see the first rejection is a rejection under 10 -- 35 U.S.C. 102(b) of Claims 1 to 2 and 7 to 10 as -- as being anticipated by Hillmen. Do you see that?

DR. STERLING: Objection. Objection; scope. Relevance.

THE WITNESS: I -- I do see it, yes.

MR. DIAMOND: I disagree with the -- the objection, but that's for the record.

BY MR. DIAMOND:

Q. And you --

DR. STERLING: Objection; scope and relevance, mentioning.

MR. DIAMOND: Well, I won't fight with you there, Counsel, but I disagree.

BY MR. DIAMOND:

Q. Hillmen -- this is the Hillmen

document that, and if you want to compare it to your, you know, Appendix B, or wherever you need, but the Hillmen document referred to here, you know, in Item 6 on Page 557 of AMG1014, that's the same Hillmen reference that was designated AMG10 -- AMG1004 within this proceeding, right?

A. So if you're asking me to verify, I -- I'm happy to do that once I --

Q. Yeah. And -- and just for the record, you see that the Hillmen document cited on Page 557 of AMG1014 is Hillmen, et al, New England Medical Journal, 2004, Volume 350, Pages 552 to 559. Do you see that?

DR. STERLING: Objection to form.

THE WITNESS: I see that the Exhibit 1004 -- I think you may have said 14 last time, but I -- I do see it in my list, and it is one of the exhibits, yes.

BY MR. DIAMOND:

Q. Right. So sorry if I misspoke. Let me just ask it again, just to be clear. So we're -- we're -- we're on Page 557 of AMG1014, which is the -- the -- the '504 patent file history. You're -- you're there with me, right,

on that page?
A. Yes. Yes.
Q. And there's a citation on that page where it says Claims 1 to 2 and 7 to 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillmen, et al, New England Journal of Medicine 2004, Volume 350, Pages 552 to 559. You -- you see that, right?
A. I do.
DR. STERLING: Objection; scope.
BY MR. DIAMOND:
Q. And you recognize that that Hillmen document referred to -- that is referred to is the same as the Hillmen document that's been designated as AMG1004 in -- in these proceedings, right?
A. Yes. That's correct.
Q. All -- all right. And if you look at the paragraph on the bottom of 557, you -- you see the examiner said here that "Hillmen does not specifically recite that the antibody that binds C5 comprises a heavy chain consisting of Sequence ID Number 2 and a light chain consisting of Sequence ID Number 4."
Do you see that?

A. I do.
DR. STERLING: Objection; scope.
BY MR. DIAMOND:
Q. And if we go to 559 in AMG1014, you see at the top of the page in Item 8 that said, "Claims 1 to 4 and 7 to 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen, et al., New England Journal of Medicine 2004, Volume 350, 552 to 9, in view of Thomas, et al., Molecular Immunology, Volume 33, Pages 1389 to 1401, 1996; and Evans, et al., U.S. 6,355,245 B1, issued 3/12/2002."
Do you see that?
DR. STERLING: Objection; scope.
THE WITNESS: Yes, I do see that.
BY MR. DIAMOND:
Q. So, again, the -- the Hillmen reference that's -- that's mentioned in that sentence is the one that's been marked as AMG1004 in this proceeding, right?
A. That's correct.
Q. And the -- the Thomas reference mentioned here is the one that's been marked as AMG1023 in this proceeding, and feel free to confirm that and let me know when you've done

that.
A. Yes. That's correct.
Q. All right. And the Evans document referred to in that sentence is the Evans patent that's been marked as AMG1007 in this proceeding, right?
A. Yes. That's correct.
Q. All right. So let's look at the third paragraph down, and I want to direct you to the -- yeah, it's in -- it's in the -- it's in the first sentence, it's a few lines down, where it says, "Hillmen discloses." You see -- you see where I am, "Hillmen discloses?"
A. I -- I do. Is there any chance you can make it a little bit bigger, if it's possible?
Q. Yeah. Yeah. Let me get -- me make it bigger here.
So you see it says on -- now, again, we're still on page -- sorry. Let me just get it clear for the record. We're on Page 559 of AMG1014. I'm going to zoom in now so you can see it. And you see it says on that page, "Hillmen discloses," with a citation to Page 553, third paragraph, "that eculizumab is a

recombinant human antibody that binds C5, and it refers to Reference Number 15, parentheses, Thomas, closed parentheses, and it's disclosing more information about eculizumab.
Do you see that?
A. I --
DR. STERLING: Objection; scope.
THE WITNESS: I --
BY MR. DIAMOND:
Q. And the examiner next says, "Thomas, in turn, discloses that eculizumab is the humanized antibody h5G1.1."
Do you see that?
DR. STERLING: Objection; scope.
THE WITNESS: I do see the sentence, yes.
BY MR. DIAMOND:
Q. All right. You reviewed the PTAB institution proceedings -- or you re -- you reviewed the PTAB institution decision in these proceedings, right?
DR. STERLING: Objection; foundation.
THE WITNESS: I think that it's possible. Is there a document number? So I --

you know, if it's one of the abbreviations, I don't know that I --
BY MR. DIAMOND:
Q. Yeah.
A. PTAB -- PTAB is --
Q. Sure.
I believe it's Paper Number 15 in each of the three proceedings, and I think in your declaration sometimes you just refer to it as "institution decision."
A. Okay. Maybe it would be helpful -- I think I -- I know what you're referring to, but maybe if you could give me the number. Is it possible to do that?
Q. Yeah. The number -- it -- it's not an exhibit number, so it's a paper number, all right, so it will be Paper Number 15.
And -- and, also, I could point out to a place in your reply declaration, if it would be helpful, where you -- where you cited to it?
A. Okay. That would be -- that would be quite helpful. I -- I'd appreciate that.
Q. Sure. No -- no problem. Let's go back to that.
I'll go back to your '504 reply.

All right.
So -- okay. Here's one.
So here you see I've got your -- your '504 reply declaration up?
A. Yes.
Q. And we're looking at Paragraph 15. Do you see that?
A. Yes, I do.
Q. And in the first sentence you cite the institution decision at -- at Page 32, right?
A. That's correct. Yeah.
Q. Does that refresh your recollection that you reviewed and -- and considered the -- the PTAB institution decision in these proceedings?
A. Yes, it -- it does. Yes.
MR. DIAMOND: Okay.
Let's take a look at, and I will upload to the site -- all right.
(Paper No. 15, Institution Decision for '504 Patent, was introduced electronically.)
BY MR. DIAMOND:
Q. So the institution decision for the '504 patent is up there. I'm also going to share it with you here. And just let me know

when you're ready either way.
A. I -- I'm ready, yeah.
Q. Okay. So you see this is the -- this is the institution decision that you were citing with respect to the -- the -- the '504 patent, right?
A. Yes. That's right.
Q. All right. So let's look at page -- you have a citation of Page 32 before. I'm going to now take you to Page 30 -- to Page 34.
Do you see the paragraph beginning, "In -- in Ground 1?"
A. Yes. Yes, I do.
Q. All right. Do you see the -- the Board says here, "In -- in -- in Ground 1, the prior art reference Hillmen discloses a clinical trial of, quote, eculizumab, end quote, but it -- but it does not otherwise identify the structure of the antibody tested, other than by referencing Thomas."
Do you see that?
A. I -- I do see that, yes.
Q. And then about seven lines down, you see it says -- where it says, "Hillmen's mere reference," do you see that?

A. I -- I do see that, yep.
Q. So it says, "Hillmen -- Hillmen's mere reference to, quote, eculizumab, would have at least invoked a molecule having the IgG4 isotype taught in Thomas."
Do you see that?
DR. STERLING: Objection; relevance.
THE WITNESS: I do see that, yep.
BY MR. DIAMOND:
Q. I'm not sure I understand that, but, okay.
At the bottom of the page it -- it says "Moreover, none of the references teaching or suggesting, going on to Page 35 -- well, let -- let's -- let -- let me orient you to the first two pages. So you see at the bottom of Page 34 where it begins, "Moreover, none of the references," --
A. Yes, I do see that.
Q. -- and then it goes down a page. Do you see that?
A. Yes, I do.
Q. All right. So I'm going to read that sentence bridging from Page 34 to -- to 35, just to the record's clear. The PTAB says here,

"More -- moreover, none of the references teaching or suggesting an IgG2/IgG4 isotype, parentheses, e.g., Bowdish, Evans, Tacken, Mueller or Mueller II, closed parentheses, is -- is cited in Hillmen."

Do you see that?

A. Yes, I do.

Q. All right. And the Board, if you look at the next sentence, said they -- they disagreed with petitioner's, Amgen's position, that such reference's teaching would have somehow overwritten Hillmen's direct indication of Thomas's disclosure of eculizumab so as to point the skilled artisan to some alternative antibody structure."

Do you see that?

A. Yes, I do.

DR. STERLING: Objection; scope.

(Paper No. 15, Institution Decision for '880 Patent, was introduced electronically.)

BY MR. DIAMOND:

Q. Okay. And let's take a look at -- I'm going to show you another document, and this will be uploaded to the Exhibit Share if you want there. I'm going to open it up here, as

well. But this is the institution decision from '880 patent. I'm going to share that with you now. And let me know when you are ready to discuss that.

A. I'm -- I'm ready.

Q. All right. And just -- just to be clear, you also considered the -- the '880 patent institution decision in formulating your opinions, at least with respect to the -- the '880 reply declaration that you -- you put forth in -- in these proceedings, right?

A. Yes. That -- that's correct.

Q. All right. So I'm going to orient you to, we'll shrink it down just so we can get the page numbers, and go to Page 37. Do you see we're on Page 37 of the '880 --

A. I do see that.

Q. -- institution decision?

All right. So looking at the third sentence -- the third sentence from the top of the page, do you see the Board says, Hill '05 --

A. Can you make it larger?

Q. I'm sorry. Larger?

A. Yeah. That would be great.

Q. Yeah. Yeah. Yeah. You got it. Let

me expand this out a bit.

Yeah. All right.

So I'm -- I'm looking at the sentence that begins, "Hill '05 further states," do you see that?

A. Yes, I do.

Q. All right. So the Board said -- and, again, we're on Page 37 of the '880 Institution Decision, the Board said that Hill '05 further states, quote, eculizumab is a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage with a -- with a Footnote 9, end quote. Do you see that?

A. Yes, I do see that.

Q. And you see that's a -- the "Id." indicates that's a quote from Page 2559 of Exhibit 1047, the -- the Hill reference, right?

A. Yes.

Q. And after that quote, the PTAB says, "Reference 9 is common, Exhibit 1023," right?

A. Yes. That's right.

Q. And in the next sentence they conclude, "Thus, Hill '05, like Hillmen, invoked Thomas as a reference for eculizumab."

Do you see that?

A. Yes, I do.

Q. Okay. And you don't cite to those statements from the PTAB Institution Decision in your reply declarations, right?

If you want to look through and confirm whether you cite to those pages or not, that would -- that's fine, but I want to confirm that you don't cite to them.

A. Yeah. So I think I make the citation to discussions that PTAB has the position that there are multiple versions of eculizumab and --

Q. That's not my question, sir.

A. Okay.

Q. I was asking specifically about what we just looked at, whether you cite to -- to that in your declarations, or the page numbers.

A. Yeah. I -- I don't remember specific citations to this section.

Q. Okay. You talk about the Chemical Abstract Services Registry in your reply declarations, right?

A. Yes. That's correct.

Q. All right. And we could take a look back at -- back there.

I want to open your '504 declaration again.

All right. So we've got your -- your '504 declaration open again, and we're looking at Paragraph 9 of your '504 reply declaration.

Are you there with me?

A. Yes, I am.

Q. All right. So here you -- you refer to, we're looking towards the bottom of the page, Alexion 5G1.1 entry, again, the Chemical Abstract Services, parentheses, CAS, closed parentheses, registry. You -- you see that -- that -- that mention of the CAS registry there?

A. Yes, I do.

Q. Right. And yet you have some citations after that, right?

A. That's correct.

Q. Now, do -- do you understand that the document you're citing there for the CAS registry is -- is -- is AMG1017?

DR. STERLING: Objection; foundation.

THE WITNESS: Well, --

BY MR. DIAMOND:

Q. Well, maybe -- let me ask you this question: Which one of these documents are you

citing for the CAS registry? Do you know?

A. So that -- you're correct that AMG1017 is being cited for reference to the CAS registry.

Q. All right. And let's take a look at that. I'll -- I'll upload it.

Oh. My marked exhibits folder says, "data is currently unavailable."

Let's see. Oh, there. We're back up. All right.

I've uploaded it to the Exhibit Share. I'm also going to show it to you. Let me pull my information back up here.

(Exhibit No. AMG1017, a document titled Opposition for EP1, was introduced electronically.)

BY MR. DIAMOND:

Q. Okay. So are you -- are you with me on -- on AMG1017?

A. Just one second. I'm still trying to download this.

Q. Okay. Well, let me know when -- just let me just know when you're -- you're ready -- oh, sorry. I've gotta stay in front of my microphone.

Let me know when you're ready and we'll continue.

A. Yes. So I -- I've downloaded it, so I'm ready to go.

Q. Okay. So the -- let -- let's -- let's go to the page that you -- you have cited -- well, actually, we -- we could look. There's -- there's two places you cite. I'm going to -- I'm going to go back for a second to -- to your reply declaration, we could have both of them open, and just orient you to Paragraph 20.

So here we see in Paragraph 20 you talk, again, about "Alexion's CAS registry for eculizumab," and the page numbers you cite in AMG1017 are Pages 277 and 291.

Do you see that?

A. Yes, I do.

Q. All right. So we can take a look at both of those pages. I'm -- I'm back now in AMG1017. I'm going to flip up to 277.

All right. So here -- and I'm -- I'm going to enlarge it for you, but if you could see, at the bottom of the page, we're on Page 2 -- 277, that's AMG1017.

A. The bottom of the page is actually cut

off on my screen, but -- oh, here it is.

Q. Oh, okay. Let me -- let me just zoom in and just confirm for you. It's a little bit hard to do this, but there we go.

A. I was toggling between -- between -- sorry. I was toggling being muted and not being muted, and so it cuts off the bottom of my screen when I do that. So I see now the bottom of the screen is 277, yes.

Q. Great. Okay. And we're -- we're zoomed in, so it'll make it more visible. Oops. It keeps scrolling back.

Okay. It's -- 2 -- Page 277 is pages, that -- that, sort of, typewriter font. Do you see that?

A. Yes, I do.

Q. All right. And you see that there's a Registry Number 219685-50-4, right?

A. Yes, I do see that.

Q. Yeah. There is no --

A. Don't ask me to read it -- don't ask me to read it back to you, though.

Q. Yeah. There's -- there's -- I know. It's a little blurry, even with this zoomed in.

There -- there's no amino acid

sequences printed on this page, right?
A. No. I don't see any amino acid sequences printed on this page.
Q. All right. Let's look at Page 291. Let's scroll down to there.
Okay. So you see we're on Page 291?
A. Yes.
Q. All right. Do you see in Item 5.1.2, the second sentence that says, "A -- a sequence for eculizumab was submitted to the Chemical Abstract Service, CAS, and entered into their STN database on 14 February 1999. Please see the attached copy of the CAS Entry Number 209684-560-4."
Do you see that?
A. Yes. I do see that -- that sentence.
Q. All right. But there -- there's no amino acid sequences printed on Page 291, right?
A. I -- I don't see any, no.
Q. Okay. And -- and those are -- those are the only two pages, if you want to check your declaration to confirm, but Pages 277 and 291 are the only two pages of AMG1017 that you cite with respect to this CAS registry for eculizumab in your declarations, right?

A. Yeah. That's my recollection.
Q. All right. You don't discuss or offer any opinions in your declarations regarding the Exhibit AMG1054, right? If you want to check your Appendix B and whatever you want just to confirm that, that -- that's fine.
A. Yeah. No, it's not listed here, so it's not included among those documents that were used in preparations of the reply declaration or my initial declaration.
Q. All right. And if you want to check your -- your -- did you download your -- your '504 initial declaration earlier?
A. I think so.
Q. All right. If you want to go back and look at that to confirm you don't cite AMG1054 there either, you know, listed among your materials included [sic]?
A. Yes. I can confirm that 1054 is not listed among the exhibits within the context of the initial '504 declaration that I provided.
Q. All right. So in your -- in your declarations, you don't discuss the fact that the eculizumab sequence information submitted to the CAS registry in February 1999 had -- had

errors in it, right?
DR. STERLING: Objection; foundation. Scope. Form.
THE WITNESS: Yeah. I don't recall any reference to that within my declaration. That's correct.
BY MR. DIAMOND:
Q. Okay. Let's go back to your reply declaration for a little bit, your '504 reply declaration. Okay. So here we are, '504 reply. And I'm going to take you to Page -- oh, shoot.
Here we go. Page 44. Let me shrink this down once. I'll just pull it back up.
All right. Sir, are you with me on Page 44 of your '504 reply declaration where you have a section titled, "A POSA would have recognized Bowdish's 5G1.1 antibody as having a human hybrid IgG2/IgG4 constant region?"
A. Yes, I do see that.
Q. All right. And Paragraph 73 appears under that header, as well as Paragraph 74, right?
A. Yes.
Q. All right. So let's -- let's look at Paragraph 73 first. You -- you say, in the

second sentence, that, "A POSA would have been aware of both the constant region sequences used in Bowdish's 5G1.1 construct and Mueller's hybrid IgG2/IgG4 constant region sequence, right?
DR. STERLING: Objection; form.
THE WITNESS: Yes.
BY MR. DIAMOND:
Q. And -- and -- and looking at the next sentence beginning, "accordingly," do you see that sentence?
A. Yes.
Q. You -- you state, "Accordingly, a POSA would have known that Bowdish's 5G1.1 construct had the same sequence, open paren, and, thus, the same isotype, closed paren, had Mueller's human hybrid IgG2/IgG4 constant region."
Do you see that?
A. Yes.
Q. Now, when I talk about Amgen's grounds in these proceedings, do you understand what I mean by that? I'm talking about you have Grounds 1, 2, 3, 4, 5, et cetera, as articulated in the -- in the three proceedings, right?
A. Yes, I do un -- yes, I do understand.

Q. So there's -- there's five grounds for the '149 proceeding and six grounds in the '880 proceeding and seven grounds in the '504 proceeding. Do you understand that?
A. Yes, I understand.
Q. All right. You understand that none of Amgen's grounds in these proceedings recite a combination that includes both Bowdish and Mueller, right?
A. So that -- you're asking none include information from both Bowdish and Mueller as the basis for sequence information?
Q. Well, let me -- let me ask this: So you understand that Amgen combines certain references in its grounds, right? For example, let's -- let's look at your -- here. I'll do it this way: Let's look at your '504 declaration. I'll take you to the table of contents. That's going to be the easiest way to -- to look at it.
So you see we're on table of contents of your 504 reply declaration?
A. Yes, I do see that.
Q. All right. So Ground 1 is anticipation of the five -- of Claims 1 to 3 and 7 to 10 of the '504 patent by Hillmen, right?

DR. STERLING: Objection; form.
THE WITNESS: Yes, I see that.
BY DR. STERLING:
Q. Grounds 2 and 3 are obviousness, in view of Hillmen and Bell or -- or Hillmen, Bell and Wang, right?
A. Yes, I do see that -- that quote, correct.
Q. Now, Ground 4 is obviousness in view of Hillmen, Bowdish and Evans, right?
A. Yes. I -- I see that listed in the table of contents, yes.
Q. Yeah. And -- and that's your understanding of the references you cite that -- that -- that comprise Ground 4, right?
DR. STERLING: Objection; form.
THE WITNESS: No. That's -- that's not my understanding. So my understanding is that these grounds; for example, Ground 4, relates to obviousness, and that obviousness is something in context of the view of a POSA, and that a POSA would have knowledge of the prior art. And so all the information of the prior art would be part of what someone would have in -- in terms of their perspective in looking at

these grounds of obviousness.
So when I think of what a POSA is using, it's not only the couple of references that are listed here, but it's the entire body of prior art that is present. So there's the -- in spite of these documents that are listed within the title, it's that these relate to, for example, sequence information that is being used and comprised in Sequence ID 2 and Sequence ID Number 4, if there's grounds.
BY MR. DIAMOND:
Q. Let -- let me ask you this --
A. That is not to say --
Q. Let me ask you the question.
A. -- that they wouldn't have additional --
Q. Sir -- sir -- you're -- you're not -- you're not answering my question. Let me ask this:
In -- in order to -- do you understand -- I guess let's -- let's focus on Ground 4. So let's just look at Ground 4 of the '504. Ground 4 of -- of Amgen's petition against the '504 patent, do you believe that additional references, aside from Bell, Bowdish and Evans,

are required to provide the disclosure of the claimed elements?
DR. STERLING: Objection; form.
THE WITNESS: I believe that for -- no, I believe that, for a POSA, no additional information would be needed, because, again, a POSA would have complete encyclopedic knowledge of all of the prior art. All the prior art relevance would be known.
BY MR. DIAMOND:
Q. So --
A. That's the reference -- that's the, you know, perspective that is being used to quote the difference of obviousness.
THE REPORTER: Excuse me. This is the court reporter --
BY MR. DIAMOND:
Q. I guess my question --
THE REPORTER: Hello.
You guys are really breaking up. Can -- can anybody else hear that on their end, or is it just me?
DR. STERLING: Yeah. Particularly when they talk over each other, it gets really broken up for me.

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MR. DIAMOND: Does -- does this sound better? I'm going to try to move closer to my microphone and speak a bit clearer. Do I --
THE REPORTER: Yes.
MR. DIAMOND: Do I sound okay?
THE REPORTER: That sounds a little bit better, yes.
DR. STERLING: That's better for me too. Thank you.
MR. DIAMOND: I'll try to -- try to keep doing that.
BY MR. DIAMOND:
Q. What I want to -- I want to -- well, let me ask you this: You don't have any grounds in your '504 reply declaration, or -- or any of your declarations, for that matter, where the ground is stated that any of these patents would have been obvious under view of Bell, Bowdish, Evans and Mueller. That's not any of your stated grounds, right?
A. So if you're looking at --
DR. STERLING: Objection; form.
THE WITNESS: -- the key references that are listed in the titles, I -- I don't recall that combination. I -- I think that you

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are correct, that if you look at the title for the grounds, that combination is not listed. But, again, I --
BY MR. DIAMOND:
Q. Okay.
A. -- I would say that, depending on the POSA, is that that individual has --
Q. That's not my -- sir, that's not my -- that's not my question. If you could -- you could -- that wasn't -- that wasn't my question.
Mueller and Mueller II don't cite to Bowdish, right?
DR. STERLING: Objection; foundation. Form.
THE WITNESS: Not to my recollection. I -- I think that tie between Mueller II and Bowdish is --
BY MR. DIAMOND:
Q. That -- that -- that's my -- not my question. My question -- sir -- sir, did I ask you about the tie? I asked you whether they cite to this, okay? And my question is simply do -- Mueller and Mueller II, do they cite to Bowdish or not?
DR. STERLING: Objection; foundation

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and form.
THE WITNESS: My recollection --
BY MR. DIAMOND:
Q. And your -- your --
A. My recollection --
Q. -- your counsel is objecting to foundation. I guess if you don't know, you could say I don't know; you don't have an opinion on it.
A. So it's not my recollection that they cite to Bowdish.
Q. And to your recollection, does Bowdish cite to Mueller or Mueller II?
DR. STERLING: Objection; form.
THE WITNESS: That's not my recollection that there's a citation from Bowdish to Mueller or to Mueller II.
BY MR. DIAMOND:
Q. To your recollection, does Bowdish cite to Tacken?
A. To my recollection, there is no citation in Bowdish to Tacken.
Q. To your rec -- recollection, does Tacken -- Tacken cite to Bowdish?
A. To my recollection, Tacken does not

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cite to Bowdish.
Q. Let's go to Paragraph 74, if you're still -- if you've got your '504 reply declaration up on the screen still, some I'm going to scroll down to 74.
In -- in this paragraph you discuss a -- a document Rother AMG1032. Do you see that?
A. Yes, I do see that.
Q. All right. And since -- and since you say that that was published in 2005, we'll -- we'll just refer to that as -- as Rother 2005. Is that okay?
A. Sure. That's fine.
Q. When -- when did you first see Rother 2005 in this case, or these proceedings?
DR. STERLING: Objection; relevance, and to the extent it gets to privileged information. If you can recall, you can give timing. But please don't discuss any --
MR. DIAMOND: Yeah. I'm -- I'm just -- I'm just --
DR. STERLING: -- privileged conversations with counsel.
BY MR. DIAMOND:
Q. I'm just asking when, if you recall or

-- or --
A. Yeah. I don't recall the exact -- I don't recall the exact date.
Q. Okay.
THE REPORTER: I'm sorry, Doctor --
BY MR. DIAMOND:
Q. Okay. You've cited it in your initial declarations, right?
A. I -- I'm sorry. You broke up a little bit.
Q. Sure. Can -- can you hear me okay right now?
A. Yes, I can.
Q. Okay. You cited Rother 2005 as the Exhibit AMG1032 in your initial declarations, your October 2019 declarations in -- in these proceedings, right?
A. I -- I think that's very likely, although I don't remember. But for this information, I know that I was referring to a different approach, you know, relevant to this particular type of process.
Q. Well, I'm not -- sir, I'm not -- I'm not asking you about -- I'm asking you about when you first saw the document. You understand

that you saw -- you -- you had Rother 1032 in your possession at the time you did your first round of declarations, right?
A. So if it's listed among the documents in Appendix B for the first declaration, then, yes, but --
Q. Well, you've got your '504 initial declaration Exhibit 10 -- 1002 from the -- from the '504 proceeding in front of you, right?
A. Yes. I'll -- I'll go and take a look. One second here.
Q. I -- I appreciate that. Thank you. And then let me know if you can confirm that you did have AMG1032 at the time that you submitted that declaration.
A. Yes. It -- it was cited within the initial '504 declaration, and I've referred to it in several places within that declaration, yes.
Q. Okay. Is -- is AMG1032 a document that you found for these proceedings or something that was given to you by counsel?
A. I'm sure that was given to me by counsel.
Q. Okay. As far as you recall, Bowdish

doesn't have a citation to -- to Rother 2005, right?
DR. STERLING: Objection; form.
THE WITNESS: Not to my recollection. I don't have any specific --
BY MR. DIAMOND:
Q. To your recollection, Rother 2005 doesn't cite to Bowdish, right?
A. I mean, if -- if you want me to check, I'm happy to do it. I don't have a specific recollection of that.
Q. All right. You -- you certainly don't say that it does in your declarations, right?
A. Not to my recollection.
Q. Okay. Rother 2005, again, talking about AMG1032, doesn't mention eculizumab, right?
A. No, not to my recollection, no.
Q. All right. And it doesn't disclose Sequence ID Numbers 2 and 4 of -- of the patents, right?
DR. STERLING: Objection; foundation. Form.
THE WITNESS: No. I mean, there's no mention, to my recollection, of Sequence ID

Number 2 in the full sequence and Sequence ID Number 4 in the full sequence, but --
BY MR. DIAMOND:
Q. Okay.
A. -- the sequence is mixed --
Q. Okay.
A. -- within --
Q. That -- that's all I was asking -- that's all I was asking. Sir -- sir, please, you've gotta stick with my questions, as we talked about earlier, okay? That's all I was asking.
DR. STERLING: And, Mr. Diamond, can you please let the witness finish his answer?
MR. DIAMOND: No. I -- I'm going to -- I'm not going to let him, you know, filibuster here. He can answer my questions and we'll move on.
BY MR. DIAMOND:
Q. Rother 2005, AMG1032, as far as you recall, didn't disclose any experiments where its antibodies were administered to human patients, right?
DR. STERLING: Objection; form.
THE WITNESS: Yeah. Not -- that's my

recollection.
BY MR. DIAMOND:
Q. All right. So you have a Figure 4 on Page 45 -- I just flipped to it, on Page 45 of your reply declaration. Do you see that?
A. Yes, I do see that.
Q. Oh, and before I -- I get to that, I just wanted to ask, you remember we were discussing earlier, with respect to the references that are cited in the -- you know, the titles of the -- of the grounds in these proceedings, none of the grounds in these three proceedings, as -- as they're stated, you know, in view of X, Y and Z, include Rother 2005 and its combinations, right?
DR. STERLING: Objection; form.
THE WITNESS: No. I don't remember, you know, the titles that are used within the grounds or within the table of contents listing Rother.
BY MR. DIAMOND:
Q. Okay.
A. It should be in some information that a POSA would be aware of.
Q. Okay. So Figure 4, now looking at

your -- your '504 reply declaration on Page 45, does it have a sequence alignment between the, quote, 5G1.1 TPO sequences from fifty -- Figure 67, or Bowdish, and IgG2 sequences and IgG4 sequences from Figures A -- 3A and 3B of Rother 2005, respectively, right?
A. Yes. That's correct.
Q. Who prepared this figure?
A. This was prepared by counsel.
Q. Okay. Back at the time of your initial declaration, you -- you had available to you all the -- the sequences that you present in this -- in this Figure 4. You had the -- the sequences in Bowdish, and you had the sequences in Rother 2005, right?
DR. STERLING: Objection; form.
THE WITNESS: That's correct.
BY MR. DIAMOND:
Q. You didn't include this alignment between Bowdish and Rother 2005 in your initial declarations in these proceedings, right?
A. Yeah. That's correct. I mean, --
Q. Okay.
A. -- this was included --
Q. Okay. Not --

A. -- there as making a comparison between --
Q. Not -- sir, I'm -- sir, I'm not asking -- that was not --
A. -- for a million ways to --
Q. Sir -- sir -- sir, I don't know what you're doing. That wasn't my question.
Fig -- Figure -- well, at the time that -- that Figure 4 was prepared, you already knew that Bowdish's Sequence ID Number 7 had a hybrid IgG2/IgG4 heavy chain constant region, right?
DR. STERLING: Objection; form. Foundation.
THE WITNESS: So, I'm sorry, could you repeat the question?
BY MR. DIAMOND:
Q. Let me -- let me -- in -- in your initial declarations in these proceedings, you discuss how Bowdish's 5G1.1 TPO sequence, you -- you -- you discussed how it has an IgG2/IgG4 hybrid constant region, right?
A. Yes. That's correct.
DR. STERLING: Objection to the extent it misstates witness's testimony.

BY MR. DIAMOND:
Q. And -- and you knew that before -- before Figure 4 was created in your reply declarations, right?
DR. STERLING: Objection; foundation. Form.
THE WITNESS: Yes, I did know that bef -- before it was created, yes.
BY MR. DIAMOND:
Q. O -- okay. Figure 4 wasn't created by -- by trying to, you know, recreate a search of the GenBank -- I'm sorry. Let me get close to my mic, because I'm not sure I was getting picked up.
Figure 4 on Page 45 of your '504 reply declaration wasn't generated by recreating a search of the -- of the GenBank database as it -- as it existed prior to March 15th, 2007, right?
DR. STERLING: Objection; foundation. Form.
THE WITNESS: No. I -- I think in my first declaration --
BY MR. DIAMOND:
Q. Okay.

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A. -- I said that GenBank could be used, and that my recollection was there was an argument about that with respect to Dr. Casadevall's testimony.

So in this reply, we just used another approach to be able to show the prospective sequence for IgG2 and 4. Because, again, there may be a zillion different approaches that one could have selected to do that, many approaches.

Q. Sure. Sure. Sure. But you didn't -- you didn't provide the results of any actual GenBank search performed in Figure 4, right?

A. No. There's -- there's not --

DR. STERLING: Objection; form.

BY MR. DIAMOND:

Q. Okay.

A. -- any search that's performed in Figure 4 here, no.

MR. DIAMOND: Okay. Is now a good time for a break? I could use one.

DR. STERLING: Okay. Let's take a break then.

MR. DIAMOND: All right.

THE VIDEOGRAPHER: Going off the record. The time is 11:24.

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(Recess taken.)

THE VIDEOGRAPHER: We are back on the video record. The time is 11:36.

BY MR. DIAMOND:

Q. All right, Dr. Balthasar. During the break, did you communicate with your counsel in any way regarding the substance of your testimony today?

A. No, I did not.

Q. All right. Let's take a look back at your '504 reply declaration. Let me get that back up there for you. And I'm going to direct you now to Paragraph 42, so we'll go there.

All right. Are you with me on Paragraph 42 of your reply -- '504 reply declaration?

A. Yes.

Q. All right. So here you -- you -- you talked about Paragraphs 68 and 75 of ALXN2024, which you understand is the declaration of Dr. Trout?

A. Yes.

Q. And you -- you -- you take issue with Dr. Trout's opinions in those paragraphs because you understand, as you say here, they were based

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on -- on the -- on the premise that eculizumab was not known to be an antibody with the claimed sequence of the '504 patent, and -- and you disagree with that, right?

A. No. I guess it's a little bit more broad in terms of the disagreement.

Q. Well, let me -- let me -- let me -- let me rephrase that.

One of these disa -- one of the disagreements you have here with respect -- with respect to Dr. Trout's opinions was that you said many of his arguments are based on what you say is an incorrect premise that eculizumab was not known to be an antibody with the claimed sequence of the '504 patent.

Do you see that?

A. Yes, I do see that.

Q. Right. And if we look at Paragraph 50 of your '504 declaration, you -- you quote Dr. Trout as saying, "If a POSA as of March 15th, 2007, had no information regarding the pharmaceutical formulations for clinical use of an antibody comprised in Sequence ID Numbers 2 and 4, it is my opinion, Dr. Trout's opinion, that a POSA would have -- would not have

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reasonably expected to succeed in doing so."

Do you see that?

A. Yes, I do see that.

Q. And you got that quote from Paragraph 75 of -- of Dr. Trout's declaration, right?

A. Yes.

Q. And you respond in the next sentence that a -- a POSA did, in your view, have information regarding the pharmaceutical formulation and clinical use of eculizumab from Bell and Wang, as well as general guidance on -- on antibody formulation. Do you see that?

A. Yes.

Q. Now, you -- you don't offer any opinions in your reply declaration regarding pharmaceutical composition elements of the '504 and '880 patent if it were true that the eculizumab antibody of Bell and Wang was not known to be an antibody with Sequence ID Numbers 2 and 4, right?

A. No, I don't make any --

DR. STERLING: Objection; form.

THE WITNESS: I -- I don't make any comments on that. And I --

BY MR. DIAMOND:

Q. Okay.
A. -- don't see the relevance of it, honestly.
Q. Okay. Let's look at Paragraph 47 of your reply declaration. And looking at the second sentence there you say, "A basic commonality between intravenous and nebulized formulations is that both need to be stably formulated as a liquid before being administered."
Do you see that?
A. Yes, I do.
Q. All right. And above that sentence, you -- you -- you -- you talk about Wang. Do you see that?
A. Are you referring to the sentence that starts with, "contrary to Dr. Trout's?"
Q. Yeah. Yeah. The sentence -- the sentence prior where you talk about the document Wang, right?
A. Yes. Yes.
Q. And when you refer to Wang here, you're talking about the -- the Wang documents, that's AMG1028, as you discussed in the -- in the paragraph prior, right? Prior to that,

there's -- there's multiple documents called Wang in -- in these proceedings, and I just want to make sure that the one you're referring to in Paragraph 47 is in AMG1028?
A. Yes. That's correct.
Q. All right. And you understand that Wang, AMG1028, didn't disclose any actual administrations of any eculizumab pharmaceutical compositions, right?
DR. STERLING: Objection; foundation. Form.
THE WITNESS: Do you -- do you mean, you know, like, clinical application? Is that what you're asking me?
BY MR. DIAMOND:
Q. Administration to any patients, or animals, for that matter, of eculizumab, Wang doesn't disclose that, right?
A. Right. Suitable formulation concepts, right.
Q. I -- I'm sorry. What was your answer?
A. So there's no reference within Wang to administration to any subject, that I'm aware of. It's just, you know, --
Q. Okay.

A. -- form -- formulations.
Q. You -- you also cite, and I'm looking at the bottom of Page 27 of your '504 reply declaration, Paragraph 47 you cite to two documents here, AMG1086 and AMG1087.
Do you see that?
A. Yes, I do see that.
MR. DIAMOND: All right. I'm going to pop those in the -- the folder now.
Bear with me one moment.
(Exhibit No. AMG1086, a document titled O'Riordan, was introduced electronically.)
(Exhibit No. AMG1087, a document titled Shoeyle 2006, was introduced electronically.)
BY MR. DIAMOND:
Q. And feel free to download them. I -- I was just going to ask general -- you know, general questions about them, so we don't need to -- I'm not going to share the screen with you right now.
A. Great. Yeah. I'm trying to download it on my -- I think I got the O'Riordan one, and I'm trying to get the other one now.

Okay. I've got them.
Q. All right. How did you get these documents, 1086 and 1087? Were -- were these something you found or something that were given to you by counsel?
A. No. These were given to me by counsel.
Q. All right. And you'd agree with me that neither AMG1086 nor AMG1087 disclosed any compositions of an antibody with Sequence ID Numbers 2 and 4, right?
DR. STERLING: Objection; form.
THE WITNESS: Maybe could you repeat that again? I just want to make sure that I had that clear, that question.
BY MR. DIAMOND:
Q. Yeah. So you -- you've got AMG1086 and AMG1087 in front of you, right?
A. Yep.
Q. Neither of those documents disclosed any compositions of an antibody with Sequence ID Numbers 2 and -- and 4, kind of, doing the designations as in the -- the '504 patent, et cetera. Do you understand?
A. Yeah. I understand. And, yes, the

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answer's, yes, you're correct.
MR. DIAMOND: Okay. Let's look at one more document that you -- you cited. I'll toss it in the folder here.
(Exhibit No. AMG1085, a document titled Akers 2002, was introduced electronically.)
BY MR. DIAMOND:
Q. So I am uploading, and I'll tell you when it's ready, AMG1085.
Do you -- do you have that? Let me know.
A. I just refreshed, and I see that it is in the folder. I'm just downloading it right now.
Q. Okay. And I could -- I could open that for you, as well.
A. So you want me to open up 1085, correct?
Q. Yeah. That's fine. I'm also sharing it on my screen, but you could open it up on your own, whatever is easiest for you.
I'm going to point you to some -- some parts of it that -- to ask you some questions.
A. Sure.

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Q. But first I have a general question, which is AMG1085 is -- is one of the references you -- you relied on in your reply declarations for a POSA's understanding of -- of antibody formulation technology, right?
DR. STERLING: Objection to the extent it misstates testimony.
THE WITNESS: Yeah. It's one of the documents that is cited and used in the reply declaration. That's correct.
BY MR. DIAMOND:
Q. Right. And -- and specifically on the issue of -- of pharmaceutical formulation technology with respect to the -- the antibodies, right?
A. Yeah. It's, you know, that title was shown here as Development and Manufacture of Protein Pharmaceuticals, and, you know, it's being referred to within the declaration within that scope.
Q. All right. So this is -- this is actually something I have a hard copy of. I -- I -- I heard -- I heard earlier where you were talking about hard copies, you know, for -- for better or worse, you know, the logistics of

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-- of making hard copies, you know, these days are a bit more challenging in view of the -- you know, the limitations for us over here in New York, but I'm going to read along with you here.
So let's take a look first at -- at Page 47 of AMG1085. Are you there with me?
A. Yes. I'm reading it on the screen.
Q. All right. And, by the way, do you -- do you know any of these authors, Michael Akers or Vasu -- Va -- Va -- Vasu Vasudevan or -- or Mary Stickelmeyer?
A. I think that I may have met Michael Akers, but I'm, you know, not positive. I'm not very good with names. I think we talked about that at the first deposition of myself.
Q. Okay. Yeah. Yeah. Well, anyway, these -- these are -- these are folks in the industry from -- from Baxter Pharmaceuticals. Do you see that? Or -- and -- from -- from Baxter Pharmaceuticals and from Lilly Research Laboratories, right?
A. Yeah. I do see that.
Q. Those -- those are, you'd say, rep -- reputable pharmaceutical companies, right?
A. Yes. I -- I do feel that they're

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reputable pharmaceutical companies, yes.
Q. All right. So under the introduction, you see in the first sentence in AMG1085, Page 47, it states that, "A formulation scientist assigned the task of developing stable, elegant and manufacturable dosage form of a therapeutic protein drug has been given a significant challenge."
Do you see that?
A. I -- I do see that, yeah.
Q. And they say, "Most proteins of natural physiological molecules are inherently unstable outside of the human or animal body," right?
A. Yeah. I do see reference to "most proteins," yes.
Q. Yeah.
And they -- then -- then they say, "Stability challenges in protein formulation development are typically enormous."
Do you see that?
A. I see, "typically enormous," yes.
Q. Yeah.
They say, "The instability of these reactive and complex molecules must be

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considered not only in the formulation process, but also in development of the packaging system and the manufacturing process," right?

A. I do see that sentence, yes.

Q. And they say, "These three areas are intimately and inseparably connected," right?

A. I see that, yes.

Q. And if we look at the next page, 48, I'm going to focus you on the text at the bottom of the page that bridges onto Page 49, so we're going to have to flip a page here. Do you see in AMG1085 it states, "Many text and articles already discuss the great difficulties scientists experience in protein dosage formulations because of the significant -- going on to Page 49 -- the significant instabilities of -- of these molecules."

Do you see that?

A. Yeah. I -- I do see that. I think it's generally --

Q. All right. No. My -- my question is about if you could see that, sir.

You see the next thing they say is, "Depending on the amino acid type and sequence, proteins are subject to various types of

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degradation mechanisms, including hydrolysis, oxidation, racemization and interaction with a variety of solutes and surfaces."

Do you see that?

A. Yes, I do see that.

Q. Right.

And going several lines down, do you see where the sentence begins, "dealings," on Page 49. Do you see that?

A. Yes, I do see that.

Q. So the authors of AMG1085 state here, "Dealing with physical instability, open paren, e.g., denaturation, aggregation and adsorption -- adsorption, closed parentheses, often is more a problem with proteins than dealing with their chemical stabilization."

Do you see that?

A. Yes, I do see that.

Q. All right. If we go to Page -- Page 50, so the next page here, you see the first sentence under General Formulation Principles for Proteins beginning "Protein Stability." Do you see that?

A. The -- the table? I -- I see the table -- table --

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Q. So -- sure. There's a -- I'm -- so are you with me on Page 50 of AMG1085?

A. Yes, I am.

Q. All right. There's a header, General -- for three -- it's a header, Number 3, General Formulation Principles For Protein. Are you there with me?

A. Yes, I do see that.

Q. All right. So the first thing the authors say under that header is, "Protein stability, both in the dry state and in solution, is the main reason why formulation science has such a presence in the commercial development of protein dosage form."

Do you see that?

A. Yes, I do see that.

Q. And if you look several lines down, and I'm indicating to it on the page, a sentence beginning, "The challenge to formulation scientists," do you see that?

A. Yes, I do see that.

Q. All right. It says, "The challenge to formulation scientists is to develop a stable formulation that could be consistently manufactured and is stable in a given packaging

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system over the shelf life of a product."

Do you see that?

A. I -- I do see that, yes.

Q. Okay. If we go to Page 52 of AMG1085, and I'll just flip there, do you see there's a -- a Section 4 titled, Why Packaging, Processing and Formulation Are Interrelated. Do you see that?

A. Yes, I do.

Q. All right. So in the second sentence it says, "A -- a formulation is not stable unless the product can be manufactured consistently on a large scale and packaged in a container/closure system that can maintain sterility and stability for a relatively long period of time."

You see that, right?

A. I do see the sentence, yes.

Q. All right. And if we go to the next page, you see there's a heading -- now -- now I'm on Page 53 of AMG1085. I'm looking at, under the Heading Number 5, Commercially Available Protein Dosage Forms. Do you see that?

A. Yes, I do see that.

Q. All right. And -- and I -- I think you -- you say in your declarations that a POSA would have looked at commercially available protein dosage forms, right?

DR. STERLING: Objection to the extent that it misstates the testimony, and form.

THE WITNESS: Yes. In some contexts within the declaration, I do say that a POSA would be knowledgeable about formulations for FDA-approved antibody products.

BY MR. DIAMOND:

Q. Okay. If you look at the second sentence under that Heading Number 5 on Page 53 of AMG1085, the author states, "Although preferential interaction with experi -- experiments, and then they have a citation, can predict which solutes can serve as protein stabilizers, the majority of protein formulation research and development requires a great deal -- a great amount, sorry -- a great amount of trial and error to finalize the type and amount of formulations components." Do you see that?

A. Yeah. I see the reference to, "the majority of protein formulation research and development," yes, I see that.

Q. Okay. Let me refer you to a few more cases in here to Page 60 of AMG1085.

Do you see there's a paragraph towards the middle of the page beginning with, "Proteins are commonly formulated?"

A. Yes. I do see that.

Q. Do you see that?

So it says, "Proteins are commonly formulated at very low doses, open paren, very dilute solutions, closed paren, although there are samples of relatively high dose protein products, such as formulations of immunoglobu -- immunoglobulin G, open paren, IgG, closed paren, at 50 milligrams per milliliter."

Do you see that?

A. Yes. I see that sentence.

Q. Yes. And in the next sentence they state, "In general, dilute solutions are less physically stable than more concentrated solutions, and adsorption -- adsorption to surfaces will -- will result in a higher fraction of loss of protein."

Do you see that?

A. Yeah. I -- I do see that sentence. I don't know that I completely agree, --

Q. Okay.

A. -- but I do see it.

Q. Okay. All right.

In the -- the last sentence in the paragraph that we're reading from on Page 60 of AMG1085, the authors state, "In general, however, there are surprisingly few literature reports of protein stability as a function of concentration."

Do you see that?

A. Yeah. I do see that sentence.

Q. Okay. If you look at page -- well, actually, yeah, if you look at Page 108 of this document, AMG1085, you'll see there is a -- I'll take you there -- a summary. There's a Table 16, Roman Numeral 16 on Page 108 AMG1085 titled, Summary Of Guidelines for Stability Testing of Biotechnological and Biological Products. Do you see that?

A. I -- I do see that. Do you mind making that a little bit larger on the screen?

Q. Absolutely. Or I guess the answer is, no, I do not mind at all.

All right. So now I -- I've enlarged you. We're on Page 108 looking at Table 16. Do

you see that?

A. Yes.

Q. All right. And I'm going to take you to the next page, Page 109. Do you see that this table Roman Numeral 16 continues?

A. Yes, I do see that.

Q. All right. And you see there's guidance for -- for "storage conditions" here?

A. Yes. I do see that.

Q. Right. And for temperature they say, "Storage conditions for real-time/real-temperature stability studies may be confined to the proposed storage temperature."

Do you see that?

A. Yes, I do see that.

Q. And they also talk about "accelerated and stress conditions," do you see that?

A. Yes, I do see that.

Q. And then it says, "Studies should be conducted on the drug substance and drug product under accelerated and -- and stress conditions."

Do you see that?

A. Yes, I do see that.

Q. All right. One of the documents

you considered in your -- in formulating your opinions in your reply declarations is ALXN2075, which is the -- the -- the GenScript sequencing report of the 5G1.1 mouse antibody. Could -- could you confirm that?

A. Yes. That's correct.

Q. All right. And let's look back at your declaration. I'll pull that back up.

I'm going to take you to Paragraph 63, and we're going to go to the top of Page 38 in your '504 reply declaration. Are you -- are you there with me?

A. Yes.

Q. Great. All right. I'm just organizing myself here.

Okay. I'm sorry. We're going to go from Page 37 onto Page 38. That's why I got lost here.

So Paragraph 63 of your '504 reply declaration, starting on the bottom of Page 37 and then we're going to bridge over to Page 38, you see you mentioned, "GenScript sequencing of the 5G1.1 hybridoma HB-11625," --

A. Yes.

Q. -- and you have a citation to

ALXN2075 at Pages 2 to 3. Do you see that?

A. Yes.

Q. And, also, if we look down on Page 38 of your '504 reply declaration at your Footnote Number 7, you also cite to ALXN2075 at -- at -- at Pages 2 to 3?

A. Yes.

Q. Do you see that?

All right. In your reply declarations, you don't provide any critique of GenScript sequencing methods or -- or -- or their -- or their sequence results, right?

A. No, I do not.

DR. STERLING: Objection to the extent it misstates witness testimony.

BY MR. DIAMOND:

Q. So your answer was, no, you do not?

DR. STERLING: Objection.

THE WITNESS: Are you saying do I give the -- the critical evaluation of their sequencing results or question their results? I'm not questioning the results.

BY MR. DIAMOND:

Q. Okay. All right.

I think I did ask you earlier about

the declaration of Dr. Michel Nussenzweig, but just to close the loop here, you don't discuss the deposition testimony of Dr. Michel Nussenzweig anywhere in your -- in your reply declaration, right?

A. Yeah. It's not anything that I've looked at.

MR. DIAMOND: Okay. And just -- I'm going to close this out. I'm going to throw another document in the folder.

(Exhibit No. ALXN2075, a document titled GenScript final report, was introduced electronically.)

BY MR. DIAMOND:

Q. Okay. So in the -- in the folder I've -- the Exhibit Share folder I've put in Exhibit AL -- ALXN2075, and I'm also going to share that with you.

Let me know when you're -- you're ready to talk.

A. Yeah. I'm going -- downloading it now, so a couple seconds yet.

Q. Yes. Do you have it?

A. Okay. I have it opened.

Q. Okay. So this -- this is the -- the

ALXN2075 document that you cite in your -- your declarations, right?

A. That's correct.

Q. And if we look at Page 2, I'm going to shrink down the size a bit, tell me if you need it bigger, you see on the -- the bottom of Page 2, bridging onto Page 3, there's the heavy chain amino acid sequence for the -- the mouse 5G1.1 antibody?

A. Yes, I do see that.

Q. And then the light chain amino acid sequence for that antibody is at the bottom of Page 3 of ALXN2075. Do you see that?

A. Yes, I do.

Q. Right.

And you don't -- you don't dispute that if a POSA were -- were to have prepared the -- the sequence for the -- the full-length mouse 5G1.1 antibody to Bowdish's Sequence 60 -- 67 and 69, that -- that those sequences would be different, right?

DR. STERLING: Objection; form.

THE WITNESS: Yeah. That's correct. That the Bowdish sequences --

BY MR. DIAMOND:

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Q. Okay.
A. -- reference the full-length mouse seq -- sequence, yeah.
Q. Okay. I want to go back to your reply declaration -- well, all right. We're back on your -- your '504 reply declaration, and I'm going to take you to Paragraph 96.
All right. Are you there with me?
A. Yes, I am.
Q. All right. It -- it's your understanding that Dr. Casadevall asserted objective indicia of nonobviousness on the issues of long-felt need, praise and -- and copying, right?
A. Yes. That's correct.
Q. Were -- were you aware that Dr. Casadevall also discusses two other objective indicia of nonobviousness, commercial success and -- and failure of others?
A. I probably looked at that in his declaration, so, yes, I -- I guess I would say I'm -- I'm aware of it.
Q. Okay. These -- these are the three that you discuss, though, in your -- in your reply declaration, long-felt need, praise

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and copying, right?
A. Yeah. These are the three that are listed in the sentence that you read, yes. Yep.
Q. So let -- let me ask you about copying first. You -- you mentioned copying in Paragraph 96 in your re -- reply declaration, and then you -- you say you disagree with each of these assertions. But beyond that statement, you don't -- you don't offer any specific opinions in your reply declaration on why you disagree with Dr. Casadevall on the issue of copying, right?
And -- and -- and if you think you do, just -- just show me where that -- that is, because I didn't see it.
A. So, overall, I guess there's a disagreement throughout the reply declaration that the -- the information that relates to eculizumab was in the prior art and so --
Q. Yeah. That's -- that's -- sir, that's not -- that's not -- what I'm talking about. I'm -- I'm asking about where -- where -- do you have any other opinions specifically on the issue of the objective indicum of -- of copying, aside from what's stated in Paragraph 96? And

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if you could point to where that is, please point me to a paragraph.
A. So you're asking, in this section that's followed below, do I specifically reference copying below. And the answer is, no, I do not.
Q. Oh, okay. All right.
In Paragraph 98, are you there with me on Paragraph 98 of your '504 reply declaration?
A. Yes, I am.
Q. All right. You -- you -- you agree that multiple prior art publications described administering eculizumab to patients during clinical trials as a pa -- as a treatment for PNH well before March 15th, 2007, and reported that eculizumab is an effective treatment for PNH, right?
A. Yeah. That's written directly in the declaration, and, I guess by the way you're asking, --
Q. Right.
A. -- you know, I'm happy that you agree with that, yes.
Q. Okay. And you -- and with respect to Hillmen 2006, you agree that that -- that stated

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that eculizumab is an effective therapy for PNH, right?
A. Yes.
Q. And you -- you agree that Hillmen disclosed that eculizumab reduces intravascular hemolysis, hemoglobinuria and the need for transfusions with an associated improvement in quality of life in patients with PNH, right?
A. Yeah. That's a direct quote from the declaration, and I'm referring back directly as a quote from the reference, yes.
Q. All right. You don't offer any opinion in your reply declarations that the -- the -- the need met by -- by Soliris in treating PNH patients was already as being satisfied by the prior practice of -- of giving patient frequent blood transfusions, right?
A. No, I'm --
DR. STERLING: Objection; form.
THE WITNESS: -- just focusing here --
BY MR. DIAMOND:
Q. Okay.
A. -- on the prior knowledge that eculizumab has utility in the treatment of PNH --

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Q. Okay.
A. -- before --
Q. Okay.
A. -- the priority date.
MR. DIAMOND: Okay. Let -- let's talk about indiscrete praise, and -- and I think you have a Paragraph 99 on that.
Well, actually, let -- let me -- let me do something different. I'm going to put two more documents into the folder.
(Exhibit No. ALXN2020, Alexion's Soliris Receives 2008 Prix Galien USA Award for Best Biotechnology Product, was introduced electronically.)
(Exhibit No. ALXN2021, a document titled the 2009 Prix Galien France Award for Most Innovative Drug for a Rare Disease, was marked.)
BY MR. DIAMOND:
Q. I put two in at once, and it makes it a little slower, so bear with me.
Getting close.
All right. So now if you refresh your -- your marked exhibit folder, you should be able to download ALXN2020 and ALXN2021.

Just let me know when you've -- you've download those -- downloaded those and you have them. I just have a few simple questions about those.
A. Yes. I was able to download them, and I have both copies available to me.
Q. All right. And you -- you considered these -- both of these documents in formulating your -- your opinions in your reply declarations that -- that are listed in your -- your Appendix B, right?
A. Yes. That's correct.
Q. All right. So ALXN2020 discusses Soliris being awarded to 2008 Prix Galien USA Award for -- for Best Biotechnology Product. Do you see that?
A. Yes, I do.
Q. And ALXN2021 discusses Soliris within the 2009 Prix Galien France Award for Most Innovative Drug for a -- for a Rare Disease, right?
A. Yes, I -- I do see that.
Q. And in your reply declaration, you don't offer any opinions criticizing the -- the prominence or significance of the

Prix Galien Award in the industry, right?
A. No, not at all.
DR. STERLING: Objection to form.
THE WITNESS: No, not at all. I -- I don't have any criticism of these awards. It's just really --
BY MR. DIAMOND:
Q. Okay.
A. -- the -- the information to what it was --
Q. Yeah. That was --
A. -- prior to --
Q. That was my question.
A. Yep.
MR. DIAMOND: I think now's a good time for a lunch break, if -- if everyone wants that.
We want to say a half hour?
THE VIDEOGRAPHER: Going off the record. The time is 12:15.
(Lunch recess taken.)
THE VIDEOGRAPHER: All right. We are back on the video record at the time of 12:47.
BY MR. DIAMOND:
Q. Dr. Balthasar, during the lunch break,

did you talk to counsel in any way regarding the substance of your testimony?
A. No, I did not.
Q. So earlier we were talking about the -- the Hillmen and the Hill publications, but I want to focus you for a moment on the actual underlying clinical trials that were conducted, and -- and not the publications themselves.
Do you understand what I'm saying?
A. Sure.
Q. All right. In your reply declarations, you don't offer any opinion regarding whether the -- the physical drug supplies of eculizumab used in those clinical trials were available to the public, right?
A. No, I don't make any --
DR. STERLING: Objection; form.
THE WITNESS: No, I don't make any statements about availability of the drug substances from those prior trials.
BY MR. DIAMOND:
Q. Okay. And you don't, in your reply declarations, offer any opinions that the investigators -- the clinical investigators or the trial subjects knew the amino acid sequence

of the eculizumab drug that was being administered, right?

DR. STERLING: Objection; form.

THE WITNESS: No. I'm not making any statement about that, other than that a POSA --

BY MR. DIAMOND:

Q. Okay.

A. -- would have had knowledge of the sequence from the prior art.

Q. Right. But the -- specifically, that the clinical investigators, the -- the doctors who administered the drugs in those trials, you're not aware of them knowing the sequence of eculizumab, right? You don't say that in your declarations, right?

A. No, --

DR. STERLING: Objection; form.

THE WITNESS: -- I would consider them to be POSA's. And so prior to the priority date, I would think they could also know the sequence, but nothing beyond that.

DR. STERLING: Excuse me, before we continue, Joe, I'm having a hard time hearing both you and Evan, if you could just lean a little closer to your microphones, --

MR. DIAMOND: Yes.

DR. STERLING: -- I'd appreciate it.

MR. DIAMOND: Yes.

DR. STERLING: Thank you.

BY MR. DIAMOND:

Q. So -- and -- and just to be clear, there's -- there's no opinion in your reply declarations saying that the investigators or the -- or the trial subjects knew that amino acid sequence, right? That's not in your declaration?

A. Again, nothing, aside from the description of what a POSA is, --

Q. Well, sir, that --

A. -- and that the --

Q. -- that's not -- that's not -- I'm not asking about a POSA. I'm asking about the actual -- sir, sorry. I need you to answer my question.

I'm asking, the actual investigator -- the clinical investigators, the actual trial subject, you don't offer any opinion as to those specific individuals as to whether or not they knew of the sequence, right?

A. I'm just offering opinions on what a

POSA would know, nothing more specific than that.

Q. Okay. Fair enough.

You don't say anywhere in your reply declarations that the investigators or the trial subjects in those clinical trials, the results of which are reported in Hillmen and Hill, were allowed to take the eculizumab drug supply out of the clinic and -- and use it for -- for purposes other than the clinical trial, right?

A. No, I made no statements --

DR. STERLING: Objection to form and foundation.

BY MR. DIAMOND:

Q. I'm sorry. What was your answer?

THE WITNESS: No, I made no statements of that subject within the declaration.

BY MR. DIAMOND:

Q. Oh, okay.

I'm going to bring you back into your '504 reply declaration.

Okay. So I've got you back in the '504 reply declaration, and I'm going to take you to Paragraph 80, okay?

A. Sure.

Q. Eighty.

And I'm going to Page 50 now, so we're on Page 50 within Paragraph 80 of your '504 reply declaration. Can you see at the top of the page -- or you see in the -- sort of, the top half of the page, you have a citation and a quote from Bell, Paragraph 12, for the proposition that Bell teaches that a range of different 5G1.1 constructs could be used according to its method of treating PNH.

Do you see that?

A. Yes.

Q. Okay. And you -- the 5G1.1 construct that you cite from Bell include, quote, h5G1.1-mAb, parentheses, eculizumab, closed parentheses; h5G1.1-scFv, open paren, pexelizumab, closed paren, and other functional fragments of h5G1.1, right?

A. Yes, that is an accurate representation of the quote.

Q. Right. But Bell only reports clinical trial data for eculizumab, not -- not for those other constructs, right?

A. Yes.

DR. STERLING: Objection; foundation.

BY MR. DIAMOND:
Q. Sorry. Did you say yes?
A. Yes. That's my understanding.
Q. Okay. And as far as you're aware, Bell doesn't present any clinical trial data for treating PNH with any full-length antibodies other than ec -- eculizumab, right?
A. Correct.
Q. And the -- the only full-length antibody, for that matter, that you discuss in your declaration as having been clinically tested prior to March 15th, 2007, for safety and efficacy in treating PNH is -- is the -- the eculizumab antibody, as described in Bell and the other clinical publications, right?
A. Yes. That's correct.
Q. Okay. Let's look at Paragraph 81 now, we're still on the same page, but I want to take you to the top of Page 51, actually, so sorry. We're, in your '504 declaration, looking at Paragraph 81 and I'm directing your attention to the -- excuse me, I'm directing your attention to the top of Page 51.
You see here you state, "Prior art studies accorded that switching from an IgG4

isotype to an IgG2/IgG4 isotype did not alter antibody binding affinity or function."
You -- do you see that?
A. Yes.
Q. And the -- the only two documents you cite there for that proposition are AMG1031 and AMG1034, right?
A. Yes. Those are the two documents I cited, yes.
Q. Right. And that's -- the AMG1031, that is Mue -- Mueller II, right?
A. Yes. That's correct.
Q. And AMG1034, that's Tacken, right?
A. Yes. That's correct.
Q. All right. Then if we look at the -- the next paragraph, Paragraph 82, Mueller II and Tacken, those are the only two documents you cite here as having directly addressed the question of whether switching to an IgG2/IgG4 isotype results in any change in antibody function, right?
DR. STERLING: Objection; form, and to the extent that it misstates testimony.
THE WITNESS: Yeah. The sentence starts with, "for example," and it refers to

these two publications as examples, yeah, that's correct.
BY MR. DIAMOND:
Q. Well, those -- those are -- I know it -- it begins with, "for example," but those are the only two publications you describe -- you cite in Paragraph 82 as having directly addressed the question of whether switching to an IgG2/IgG4 isotype results in any change in antibody function.
You don't cite any other publications in this Paragraph 82, right?
A. You're right. Those are the two references that are included as examples to the cite, yes.
Q. All right.
So you -- you state in Paragraph 82 that Mueller II -- Mueller Roman Numeral 2, "constructed IgG4 and IgG2/IgG4 versions of two anti-VCAM, that's V-C-A-M, antibodies."
Do you see that?
A. Yes.
Q. And the -- the two anti-VCAM antibodies that you're discussing here in Mueller II are called 2A2, that's --

A. Mm-hmm.
Q. -- Number 2, Letter A, Number 2, and the other one's called 3F4, that's the Number 3, the Letter F and the Number 4, right?
A. Yes.
Q. All right. And the -- the 2A2 and 3F4 antibodies, those are different from eculizumab, right?
DR. STERLING: Objection; foundation.
THE WITNESS: Yes. That's fair.
BY MR. DIAMOND:
Q. And in your declarations, you don't offer any opinions that 2A2 and 3F4 have any anti-C5 activity, right?
A. No, I do not make any statements about anti-C5 activity.
Q. Okay. You say that -- in the next sentence, that "Mueller II tests the functions of -- of these antibodies." Do you see that?
A. Yeah.
Q. Okay. So the "these antibodies," you're referring to as the anti-VCAM antibodies, right?
A. Yes.
Q. So you say, "Mueller II tested the

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functions of these antibodies and found that, quote, the ch3F4, HuG2/G4 and ch2A2, HuG2/G4 antibodies maintains the ability to bind, in brackets, their antigens, end bracket, quote -- no, end quote, relative to the IgG4 isotypes of the antibodies."

Do you see that?

A. Yes. I mean, the purpose of this is just --

Q. Well, sir -- sir -- sir, I didn't ask that. I just asked if you saw that. You see that, right?

A. Yes. I see it.

Q. Okay. Great.

When you say the -- the -- the -- where you put brackets around, "their antigens," "their antigen" is -- is the -- is a VCAM antigen, the porcine VCAM antigen, right?

A. Yes. That's correct.

Q. All right. And the -- excuse me for just one moment. We don't need to go off the record. I just need to --

Thank you.

And the -- the quote that you have that we just read from in Mueller II, you're --

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you're quoting from Page 448 of -- of Mueller II?

A. Yes.

Q. All right. You also continue on in citing Mueller II for the proposition that, quote, in addition to binding with the chimeric HuG2/G4 was equivalent to the HuG4 or original murine anti-pVCAM antibodies, right?

A. Yes. That's a direct quote from Mueller II, yes.

Q. Okay. Now, nothing in the portions of -- of Mueller II that you were quoting from and referencing here assessed the abilities of any antibodies to prevent cleavage of the VCAM antigen, right; they -- they were assessing the ability to bind, right?

DR. STERLING: Objection to form, foundation.

THE WITNESS: So I think that the sentence that we just read is a good description of the function of these antibodies not being effective.

BY MR. DIAMOND:

Q. That wasn't my question, sir. Let me ask you my question again. Just listen

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carefully, okay?

Not -- nothing in the passages of Mueller II, or -- or the figures in Mueller II that you're discussing here, assess the ability of these antibodies to prevent cleavage of the pVCAM antigen, right?

DR. STERLING: Objection; form. Foundation.

THE WITNESS: Yes. I do not have any knowledge of any of these antibodies having that function.

BY MR. DIAMOND:

Q. Okay. And -- and nothing in this passage of Mueller II, or these passages of Mueller II, says that Mueller assessed the ability of these antibodies to bind the -- the C5 antigen, right?

A. Yes. I believe there's no reference to C5 binding for these antibodies within the Mueller II reference.

Q. Okay. Let's -- let's talk about Tacken. So still staying in Paragraph 82 of your '504 reply declaration, you -- you -- you talk about Tacken at the bottom of the page. And you cite Tacken for comparing a -- a murine,

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or mouse, IgG1 antibody with -- with a -- with a -- with what you say is a related antibody containing a human hybrid IgG2/IgG4 constant region, right?

A. Yes. That's correct.

Q. And I don't -- I don't think you have the names here, but do you recall the -- the -- the mouse antibody was AZND1 and the -- and the humanized antibody was hD1?

A. Yes, I recall that.

Q. All right. The -- the -- the AZND1 mouse antibody, that would have a different variable and constant region from the humanized hD1 antibody, right?

DR. STERLING: Objection to foundation, form.

THE WITNESS: So there would be portions of the variable region that would be different between the two antibodies and portions that would be the same. And the portions that would be the same would be the CDR repeats, which are responsible for binding.

BY MR. DIAMOND:

Q. There would be portions of the constant regions that are the same, and portions

of the constant regions that are different, as well, right?
DR. STERLING: Objection to form, foundation.
THE WITNESS: Yeah. So I -- I think that most POSAs would consider the constant regions to be completely different, although there probably is some similarity. One is mouse and one is human.
BY MR. DIAMOND:
Q. Okay. Fair enough.
You -- you don't cite any data -- in your declarations, you don't report any data from Tacken that compared the binding affinity of any humanized IgG2/IgG4 isotype antibody to a humanized IgG4 isotype antibody, right?
DR. STERLING: Objection; form.
THE WITNESS: No. My -- there's -- I have no recollection that that exists within Tacken.
BY MR. DIAMOND:
Q. DC-SIGN is a different antigen from C5, right?
DR. STERLING: Objection; foundation. Form.

THE WITNESS: Yes. DC-SIGN is referring to a different substance, yes, than C5.
BY MR. DIAMOND:
Q. You -- you don't cite any data from Tacken comparing the binding affinity of the AZND1 and hD1 antibody for C5, right?
DR. STERLING: Objection; form.
THE WITNESS: No, there's no reference that I'm aware of within Tacken that refers to the binding to C5 for either of those two antibodies.
BY MR. DIAMOND:
Q. Okay. And let's go to the top of Page 52 of your reply '504 declaration. You report that these two antibodies had, quote, similar, end quote, affinities of 3.8 plus/minus 1.1 nanomolar and 3.7 plus/minus 0.7 nanomolar, respectively. Do you see that?
A. Yes, I do see that.
Q. So that -- that's -- that's binding affinity data for the DC-SIGN antigen, right?
A. Yeah. I mean, it's, likely, an equilibrium dissociation constant, but it's reflective of them.

Q. Right. They -- they -- they measured -- they measured dissociation constants of -- of the -- as a measure of binding affinity using, I think, surface plasmon resonance, right?
DR. STERLING: Objection; foundation. Form.
THE WITNESS: That's my recollection.
BY MR. DIAMOND:
Q. Okay. You don't cite data in your reply declarations from Tacken regarding the -- comparing the specificity or binding specificity of the AZND1 antibody to the -- to the HD1 antibody for the DC-SIGN antigen, right?
DR. STERLING: Objection; form.
THE WITNESS: No. I -- I wouldn't say that a description of specificity is given by the target that they bind to DC-SIGN.
BY MR. DIAMOND:
Q. Okay. So you don't -- you don't -- that's -- that's the -- in other words, just to answer my question, you -- you don't cite data from Tacken -- well, the -- in your reply declarations, you don't cite any data from Tacken comparing the specificity or SIGN specificity of the AZND1 mouse antibody and --

and the HD1 humanized antibody with respect to the DC-SIGN antigen, right?
DR. STERLING: Objection; form.
THE WITNESS: So that's a little bit of a difficult question to answer because specificity is referring to, like, a specificity of binding, and so it's kind of, like, specific to relevance of something else.
BY MR. DIAMOND:
Q. Right. And the only thing that you talk about binding with respect to these antigens of these antibodies in your reply declarations is just they're binding to DC-SIGN, measured -- measured in terms of dissociation constant, right?
A. Right. So dissociation constants and affinities are reflective of their specificity for their particular target, not relatively specificity or comparative specificity, but reflective of their specificity between a target. In other words, --
Q. Right. It -- it --
A. -- it --
Q. -- it shows that that they bind specifically to this particular target.

DR. STERLING: Objection; form.
THE WITNESS: Yes. It's demonstrative of specificity for this particular target, correct.
BY MR. DIAMOND:
Q. Okay. But not specificity relative to other targets, right?
DR. STERLING: Objection; form.
THE WITNESS: Yeah. There's no relative specificity such that -- that I'm aware of.
BY MR. DIAMOND:
Q. Okay. You -- you don't cite any data from Tacken comparing AZND1 and hD1 in their ability to prevent cleavage of -- of the DC-SIGN antigen, right?
A. No. I have no knowledge that either of these antibodies have that function, and there's no comparison --
Q. Okay.
A. -- of that included within Tacken.
Q. Okay. If you go to Paragraph 83, I guess we're already there, of your reply declaration, here you cite Evans and Thomas for the proposition that 5G1.1 antibodies retain

their function when changing isotype.
Do you see that?
A. Yes.
Q. And just to be clear, Mueller II and -- and -- and Tacken -- actually not. Let me -- let me ask a different question.
In the next sentence here in Paragraph 83, you -- you say that Thomas compared murine 5G1.1 to humanized 5G1.1 with an IgG4 isotype and found that, quote, the humanized h5G1.1 HuG4 antibody was equipotent with the murine antibody, end quote. Do you -- do you see that?
A. Yes, I see that. That's consistent with what a POSA would expect at the time and reflected in --
Q. Well, that -- sir, I -- I just asked you if you saw that. That's all I -- really all I asked is if you saw that, because I have another question for you. Okay?
So -- so Thomas made a humanized IgG4 isotype antibody, right?
A. There is --
DR. STERLING: Object to form.
THE WITNESS: -- a humanized IgG4 antibody that -- for which data is -- is

presented within Thomas.
BY MR. DIAMOND:
Q. Right. Right. And the data that Thomas presented showed that it had similar activity to the mouse 5G1.1 antibody in -- in binding C5, as well as in -- in -- inhibiting complement-mediated cell lysis in -- in PAEC cells, right?
DR. STERLING: Objection; foundation and to form.
THE WITNESS: Yes. That's -- my recollection is that the --
BY MR. DIAMOND:
Q. Okay.
A. -- antibodies that were developed, that, you know, the fragments, I guess, were compared, including comparison to a -- within G4, and that there was a conclusion that there was similar binding between them.
Q. Similar binding, and also similar inhibition of complement-mediated cell lysis, right?
DR. STERLING: Objection; foundation and form.
THE WITNESS: Yes. That's my

recollection.
BY MR. DIAMOND:
Q. Okay. In the -- in the next sentence talking about Evans, you say that Ev -- still in Paragraph 83 of your '504 reply declaration, you say that "Evans compared the function of a murine 5G1.1 scFv to the full-length murine 5G1.1 antibody, and show that the scFv gave, quote, similar results, end quote, while, quote, repeating the capacity to block the generation of both C5a and C5b-9, end quote.
Do you see that?
A. Yes, I do see that.
Q. Okay. So the -- the data from Evans' Example 12 that you're discussing here compared the mouse -- the -- the -- the mouse 5G1.1 scFv to the full-length mouse 5G1.1 antibody of Evans, right?
A. Yes. That's correct.
Q. All right. And Evans found the mouse 5G1.1 scFv retained the capacity to block generation of both C5a and C5b-9, right?
A. Yes. That's correct.
Q. Okay. The assay that Evans did tests for whether the -- the -- the mouse scFv

retained the capacity to block the generation of both C5a and C5b-9, that's a different assay than just mea -- measuring for -- for binding affinity for C5, right?

DR. STERLING: Objection; foundation and form.

THE WITNESS: Yes. That's correct.

BY MR. DIAMOND:

Q. All right. And none of the experiments that you discuss in your reply declarations from Evans or Thomas compared a humanized 5G1.1 IgG4 antibody to a humanized 5G1.1 IgG2/IgG4 antibody, right?

A. Yes, none of them --

DR. STERLING: Objection to form.

THE WITNESS: -- in my reply declaration, nor none of the discussions in Dr. Casadevall's declaration, provide that demonstration.

BY MR. DIAMOND:

Q. Well, you -- you don't cite to any such data from Thomas or Evans, right?

DR. STERLING: Objection to form.

THE WITNESS: Yes. I do not cite to any such data from Thomas or Evans.

BY MR. DIAMOND:

Q. Okay. Let's look at Paragraph 84 of your reply declaration, and I want to flip to the -- the -- Page 53. And you have a number Of references cited here at the end, AMG1084, AMG1040, AMG1030, AMG1041 and AMG1083, right?

A. Yes.

Q. Now, none -- none of those references mentioned ec -- eculizumab, or any other anti-C5 antibodies, as far as you can recall, right?

DR. STERLING: Objection to form.

THE WITNESS: That's correct.

You know, if you're interested in -- in a reference -- references to C5, the Thomas reference provides a similar statement.

BY MR. DIAMOND:

Q. Sir -- sir, the -- I wasn't ask -- I'm not interested in that right now. I was asking about Thomas earlier, but now I'm asking about these references, so -- but please do focus on my question.

My question is, simply, AMG1084, AMG1040, AMG1030, AMG1041 and AMG1083, do you have those -- those references in mind?

A. If those are the ones that are cited in the declaration, that's fine, yes.

Q. Yeah. Okay. So for my question, I want you to keep those references in mind. I've asked about those referenced, not -- not Thomas or anything else, okay?

With respect to those references we just listed, 1084, 1040, 1030, 1041 and 1083, they don't mention eculizumab, or any other anti-C5 antibody, as far as you can recall, right?

DR. STERLING: Objection; form.

THE WITNESS: That's --

BY MR. DIAMOND:

Q. I'm sorry. Did you say yes?

DR. STERLING: Same objection.

THE WITNESS: Yes. That's my recollection.

BY MR. DIAMOND:

Q. Okay. And to your recollection, none of those five documents, 1084, 1040, 1030, 1041 or 1083, included any experimental data comparing the properties of humanized IgG4 antibody with humanized IgG2/IgG4 antibody, right?

DR. STERLING: Objection; form.

THE WITNESS: Yes. That's correct. That's my recollection.

MR. DIAMOND: Okay. Okay. Let's take a break. I -- I feel like I -- I may be close to wrapping up in the next session. I just want to see what we have left and confer here.

DR. STERLING: Okay.

MR. DIAMOND: All right. I'm going to go off the record and we'll just --

THE VIDEOGRAPHER: Going off the video record at the time of 1:18.

(Recess taken.)

THE VIDEOGRAPHER: We are back on the video record. The time is 1:27.

BY MR. DIAMOND:

Q. Dr. Balthasar, during the last break, or any of the breaks today, did you speak with your counsel at -- at all regarding the -- the substance of your testimony?

A. No.

Q. Did you speak with your counsel during any of the breaks today regarding any questions that your counsel may ask you after I'm finished asking my questions today?

A. No.

Q. How did you prepare for your deposition today?
A. So I prepared for this deposition by reviewing --
DR. STERLING: Sorry.
THE WITNESS: -- my declar --
DR. STERLING: Excuse me. I was on mute.
I'm going to object to the extent it gets to privilege. I'm going to instruct you to answer generally about who or when or timing, but do not disclose any substance of the discussions that you had with the attorneys. And I apologize for being on mute when I started that.
MR. DIAMOND: No worries.
BY MR. DIAMOND:
Q. Do you have the question?
A. Yeah, I do.
Q. Okay.
A. I reviewed my reply declaration, --
Q. Yeah.
A. -- my declaration. I re -- reviewed the declarations that were provided by Dr. Trout and Dr. Casadevall.

Q. Mm-hmm.
A. And I met with counsel on Monday and on Tuesday by video conference. We discussed the materials within the declarations and discussed possible questions that might come up in the deposition. And those are the -- the main things that I did. My -- that's pretty comprehensive.
Q. Okay. Fair enough.
You said the meetings with your counsel to prepare for your deposition were this past Monday and Tuesday?
A. Yes. Yesterday and the day before.
Q. All right. And you said those were meetings by -- by video conference?
A. Yes.
Q. Okay. How long were each of those meetings?
A. I mean, like today, there were a number of breaks, but they took place over the time frame, roughly, from 9 to 5 on Monday, and, roughly, 9 to 2:30 on Tuesday.
Q. Okay. And who -- who at each of those meetings was present?
A. So Dr. Sterling, Dr. Holman,

Dr. Roadcap, and then two representatives from Amgen who are here today, Paula Fritsch and Angie Mah.
Q. Okay. And including, you know, your review of documents in those meetings and everything, how long would you say you spent in total preparing for today's deposition?
A. You know, I've written down notes, but I don't -- I haven't done it offhand, but I'm going to say it's, roughly, 25 hours.
MR. DIAMOND: Okay. So I have no further questions for -- for you today, Dr. Balthasar. Thank you for attending and accommodating the -- the -- the -- the new technological circumstances under which we -- we all are. I do -- do appreciate you adapting to that.
THE WITNESS: No problem. Thank you very much.
DR. STERLING: Dr. Balthasar, we don't have any questions for you today either. I also appreciate your attending today and accommodating this remote deposition.
Thank you for your time.
THE WITNESS: All right. Thank you

very much.
THE VIDEOGRAPHER: That concludes the deposition going off the record the time is 1:31.
(Deposition concluded -- 1:31 p.m.)

Joseph P. Balthasar, Ph.D

CERTIFICATE

I do hereby certify that the aforesaid testimony was taken before me, pursuant to notice, at the time and place indicated; that said deponent was by me duly sworn to tell the truth, the whole truth, and nothing but the truth; that the testimony of said deponent was correctly recorded in machine shorthand by me and thereafter transcribed under my supervision with computer-aided transcription; that the deposition is a true and correct record of the testimony given by the witness; and that I am neither of counsel nor kin to any party in said action, nor interested in the outcome thereof.

WI al seal this
24th da

Ryan K. Black

Deborah Sterling, Ph.D.,Esq.
dsterling@sternekessler.com
April 24, 2020
RE: Amgen Inc. v. Alexion Pharmaceuticals, Inc.
4/22/2020, Joseph P. Balthasar , PhD (#4080290)

The above-referenced transcript is available for review.

Within the applicable timeframe, the witness should read the testimony to verify its accuracy. If there are any changes, the witness should note those with the reason, on the attached Errata Sheet.

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Amgen Inc. v. Alexion Pharmaceuticals, Inc.
Joseph P. Balthasar , PhD (#4080290)

ACKNOWLEDGEMENT OF DEPONENT

I, Joseph P. Balthasar , PhD, do hereby declare that I have read the foregoing transcript, I have made any corrections, additions, or changes I deemed necessary as noted above to be appended hereto, and that the same is a true, correct and complete transcript of the testimony given by me.

_____ _____
Joseph P. Balthasar , PhD Date
*If notary is required

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Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

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We hereby acknowledge receipt of the following submission by the proprietor:

Submission number	8507050	
Application number	EP11001632.6	
Patent number	EP2359834	
Date of receipt	06 April 2020	
Your reference	C411599EP	
Proprietor	ALEXION PHARMACEUTICALS, INC.	
Title	Treatment of paroxysmal nocturnal hemoglobinuria patients by an inhibitor of complement	
Documents submitted	package-data.xml ep-oppo.pdf (2 p.)	ep-opposition-data.xml OTHER-1.PDF\Response 6 April 2020 C411599EP PXT ALS.PDF (11 p.)
Submitted by	CN=Amanda Simons 23469	
Method of submission	Online	
Date and time receipt generated	06 April 2020, 11:46 (CEST)	
Message Digest	D5:B3:8F:C2:0D:3C:B9:B6:B0:40:D0:A0:81:D6:29:9A:DD:F1:B2:6A	

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).

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Submission in opposition proceedings

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Proprietor/representative's reference	C411599EP

The information given below is pertaining to the following patent in opposition proceedings:

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
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 - Response	Response 6 April 2020 C411599EP PXT ALS.PDF	OTHER-1.PDF

Payment

1	Method of payment	Not specified
	Currency:	EUR

Signatures

C411599EP

Place:	
Date:	**06 April 2020**
Signed by:	**Amanda Simons 23469**
Association:	**J A Kemp LLP**
Representative name:	**/Amanda Simons/**
Capacity:	**(Representative)**

J A • K E M P

BY ONLINE FILING

The European Patent Office
80298 Munich
Germany

6 April 2020

Dear Sirs

Opposition to European Patent No. 2359834
Appeal No. T1087/19-3.3.01
(Application No. 11001632.6)
ALEXION PHARMACEUTICALS, INC.
Our Ref: C411599EP PXT/ALS

I write to provide the patentee's comments on the arguments raised in the response to grounds of appeal filed by opponent 1, Amgen Inc., on 8 November 2019, and by opponent 2, Hoffman Eitle, on 8 November 2019.

Requests

The patentee's requests remain as set out in the grounds of appeal.

Admissibility of Auxiliary Requests

Objection has been raised by the opponents in relation to the admissibility of the auxiliary requests. The patentee has the following response on this matter.

The auxiliary requests submitted with the grounds of appeal seek to introduce three classes of amendment as follows:

a) Limitation to IV administration, in particular following dilution to 5mg/ml.
b) Limitation to pH 7.0.
c) Limitation to specify the sequence of eculizumab in the claims.

Auxiliary requests 6 and 8 are amendments relating to IV administration (limitation a above) and were admitted into proceedings by the opposition division. Auxiliary requests 1 to 5 and 7 contain limitations in relation to features b and c above. Although requests containing these limitations were presented at oral proceedings before the opposition division, these were not admitted into proceedings at the time. The patentee therefore accepts that the auxiliary requests 1 to 5 and 7 represent amendments to the case which was on file before the opposition division.

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Nevertheless, the admission of these requests into the appeal is justified. The Board of Appeal is therefore asked to exercise its discretion in favour of admitting these auxiliary requests.

Limitation to pH 7.0

The limitation to pH 7.0 is set out in auxiliary request 3, and also appears in auxiliary requests 4, 5 and 7 in combination with other features. As explained in the grounds of appeal, this limitation to the claims has been made to address the objection raised by the opponents that the claim scope is overly broad (i.e. the advantage put forward by the patentee is not achieved across the full scope of the claim).

The objection relating to claim scope is one which was first raised by the opponents only shortly before the oral proceedings. It was therefore not possible for the patentee to have filed auxiliary requests in response to this objection before the Rule 116 deadline in advance of oral proceedings before the opposition division.

Furthermore, the request was not admitted by the opposition division on the grounds that the opposition division could not "*prima facie* see how such a feature would be able to overcome the objection for lack of inventive step detailed under 2.4.3 [of the decision]" (see section 4.2 of the Opposition division's decision). The objection of lack of inventive step detailed in section 2.4.3 of the decision stated the opposition division's view that the long term stability of the administered solution has no bearing on the patient, such that this was not an advantage which could be taken into account at all in considering inventive step. However, the amendment to pH 7.0 was not filed to address this particular issue. Rather, the limitation to pH 7.0 assists in relation to another objection raised by the opponents, namely that of overly broad claim scope. The patentee should not be prevented from filing requests which address further issues raised by the opponents, even if the opposition division did not consider such issues in their decision.

The patentee is of the view that the opposition division was wrong to reject the use of stability data in the definition of the problem to be solved (as discussed in detail in the grounds of appeal). In the event that the Board of Appeal considers that the data submitted by the patentee is relevant to inventive step, but yet considers that the problem of improved stability has not been demonstrated across the scope of the claim, the limitation to pH 7.0 which is presented in auxiliary requests 3, 4, 5 and 7, is of *prima facie* relevance. Its admission into appeal proceedings is therefore justified since it directly addresses an objection raised by the opponents.

Sequence of Eculizumab

In relation to the sequence, the opponents have argued that the term "eculizumab" as used in claim 1 does not describe the sequence of the specific antibody which is known as "eculizumab", but rather the term refers to a group of antibodies.

The patentee does not consider this to be a reasonable interpretation of an international non-proprietary name (INN) such as eculizumab, nor is it consistent with the position adopted in previous submissions by the opponents. As discussed

further below, the skilled person would be well aware that an INN such as eculizumab always refers to a single, specific active ingredient.[1]

Despite the fact that the patentee considers the opponents' position on the interpretation of "eculizumab" to be unreasonable, it is nevertheless justified that the patentee files auxiliary requests to address this issue which has been raised in the opposition division's decision. Auxiliary requests 1 and 2 (as well as axillary requests 4 and 5 which also contain the same limitations) should therefore be admitted into the appeal as they address the questions raised in the decision in relation to the scope of the term "eculizumab".

The Board is therefore asked to exercise its discretion in favour of admitting auxiliary requests 1 to 8 filed with the grounds of appeal.

Convergent Requests

Opponent 2 argues that the auxiliary requests filed should not be allowed since they are not convergent and, since all requests are relevant to a single objection of lack of inventive step, such non-convergence should not be accepted.

In this regard, it is noted that there is no requirement laid down by the Boards of Appeal that auxiliary requests should always represent a convergent development. Thus, it is at the Board's discretion as to whether this should be required or not.

Moreover, the new requests filed relate to just two different limiting features, namely the sequence (presented in two different formats for formal reasons) and the pH. These two different limitations clearly address two very separate aspects of the opponents' objections, namely the definition of the term "eculizumab" and the question of whether the advantage of improved stability applies across the scope of the claim. It is therefore considered appropriate in the present case to present the requests in the manner set out in auxiliary requests 1 to 8, which include a small number of limitations combined in an appropriate manner. The issue of lack of "convergence" as set out by opponent 2 is not therefore an objectionable matter in relation to the present auxiliary requests.

Admissibility of documents

Opponent 2 argues that D33 and D54 to D60 should not be introduced into proceedings.

D33 and D54 are already in the proceedings since these were introduced by the opposition division. Both documents relate to a potential advantage of the claimed composition and are therefore clearly of *prima facie* relevance to the question of inventive step. Whether or not the opposition division ultimately agreed with the patentee's position on inventive step, the opposition division was right that these documents were of *prima facie* relevance and should therefore be introduced into proceedings.

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[1] This interpretation is relevant to the disclosure of D1. Whilst D1 uses the term "eculizumab" it does not describe the sequence of the antibody and thus does not enable a skilled person to produce the specific drug, eculizumab.

Opponent 2 further objects to the introduction of D55 which includes further supporting data on the issue of improved stability. These data were submitted to address the objection, raised in preparation for opposition division oral proceedings, that the advantage put forward in D33 did not apply across the scope of the claims. Given the nature of the experiments described in D55 (which are stability studies carried out over a period of 12 weeks), it clearly would not have been possible for the patentee to complete and file declarations in relation to this work in the period between the opponents' objections being raised and the oral proceedings. Filing this new data with the grounds of appeal is therefore considered to be justified under the present circumstances.

In relation to D56, opponent 2 objects that the abstracts of cross-referenced applications referred to at page 24 of the application as filed are not mentioned anywhere in the grounds of appeal, save for the list of documents. To assist the Board, it is noted that these documents, and their relevance, are discussed in paragraph 5.3.7 of the grounds of appeal. The abstracts were provided in a single document as D56 for convenience.

Documents D57 to D59 merely provide evidence of matters that would have been known to all parties (i.e. that eculizumab was not commercially available at the filing date of the patent), confirm the confidentiality of clinical trials using eculizumab, or provide evidence in relation to the leader sequence of an antibody, a matter which would be well known to a skilled person in the art. D60 is cited to refute the assertion made by the opposition division that a drug formulated in a chosen concentration for one means of administration would be assumed to be safe and efficacious at that concentration and dosage when administered in a different way. This is not a principle which is generally correct, as would be well known to the skilled person in the art. D60 was merely put forward as evidence of this point. Since this directly addresses a matter raised in the decision of the opposition division, it is requested that this evidence be introduced into the appeal.

Added Matter

Opponent 1 raises on appeal an objection of added matter which is similar to the argument raised before (and rejected by) the opposition division. The patentee's position in relation to added matter is identical to that put forward before the opposition division, a position with which the opposition division agreed (see 2.2 of the decision).

In brief, the patentee considers that basis for the wording in claim 1 of the patent as granted is provided at the following passages of the application as filed:

- Page 5, lines 9 to 10: *"In certain embodiments, the 300mg single-use dosage form comprises 30ml of a 10mg/ml sterile, preservative free solution."*
- Page 6, lines 21 to 23: *"In certain embodiments, the pharmaceutical composition comprises a 300mg single-use formulation of 30ml of a 10mg/ml sterile, preservative free solution."*
- Page 22, lines 11 to 13: *"In certain embodiments, the pharmaceutical composition comprises a 300mg single-use*

formulation of 30ml of a 10mg/ml sterile, preservative free solution."

In their response to grounds of appeal, opponent 1 focused on the fact that the term "single unit dosage form" appears five times in the paragraph at set out at page 5, lines 3 to 9. The opponent concludes from this that the term "single unit dosage form" should also be read into the final sentence. However, the opposition division was correct to find that claim 1 could be based on the final sentence of, for example, page 5, lines 3 to 9 (or indeed one of the other passages mentioned above) without needing to include reference to single unit dosage form.

The claim is based on the *precise wording* of the application as filed. This wording in the application as filed is not unclear or incomplete in any way. Moreover, it is evident that each of the "embodiments" described in the paragraph at page 5, lines 3 to 9 are separable embodiments. For instance, one embodiment relates to a lyophilised composition, whilst a separate embodiment relates to a sterile solution. It cannot be argued that the later-described embodiments must inherit features of earlier-described embodiments. In fact the opposite must be true as these embodiments are not convergent with one another. It is therefore clear that each of the sentences in the paragraphs set out above can be taken in their own right. The amendment to claim 1 which is based on a single sentence from this paragraph therefore does not introduce new subject matter.

For completeness, it is noted that the patentee disagrees with the opponent's discussion of the meaning of the term "single unit dosage form" and does not consider that D10 supports the opponent's position since it does not define either the term "single use" or the term "single unit dosage form".

Sufficiency

The patentee's position is summarised in section 4 of the grounds of appeal. The opponents' argument in relation to sufficiency relates solely to the question of whether the inclusion of the leader sequence in SEQ ID NO: 4 leads to a lack of sufficiency under Article 83 EPC. This point has been addressed in detail in previous submissions (see submission of 22 March 2018, section 6; submission of 21 November section 4, grounds of appeal section 4).

Inventive Step

Definition of Eculizumab

In their discussion of inventive step, both opponents spend some time discussing the meaning of the term "eculizumab" in the claims. The question which is raised is whether the term "eculizumab" relates solely to the mature antibody having the sequences shown in SEQ ID NOs: 2 and 4, i.e. the antibody which is now commercially sold under the trade name "Soliris" and the INN "eculizumab", or whether the term, as it is used in claim 1 of the patent, is broader than this such that it encompasses different antibodies. The opponents put forward the position that the term "eculizumab" in claim 1 refers to a group of antibodies ("an antibody that binds C5" - see e.g. para 41 of opponent 2's submission). The opponents' interpretation is not

a sensible approach and is not an interpretation which would even be contemplated by a skilled person in the art.

Firstly, it would be very clear to the skilled person that the term "eculizumab" is an international non-proprietary name (INN) as it is in the required format for such names, having the standard identifiers "li", "zu" and "mab" (indicating a immunomodulating and humanised monoclonal antibody). INNs, having such standard formats for antibody type drugs, are a unique name given to enable identification of a particular active agent. Since the purpose of the INN is to enable identification of an active agent, the skilled person would understand that any INN must refer to a single, unique active agent. No person having any familiarity with antibody drugs would consider that a specific term such as "eculizumab" could refer to "any antibody that binds C5" as is suggested in paragraph 41 of opponents 2's submission. The opponents' interpretation is therefore in conflict with the normal meaning of such terms in the art.

Secondly, the opponents' references to the description do not support the broad interpretation they put forward. They reference, for example, various sections of the description of the patent that use terminology such as "in certain embodiments". The Board will appreciate that the application as filed was drafted more broadly than the present scope of the claims, and the claims were limited during prosecution. Sentences such as "in certain embodiments..." may previously have related to one of several embodiments encompassed by the claims as filed, but may now relate to the only embodiment which is claimed.

The opponents also refer to the language used in paragraphs 11 and 16 of the patent specification, suggesting this supports their broad interpretation. However, the opponents misread these sentences to suit their needs. For example, the sentence:

> *"The antibody that binds C5 or an active antibody fragment thereof is eculizumab"*

at paragraph [0011] is clearly intended to make clear that the claimed invention is *limited* only to the specific drug eculizumab. This ensures that the reader of the specification is aware that reference therein to an antibody which binds C5, in the context of the claimed invention, only extends to eculizumab. Such language is commonly found in patent specifications. It does not in any way imply that "eculizumab" *means* "any antibody that binds C5". Thus, these paragraphs do not support the opponents' interpretation.

The opponents also refer to paragraph 54 of the patent specification and the reference therein to document D17 (US, 6,355,245). The corresponding passage in the application as filed (found at page 16, line 23) reads as follows:

> *"These antibodies disclosed in US,6,355,245 include a whole antibody (now named eculizumab)"*

The application as filed therefore states that D17 discloses a group (i.e. a genus) of antibodies, of which eculizumab is one. It does not state that *all* of the antibodies

referred to in D17 are "eculizumab" antibodies. Again, this passage does not support the opponents' interpretation.[2]

The wording of the application as filed is wholly consistent with the patentee's (and indeed only reasonable) interpretation that eculizumab refers to a specific active agent. Paragraph [0054] of the patent is further considered to be consistent with this. However, in this regard, if the Board of Appeal considers that the description should be amended to reflect the original wording of page 16, line 23 of the application as filed, or to delete the reference to D17, it is requested that an opportunity be provided to make such an amendment.

Thus, the term "eculizumab" would be readily understood by the skilled person in the art as referring to a single specific antibody. That antibody is defined in the application as filed, in SEQ ID NOs 2 and 4. It is therefore quite clear from the application as filed that the term "eculizumab" refers to this specific antibody, and not to a broader group of antibodies. There is, accordingly, no need to have recourse to the case law suggested by opponent 1, which relates to the interpretation of highly unclear expressions in a claim.

Differences compared with D1

In light of the above, it is clear that claim 1 of the patent relates to the specific antibody known as "eculizumab", having the sequence set out in SEQ ID NOs: 2 and 4 of the patent. D1 does not disclose this specific antibody in a way which would enable the skilled person to reproduce it. Whilst the term "eculizumab" is used in D1, there is no indication of the sequence of the antibody. The lack of any sequence means that there is no enabling disclosure of the antibody.

The claimed invention therefore differs from the D1 in the manner set out in section 5.1.6 of the grounds of appeal, namely D1 does not disclose:

(i) the sequence of eculizumab; and
(ii) the composition of eculizumab, namely a single-use dosage form of a sterile, preservative-free solution comprising 300 mg eculizumab at a concentration of 10 mg/ml.

For completeness, it is noted that the difference between the disclosure of D1 and the claimed subject matter is a matter of fact, and depends on the subject matter which is actually disclosed in D1. The sequence of eculizumab is not disclosed in D1. The fact that the patent specification itself does not explain that the prior art does not provide an enabling disclosure of eculizumab is not relevant to this matter. Opponent 1's comments at paragraph 52 of the submission of 8 November 2019 should not therefore be taken into account.

Technical Problem and Claimed Solution

The patentee's position in relation to this matter was set out in section 5.2 onwards of the grounds of appeal. Paragraph 5.2.12 of that document sets out the objective

[2] Nor does the application as filed state that D17 provides an enabling disclosure of the antibody known as "eculizumab". It is a fact that D17 does not disclose the complete sequence of "eculizumab."

technical problem as:

The development of an antibody for use in the treatment of PNH, in a composition which is highly stable, and which can be provided in a low volume liquid formulation.

Opponent 1 argues that any problem solved by "the development of an antibody for use in the treatment of PNH" is entirely unrelated to the stability and volume of any composition which contains that antibody. It is submitted that this cannot be correct. Rather, the development of any antibody composition is a process which must be studied uniquely for each antibody, as degradation behaviour will differ in each case. It therefore cannot be said that the sequence of the antibody and the composition in which it can be provided are unrelated.

Data to Support Technical Problem

Opponent 1 further makes a number of comments on the data put forward by the patentee in support of the improvement in stability of the 10 mg/ml composition. The patentee has provided evidence in D33 which demonstrates that the 30 mg/ml composition leads to a higher generation of aggregate in comparison with the 10 mg/ml composition. Further, in D54, the patentee provides evidence that this aggregate is associated with a loss of activity of about 50%. Opponent 1 questions whether, despite this evidence, the 30 mg/ml composition might in fact have a higher activity than the 10 mg/ml composition, due to the potential presence of other degradation products such as acidic isoforms.

Opponent 1's comments in this regard, however, are not supported by the evidence. In D55, the patentee tests a number of different formulations of eculizumab at both 10 mg/ml and 30 mg/ml. These formulations are assessed, both initially and during storage, to determine the degradation products which are present. Degradation products will differ from the antibody itself either in terms of the molecular weight (e.g. aggregates or fragments of the antibody) and/or in terms of the charge (e.g. deamidation products). D55 therefore reports the use of two assays to determine the degradation products present. Firstly, SEC-HPLC (size exclusion chromatography-HPLC) was used to detect degradation products having a different molecular weight from the antibody. Secondly, icIEF was used to detect charged species.

D54 reports in paragraph 7 that SEC-HPLC detected differences in the degree of aggregation between the two compositions. D54 paragraph 7 further reports that no difference was detected between the different compositions in the icIEF assay. Thus, the *only* difference observed between the two compositions was in the degree of aggregation. Opponent 1's assertion that different types of degradation, e.g. acidic variant formation, might lead to a higher biological activity for the 30 mg/ml composition is thus unfounded. Neither opponent has put forward any data which supports the assertion. On the other hand, the patentee's data confirms that aggregation is the *only* degradation product which has been observed to differ between the two concentrations, and such aggregation leads to a loss of activity.

Thus, D54 confirms that the increase in aggregate formation in the 30 mg/ml composition will lead to a loss of biological activity.

Opponent 1 also criticises D55 and suggests that D55 does not provide evidence of stability of the composition across the scope of the claims.

In this regard, opponent 1 disregards the fact that for ALL formulations tested, and for ALL pH levels tested, the 10mg/ml composition was found to be more stable (and, in accordance with D54, have a higher biological activity) than the corresponding 30 mg/ml composition. The opponent attempts to show that Formulation F9 of D55 is not stable, since aggregation occurs more readily in this formulation than for other formulations. However, the opponent makes an incorrect comparison here. The correct way to analyse the data is to compare the 10 mg/ml and 30 mg/ml compositions *having the same formulation and pH*. It is not correct to compare, as the opponent has done, compositions having different concentrations AND different excipients. Contrary to the opponent's suggestion, D55 clearly shows an improvement in stability (and thus biological activity) for the 10 mg/ml composition in all cases.

Opponent 1 also suggests that all compositions tested in D55 contain a stabiliser which suppresses antibody aggregation in such compositions. Some of the tested compositions do indeed contain a polysorbate. However, Formulations 4, 5 and 6 do not. The opponent points to D21, pages 694-695, as evidence that mannitol (present in Formulations 4, 5 and 6) is also used to prevent aggregation. However, the passage to which the opponent refers relates to prevention of aggregation in *lyophilised* formulations. This passage is not relevant to solutions such as that claimed[3]. Thus, the opponent's argument is not a valid criticism of the D55 data.

Finally, opponent 1 argues that the experiments carried out using the commercial formulation of eculizumab by Dr Miano (in D33, D54, and D55) are not relevant to the claims because the patent defines eculizumab as having the light chain amino acid sequence of SEQ ID NO:4 which is different from the light chain of eculizumab in the commercial formulation. These arguments carry no weight because eculizumab in the commercial formulation comprises a light chain having the mature amino acid sequence of SEQ ID NO:4. As explained in section 4 of the grounds of appeal it would have been known to the skilled person, as part of his common general knowledge at the effective filing date, that the signal peptide shown in SEQ ID NO:4 would be cleaved during antibody production in a cell. Accordingly, the skilled person would immediately recognise eculizumab in the patent includes only the mature portion of SEQ ID NO:4 and would interpret the patent in this way (G1/10, reason 8).

In summary, the data put forward by the patentee (a) demonstrates that aggregation of eculizumab occurs less rapidly in the claimed 10 mg/ml concentration; (b) that this reduction in aggregation is associated with the maintenance of the biological activity of eculizumab and (c) that the reduction in aggregation at 10 mg/mL occurs across a variety of formulations and pH levels. The data therefore demonstrates that the objective technical problem set out above is solved by the claimed invention.

Claimed Solution is not Obvious

The patentee's reasoning in relation to inventive step of the claimed solution was set out in detail in section 5.5 onwards of the grounds of appeal. Detailed arguments

[3] In relation to solutions, D21 only mentions polysorbate as a possible stabiliser, at page 693, right column, as highlighted by the opponent.

were provided there on the positions argued by the opponents at oral proceedings before the opposition division, namely inventive step based on D1 combined with D22, D20, D21 or D29. Opponent 1 also briefly mentions in the response to the grounds of appeal, an argument of lack of inventive step based on D1 with D45. The patentee's comments on the combination of D1 with D45 are set out below.

D1 combined with D45

As set out above, the objective technical problem to be solved over D1 is:

The development of an antibody for use in the treatment of PNH, in a composition which is highly stable, and which can be provided in a low volume liquid formulation.

The skilled person starting from D1 and faced with this problem would not have turned to D45. D45 has, as its objective, to provide "*methods for the preparation of antibodies which are less antigenic in humans than non-human antibodies but have desired antigenic binding and other characteristics and activities*". Further objects relate to methods for the efficient humanization of antibodies, and providing humanized antibodies capable of binding p185 (see column 4, lines 24 to 40 of D45). There is nothing to suggest that D45 is directed towards providing suitable *compositions* for antibodies, or that it has any relevance to *antibodies capable of binding C5*. None of the examples of this document relate to anti-C5 antibodies. None of the examples discusses suitable compositions or formulations of the antibodies. Rather, the examples focus on methods for humanising different antibodies.

D45 therefore has no particular relevance to the present problem, and would not be singled out for consideration over the numerous other publications in the field of antibody therapeutics. Opponent 1's suggestion that the skilled person would look to this particular document for guidance in providing stable compositions of antibodies for treating PNH, is not therefore credible.

Moreover, even if the skilled person had considered D45, he/she would have been well aware that each antibody needs to be considered separately when looking to develop suitable formulations (this is known from the skilled person's common general knowledge, e.g. from D20, see abstract). He/she would also have been aware that it is not the case that all humanised antibodies are even formulated in solution, let alone in a 10 mg/mL solution. D35, for instance, lists several humanised antibodies (trastuzumab, efalizumab, palivizumab and omalizumab) which are formulated as powders, rather than in the more convenient solution form.

Even in light of the knowledge of D1 and D45, therefore, the skilled person would not be aware as to how (or indeed whether) the uniquely structured eculizumab, having an engineered structure which was not even known from D1 or D45, could be provided in a highly stable, low volume liquid composition. The combination of D1 with D45 therefore does not lead to the claimed subject matter.

Auxiliary Requests

For completeness, a comment is provided here in relation to the opponents' argument of lack of support of Auxiliary Request 8. Opponent 1 argues that the

feature of dilution to 5 mg/mL is not in the patent specification and therefore formal support under Article 84 EPC is lacking. As noted in the oral proceedings before the opposition division, the deletion of this passage is a clerical error made by the EPO in processing the application for grant.

The Communication under Rule 71(3) issued on 24 March 2016 contained the text proposed for grant and included the relevant passage at page 22, lines 28 to 29. This text was approved, subject to amendments set out in the letter of 13 May 2016 which included some amendments to page 22 (part 1). Specifically, correction of the word "minute" to "minutes" was requested at page 22. However, on reproducing the text proposed for grant, the EPO replaced the entirety of page 22 with the replacement page 22 (part 1), and therefore omitted the latter part of page 22 from the final text. However, in this case, the applicant's approval was for the text set out in the text proposed for grant of 24 March 2016, subject to the amendments requested in the letter of 13 May 2016. The applicant did not, therefore approve a text in which the latter part of page 22 was deleted.

Thus, the approved text is that as set out in the communication of 24 March 2016, subject to the amendments detailed by the applicant. This text provides support for the wording of Auxiliary Request 8.

Nevertheless, should the Board consider granting a patent on the basis of Auxiliary Request 8, the patentee requests correction by inclusion of the omitted wording:

"IV infusion and diluted to a final concentration of 5mg/ml prior to administration."

at the end of paragraph [0058] of the B print.

Conclusion

In summary, the arguments presented above, together with those set out in previous submissions demonstrate that the Opposition Division's decision should be set aside and a patent granted on the basis of the main request, or one of auxiliary requests 1 to 8 filed with the grounds of appeal.

Yours faithfully

Electronically Signed
AMANDA SIMONS
FOR J A KEMP LLP
ASSOCIATION NO. 811

Electronically Signed
PAMELA TUXWORTH
FOR J A KEMP LLP
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Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	8464724	
Application number	EP16172335.8	
Date of receipt	24 March 2020	
Receiving Office	European Patent Office, The Hague	
Your reference	N411599EP-A	
Applicant	All applicants as on file	
Documents submitted	package-data.xml epf1038.pdf (2 p.)	ep-sfd-request.xml APPEAL.PDF\File Notice of Appeal N411599EP-A PXT.PDF (1 p.)
Submitted by	CN=Pamela Tuxworth 23470	
Method of submission	Online	
Date and time receipt generated	24 March 2020, 16:10 (CET)	
Message Digest	47:A1:87:9C:67:6D:12:B8:38:41:92:F2:FB:C6:C5:D4:20:67:18:C1	

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).

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Letter accompanying subsequently filed items

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number	16172335.8
Applicant's or representative's reference	N411599EP-A

	Description of document	Original file name	Assigned file name
1	Notice of appeal	File Notice of Appeal N411599EP-A PXT.PDF	APPEAL.PDF

	Fees	Factor applied	Fee schedule	Amount to be paid
15-1	011 Appeal fee for an appeal filed by an entity other than those referred to in Rule 6(4) and (5) EPC	1	2 255.00	2 255.00
	Total:		**EUR**	**2 255.00**

	Payment	
1	Method of payment	Debit from deposit account
	Currency:	EUR
	The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated on the fees page.	
	Deposit account number:	28050038
	Account holder:	J A Kemp LLP
2	Refund/Reimburserment	
	Reimbursement (if any) to be made to EPO deposit account:	28050038
	Account holder:	J A Kemp LLP

Signatures

Place:	**Oxford, GB**
Date:	**24 March 2020**
Signed by:	**Pamela Tuxworth 23470**
Association:	**J A Kemp LLP**

Representative name:	**TUXWORTH, Pamela Mary**
Capacity:	**(Representative)**

Samsung Bioepis Exhibit No. 1002
Page 1270

J A • KEMP

BY ONLINE FILING

The European Patent Office
80298 Munich
Germany

24 March 2020

Dear Sirs

European Patent Application No. 16172335.8
ALEXION PHARMACEUTICALS, INC.
Our Ref: N411599EP-A PXT

We give notice of appeal against the examining division's decision of 28 January 2020 to refuse this application.

Please debit the appeal fee (2255 EUR) from J A Kemp LLP's deposit account 2805.0038. We request that any underpayment of this fee be deducted from, or any overpayment of this fee be credited to, deposit account 2805.0038.

The name and address of the appellant are as follows:

Alexion Pharmaceuticals, Inc.
100 College Street
New Haven, CT 06510 / US

The impugned decision is the decision of the examining division of 28 January 2020.

The appellant requests that the decision be set aside and that the application be allowed on the basis of the main request or, failing that, on the basis of one of the auxiliary requests on file.

We request oral proceedings in the event that the board is minded not to allow the main request.

Yours faithfully

Electronically Signed
DR PAMELA M TUXWORTH
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Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	8464756	
Application number	EP16195355.9	
Date of receipt	24 March 2020	
Receiving Office	European Patent Office, The Hague	
Your reference	N411599EP-B	
Applicant	All applicants as on file	
Documents submitted	package-data.xml epf1038.pdf (2 p.)	ep-sfd-request.xml APPEAL.PDF\File Notice of Appeal N411599EP-B PXT.PDF (1 p.)
Submitted by	CN=Pamela Tuxworth 23470	
Method of submission	Online	
Date and time receipt generated	24 March 2020, 16:15 (CET)	
Message Digest	0D:47:8D:A5:00:6A:F9:D6:95:20:A8:40:70:93:BE:F9:08:19:5C:F2	

Correction by the EPO of errors in debit instructions filed by eOLF
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/European Patent Office/

Europäisches Patentamt
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Letter accompanying subsequently filed items

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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	N411599EP-B

	Description of document	Original file name	Assigned file name
1	Notice of appeal	File Notice of Appeal N411599EP-B PXT.PDF	APPEAL.PDF

	Fees	Factor applied	Fee schedule	Amount to be paid
15-1	011 Appeal fee for an appeal filed by an entity other than those referred to in Rule 6(4) and (5) EPC	1	2 255.00	2 255.00
	Total:		**EUR**	**2 255.00**

	Payment	
1	Method of payment	Debit from deposit account
	Currency:	EUR
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	Deposit account number:	28050038
	Account holder:	J A Kemp LLP
2	Refund/Reimburserment	
	Reimbursement (if any) to be made to EPO deposit account:	28050038
	Account holder:	J A Kemp LLP

Signatures

Place:	**Oxford, GB**
Date:	**24 March 2020**
Signed by:	**Pamela Tuxworth 23470**
Association:	**J A Kemp LLP**

Representative name:	**TUXWORTH, Pamela Mary**
Capacity:	**(Representative)**

Samsung Bioepis Exhibit No. 1002
Page 1274

J A • KEMP

BY ONLINE FILING

The European Patent Office
80298 Munich
Germany

24 March 2020

Dear Sirs

European Patent Application No. 16195355.9
ALEXION PHARMACEUTICALS, INC.
Our Ref: N411599EP-B PXT

We give notice of appeal against the examining division's decision of 11 February 2020 to refuse this application.

Please debit the appeal fee (2255 EUR) from J A Kemp LLP's deposit account 2805.0038. We request that any underpayment of this fee be deducted from, or any overpayment of this fee be credited to, deposit account 2805.0038.

The name and address of the appellant are as follows:

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100 College Street
New Haven, CT 06510 / US

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We request oral proceedings in the event that the board is minded not to allow the main request.

Yours faithfully

Electronically Signed
DR PAMELA M TUXWORTH
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Our registered office is at 14 South Square, Gray's Inn, London WC1R 5JJ, UK. Our use of the word 'partner' refers to a member of J A Kemp LLP.

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.

ALXN2095
IPR2019-00739
Samsung Bioepis Exhibit No. 1002
Page 1276

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

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.*

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Page 1278

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
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(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:				

Samsung Bioepis Exhibit No. 1002
Page 1280

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

Samsung Bioepis Exhibit No. 1002
Page 1281

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:	

Samsung Bioepis Exhibit No. 1002
Page 1282

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

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Page 1283

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 35b0c44f869fb5bf7052157a0ebc1a4e3b11f36b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	14070524		

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Page 1284

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.

Samsung Bioepis Exhibit No. 1002
Page 1285

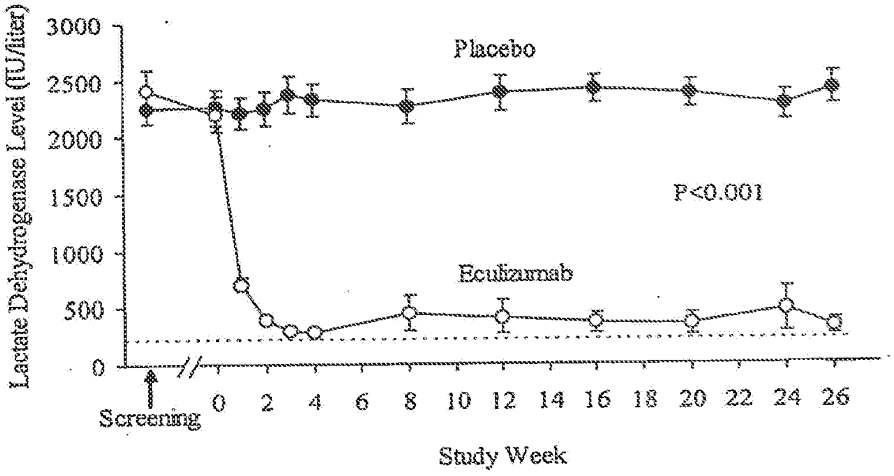

Lactate Dehydrogenase Level (IU/liter)
3000
2500
2000
1500
1000
500
0
Placebo
P<0.001
Eculizumab
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1A

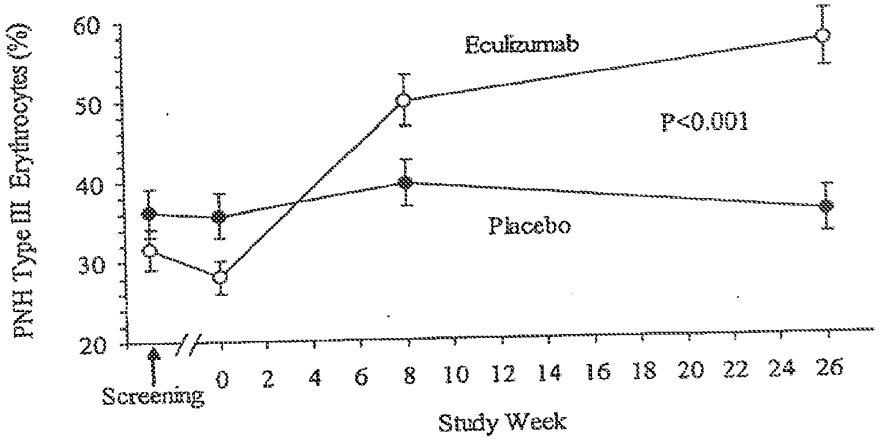

PNH Type III Erythrocytes (%)
60
50
40
30
20
Eculizumab
P<0.001
Placebo
Screening
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week

FIGURE 1B

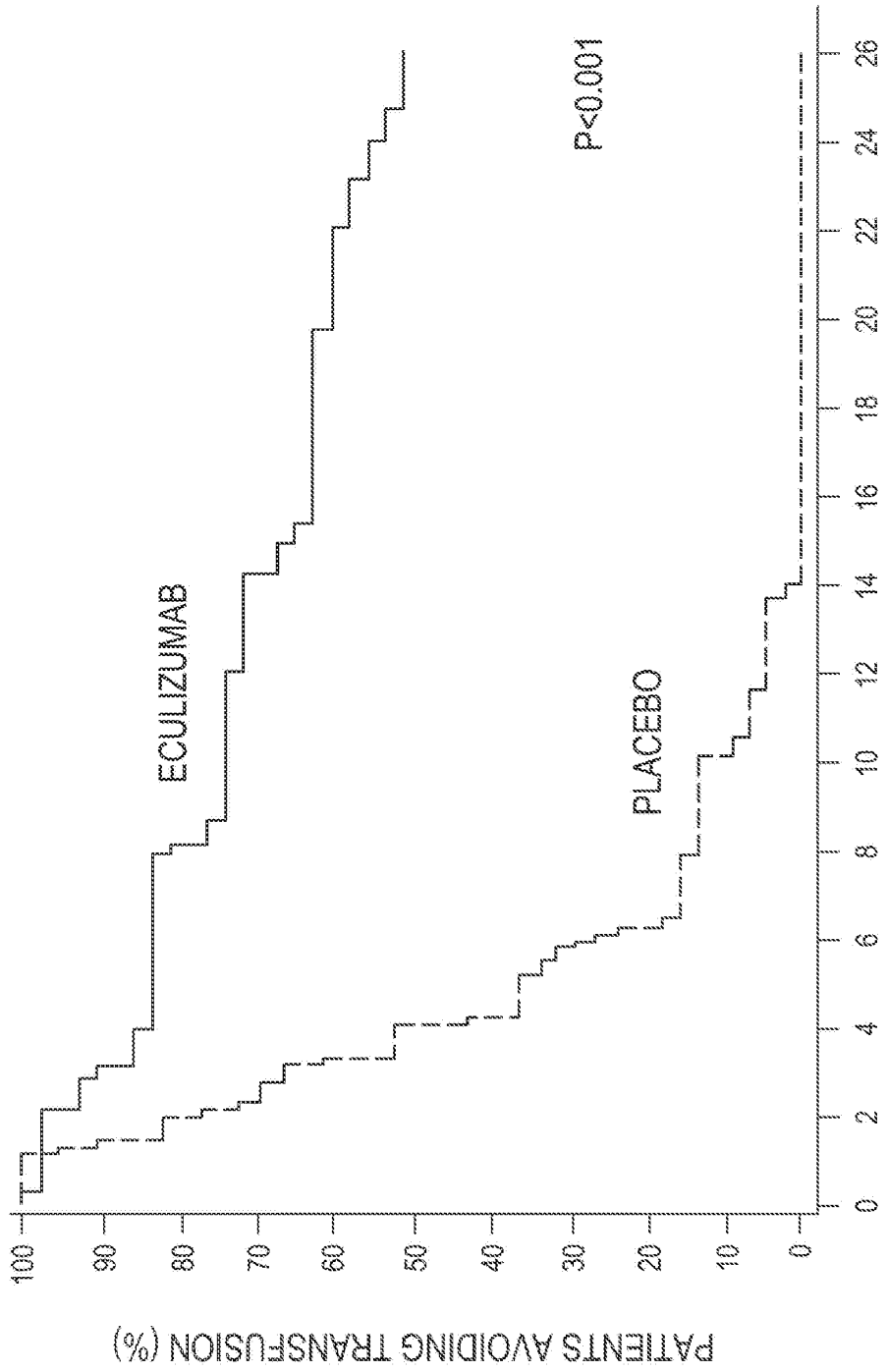

PATIENTS AVOIDING TRANSFUSION (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
26
STUDY WEEK
ECULIZUMAB
PLACEBO
P<0.001

FIGURE 2

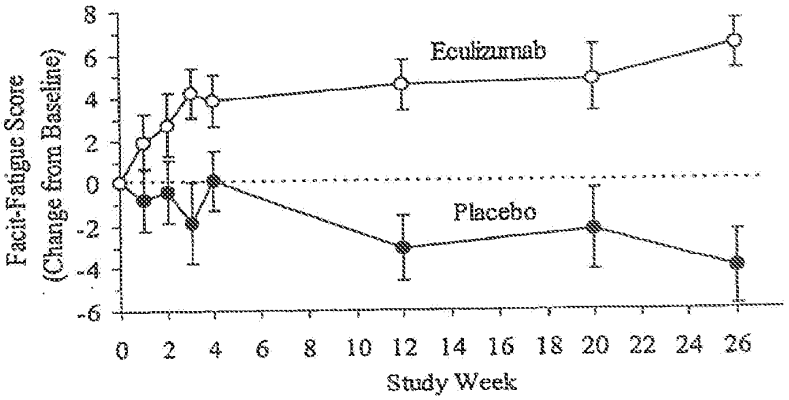

Facit-Fatigue Score
(Change from Baseline)
8
6
4
2
0
-2
-4
-6
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Study Week
Eculizumab
Placebo

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.

PTO/SB/AIA02 (07-13)
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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

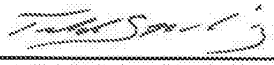
- [ ] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

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.

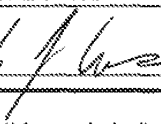
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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./

Samsung Bioepis Exhibit No. 1002
Page 1294

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

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) 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 patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[X] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number:

OR

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)

[X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

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		

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

[ ] Total of 1 forms are submitted.

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Page 1295

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 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.

Samsung Bioepis Exhibit No. 1002
Page 1296

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.

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

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.

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.

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

(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.

Oncol. 12(Suppl. 3):S7, 2001; Webster et al., Health and Quality of Life Outcomes. 1:79, 2003, www.hqlo.com/content/1/1/79; 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

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

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

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

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

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

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

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

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

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

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

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

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

(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

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

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.

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]

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]

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.

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

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

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.

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.

PTO/AIA/14 (11-15)
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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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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.

Samsung Bioepis Exhibit No. 1002
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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)
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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.

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.

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.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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.

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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Page 1359

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 07/27/2017

ERIMANDO	SALE	#00000002	Mailroom Dt:	07/05/2017	120080	15642096	
		01	FC : 1201	420.00 DA			
		02	FC : 1202	2,480.00 DA			

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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

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Page 1362

SEQUENCE LISTING

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

<130> AXJ-114BUSCN5

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35 40 45

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

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Lys Asp Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Tyr Phe Phe Gly Ser Ser Pro Asn Trp Tyr Phe Asp Val Trp
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Page 1364

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Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
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Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
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His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
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Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val
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Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
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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
        355                 360                 365

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
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
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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
65                  70                  75                  80
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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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Val Leu Asn Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
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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
        115                 120                 125
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```
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

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
            180                 185                 190

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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Asp

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Page 1368

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peptide

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1 5

Samsung Bioepis Exhibit No. 1002
Page 1369

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

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Samsung Bioepis Exhibit No. 1002
Page 1375

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

		(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.

Samsung Bioepis Exhibit No. 1002
Page 1376

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.

Samsung Bioepis Exhibit No. 1002
Page 1377

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

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. 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	1662
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Attorney Docket Number	AXJ-114BUSCN5

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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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	4	6171586		2001-01-09	Lam et al.	
	5	6355245		2002-03-12	Evans et al.	
	6	7361339		2008-04-22	Bell	
	7	7482435		2009-01-27	Bowdish et al.	
	8	9718880		2017-08-01	Bell et al.	

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	9	9725504		2017-08-08	Bell et al.	
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	4	20040219147	A1	2004-11-04	Bell	
	5	20040038308		2004-02-26	Rother et al.	
	6	20040253242	A1	2004-12-16	Bowdish et al.	
	7	20050036991	A1	2005-02-17	Fodor	

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	8	20050191298	A1	2005-09-01	Bell et al.	
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	1	0411306	EP	A1	1991-02-06	Goetze, Otto Prof. Dr. Med		X
	2	2 359 834	EP	B1	2016-11-09	Alexion Pharmaceuticals, Inc		☐

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	3	05/007809	WO	A2	2005-01-27	Alexion Pharmaceuticals, Inc		☐
	4	2004/029207	WO	A2	2004-04-08	Xencor Inc		☐
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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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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
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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

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Information:					
2	Other Reference-Patent/App/Search documents	11050543.pdf	1247825 7837b49a9ad0a9a9a71bee8509656534a32ee811	no	27
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3	Other Reference-Patent/App/Search documents	11595118.pdf	1023802 3980100742 8a69541cf9589fcc8eb861849d1b0a	no	22
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4	Other Reference-Patent/App/Search documents	12225040.pdf	792607 24cdff8c44fa196353023d743ae388be403647c9	no	17
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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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8	Other Reference-Patent/App/Search documents	15148839.pdf	1551393 1641048cc4f5db924c1f4c3275695b83fb3a0f50	no	28
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9	Other Reference-Patent/App/Search documents	15260888.pdf	1811728 ae7d46cae0c2dc67f5e18cae127220283dff9ca4	no	34
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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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12	Foreign Reference	EP2359834B1.pdf	1596309 3470fcbcde5862bb5c370381145156 42fd97cbe9	no	31
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13	Foreign Reference	WO9711971A1.pdf	3985644 bd17f93eca161fa81aa818b3487486a1e7af44bb	no	105
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14	Foreign Reference	WO2005007809A2.pdf	7180265 90d9281ee5e6b01b63c8ff00cd83ce8dae706173	no	87
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15	Non Patent Literature	Maloney_et_al.pdf	1286875 5c28d9b9ebe3506f8431e449d1aecd6bcf00aead	no	9
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16	Non Patent Literature	Annex_I.pdf	47259 c098281a76841cf64f6f80cd4d8256028dabfa87	no	1
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17	Non Patent Literature	Annex_II.pdf	41594 e9f02da9f33293c3aab9643e707bd2a96a1e039a	no	1
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18	Non Patent Literature	C_Priority_Doc_60783070.pdf	1736059 822836e215cdb7381b569f2dc5ebb0185e4c2e98	no	43
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19	Non Patent Literature	D10_Wang.pdf	2193569 0cf2c02a35af654413df951a39e68b6563a1cb4a	no	26
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20	Non Patent Literature	Hoffmann_Opposition-EP2359834.pdf	817840 b4f127ddaead938aec8a547bd935d6ad181675c1	no	25
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21	Non Patent Literature	Amgen_Opposition_003.pdf	965195 60fa453764eb608e5813f7bdc7f5f7f027c94a65	no	22
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22	Non Patent Literature	SOLIRIS.pdf	3103708 e5c6544ad5591e04f8a584f6f39c458b7fa0ec82	no	8
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23	Non Patent Literature	MUELLER.pdf	1038791 d09afafe866667edd707ec10cd368a6a17157d3c	no	12
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24	Non Patent Literature	MORRIS.pdf	133291 9930bc43948c70f75bddfb48bf1757f993dca8f0	no	2
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25	Non Patent Literature	US_Pharmacopeia.pdf	282491 f66276901aa2d43791255e4f7c311408270b4333	no	4
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26	Non Patent Literature	Declaration_Treuheit.pdf	2124400 795c6bb664537e1b7e3efb401e4cbb1f3a98b5ff	no	12
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27	Non Patent Literature	CORVINI.pdf	1901504 02405d23d13c6e0847ff9940bb53bd1e2628af82	no	6
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28	Non Patent Literature	EMEA.pdf	1776326 ad2333a82ba39a8f5c5aabcfc4d67bfe35d101f3	no	10
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30	Other Reference-Patent/App/Search documents	12621792.pdf	860198 5e0de08761b7e026bb9e0dd02ad426401c5855f9	no	15
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31	Information Disclosure Statement (IDS) Form (SB08)	IDSTRANS.pdf	35868 44304835e7036e7a7a8a3b16d16c0c6882349779	no	4
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This is not an USPTO supplied IDS fillable form					
32	Information Disclosure Statement (IDS) Form (SB08)	SB02.pdf	1092227 588389a7f5190c3e75f49e854085cfdeab47abf3	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
33	Information Disclosure Statement (IDS) Form (SB08)	SB03.pdf	1081733 389dab8d6d99f5c7775a04dfcf77d49751d4a04a	no	6
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A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
34	Information Disclosure Statement (IDS) Form (SB08)	SB01.pdf	1122651 08bca53a5821f402271ccd5c93e214c0d80d7ed3	no	12
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Information:					
			Total Files Size (in bytes):	56465931	

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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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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.*

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.

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

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Information:					
2	Specification	AXJ_114BUSCN5_SubSpec_Clean.pdf	540968 f3f2e6ca528a3a04ddfd238e04a78688d126c547	no	52
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Information:					
3	Request for Corrected Filing Receipt	AXJ_114BUSCN5_Request_Corrected_FR.pdf	168928 5bb222a812f76cb29917cb99b43ff142d8553823	no	2
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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

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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.

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]

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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,

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 ≥ 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 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.

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

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

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

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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.

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

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

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

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.

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 "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.,

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

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 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

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

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

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

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

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.

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.

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

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.

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.

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

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.

lntravascular 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]

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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

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 ≥ 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 ≥ 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 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.

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

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

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

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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.

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

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

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.

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 "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.,

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

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

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

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

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

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,

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

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

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.

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

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
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.

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.

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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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

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;

Samsung Bioepis Exhibit No. 1002
Page 1527

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
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Attorney/Agent For Applicant

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

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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.

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Page 1529

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./
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PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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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



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)

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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

GRANTED

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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

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

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.

Samsung Bioepis Exhibit No. 1002
Page 1536

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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	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/

Samsung Bioepis Exhibit No. 1002
Page 1537

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United States Patent and Trademark Office
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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

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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).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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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

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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/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

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Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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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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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
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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	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.	☐

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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 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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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:	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:

Samsung Bioepis Exhibit No. 1002
Page 1547

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:					
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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		

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.

Samsung Bioepis Exhibit No. 1002
Page 1549

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,

Samsung Bioepis Exhibit No. 1002
Page 1550

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] ¡	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.

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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:					

Samsung Bioepis Exhibit No. 1002
Page 1556

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.

Samsung Bioepis Exhibit No. 1002
Page 1557

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

Samsung Bioepis Exhibit No. 1002
Page 1558

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

Electronic Acknowledgement Receipt	
EFS ID:	35848088
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:	29-APR-2019
Filing Date:	05-JUL-2017
Time Stamp:	16:33:16
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	AXJ-114BUSCN5_-_1060_-_Erbitux_2004.pdf	307588 ce9df29c5bee657663cae668b77854466db fa18e	no	18

Warnings:

Samsung Bioepis Exhibit No. 1002
Page 1560

Information:					
2	Non Patent Literature	AXJ-114BUSCN5_-_1059_-_CEA-scan.pdf	212183 bdf218040b8dc3eba4d642ff7eb1ae7c0dd8f66d	no	11
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Information:					
3	Non Patent Literature	AXJ-114BUSCN5_-_EX1040.pdf	363405 2ba8bc3384c0fda464dfe0bdbeb9c76ad83a732f	no	38
Warnings:					
Information:					
4	Non Patent Literature	AXJ-114BUSCN5_-_EX1039.pdf	8001731 f52f88fcd415e5ea0cb6795974c82cd70eb16f31	no	6
Warnings:					
Information:					
5	Non Patent Literature	AXJ-114BUSCN5_-_1071_-_Synagis_label_2002.pdf	235174 7e6aefb443c90d322c0bbfff87fffce77f06d0b3	no	7
Warnings:					
Information:					
6	Non Patent Literature	AXJ-114BUSCN5_-_1058_-_Campath_2001.pdf	260067 91689ccec1d9b67fa4fd51a8142157173e713edb	no	13
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7	Non Patent Literature	RATIONAL_VOL.pdf	6660732 1f2a3f198292c6b5f5d997c660c22aaaee91a57f	no	94
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Information:					
8	Non Patent Literature	RITUXAN.pdf	333315 036251afb4f334e32163bfe4f3404b385b147d52	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	16374195	

Samsung Bioepis Exhibit No. 1002
Page 1561

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.

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New International Application Filed with the USPTO as a Receiving Office

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Samsung Bioepis Exhibit No. 1002
Page 1562

Electronic Acknowledgement Receipt	
EFS ID:	35846158
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:	29-APR-2019
Filing Date:	05-JUL-2017
Time Stamp:	16:30:57
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	clinical_trial_protocol_C04-001.pdf	1047682 0a3d04ce69266187367d7746caee3f8d05d0a519	no	9
Warnings:					

Samsung Bioepis Exhibit No. 1002
Page 1563

Information:					
2	Non Patent Literature	clinical_trial_protocol_CO2-002.pdf	1378584 b1316a7b1ee76d3c21a7042be6774ceabf19de38	no	6
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Information:					
3	Non Patent Literature	PRESS_RELEASE.pdf	243803 a41e04db4acc4d9fa7b796184a136e87a7a9bf03	no	3
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26	Non Patent Literature	AXJ-114BUSCN5_-_2019-02-28_Petition-114USCN2.pdf	1057343 b65c74be1ed86e35592f7f61601cdd2fdcc1a7fd	no	84
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Electronic Acknowledgement Receipt	
EFS ID:	35847895
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:	29-APR-2019
Filing Date:	05-JUL-2017
Time Stamp:	16:32:05
Application Type:	Utility under 35 USC 111(a)

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1	Non Patent Literature	AXJ-114BUSCN5_-_EX1045pt1.pdf	16678737 8993a2afc7771f87f976811697ab4d9b2d1761c0	no	25
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PTO/SB/08a (02-18)
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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

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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

	1	Genentech, Inc., Lucentis 2006 Package Insert, 7 pages.	
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	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

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	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

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	Application Number	15642096
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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
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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

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)	2019-04-29
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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EFS ID:	35859682
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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:	29-APR-2019
Filing Date:	05-JUL-2017
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Application Type:	Utility under 35 USC 111(a)

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1	Non Patent Literature	clinical_trial_protocol_C04-001.pdf	1047682 0a3d04ce69266187367d7746caee3f8d05d0a519	no	9

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14	Foreign Reference	WO2006122257A2.pdf	3839905 fcdeac251c355bbadf1d30cd75b081fceccc905b	no	68
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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

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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	6407213		2002-06-18	Carter et al.	

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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	20030232972	A1	2003-12-18	Bowdish et al.	
	2	20040146948	A1	2004-07-29	Britton et al.	

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	1	1720571	EP	B9	2012-10-24	Alexion Pharmaceuticals, Inc		
	2	1755674	EP	B1	2014-11-19	Alexion Pharmaceuticals, Inc		

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	3	2006122257	WO	A2	2006-11-16	Alexion Pharmaceuticals, Inc		
	4	1988882	EP	B1	2014-12-17	Alexion Pharmaceuticals, Inc		X
	5	2013235	EP	A1	2009-01-14	Alexion Pharmaceuticals, Inc		☐
	6	2061810	EP	B1	2014-11-12	Alexion Pharmaceuticals, Inc		☐
	7	2089058	EP	A2	2009-08-19	Alexion Pharmaceuticals, Inc		☐
	8	2815767	EP	A1	2014-12-24	Alexion Pharmaceuticals, Inc		☐
	9	2910253	EP	A1	2015-08-26	Alexion Pharmaceuticals, Inc		☐
	10	3056218	EP	A1	2016-08-17	Alexion Pharmaceuticals, Inc		☐
	11	2380907	EU	B1	2016-11-30	Alexion Pharmaceuticals, Inc		☐
	12	2004/050017	WO	A2	2004-06-17	Alexion Pharmaceuticals, Inc		☐
	13	2004/071439	WO	A2	2004-08-26	Elan Pharmaceuticals, Inc		☐

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	14	2004/108158	WO	A1	2004-12-16	Alexion Pharmaceuticals, Inc		☐
	15	2005/092073	WO	A2	2005-10-06	Protein Design Labs, Inc		☐
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	1	ADDERSON, E., et al., "Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to Haemophilus influenza Type b Capsular Polysaccharide Are Dominated by a Limited Number of Vk and VI Segments and V J Combinations," J. Clin. Invest. vol. 89: 729-738 (1992).	
	2	ALBERTS, B. et al., "Intracellular Compartments and Protein Sorting," in Molecular Biology of the Cell, Chapter 12:55 pages (1994).	
	3	Alexion Pharmaceuticals, Inc.: "FDA Approves Alexion's Soliris(TM) for All Patients With PNH Alexion First Therapy Approved for This Rare and Life-Threatening Blood Disease," Press Release, March 16, 2007, 3 pages.	
	4	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,718,880," Case IPR2019-00740, filed February 28, 2019, 84 pages.	
	5	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,725,504," Case IPR2019-00739, filed February 28, 2019, 88 pages.	
	6	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,732,149," Case IPR2019-00741, filed February 28, 2019, 62 pages.	

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	7	ASHP statement on unit dose drug distribution, Am. J. Hosp. Pharm., vol. 46:2346: 3 pages (1989).	
	8	Australian Government Department of Public Health, Pharmaceutical Benefits Advisory Committee, "Public Summary Document" for Eculizumab, 6 pages (2009).	
	9	Bessler, M., et al., "Paroxysmal nocturnal haemoglobinuria (PNH) is caused by somatic mutations in the PIG-A gene," The EMBO Journal, vol. 13: 110 - 117 (1994).	
	10	Biogen Idec Inc., Tysabri 2004 Package Insert, 11 pages.	
	11	Boehringer Ingelheim Int'l GmbH, Verluma 1996 Package Insert, 25 pages.	
	12	Centocor Ortho Biotech, LP, Orthoclone OKT3 Package Insert, retrieved 1/24/2019, 14 pages.	
	13	Centocor, Inc., Remicade 1998 Package Insert, 12 pages.	
	14	Corixa Corp., Bexxar 2003 Package Insert, 49 pages.	
	15	Cytogen Corp., ProstaScint 1996 Package Insert, 17 pages.	
	16	Declaration by Prof. Ronald Taylor and Curriculum Vitae, November 21, 2018, 9 pages.	
	17	Declaration of Dr. Alexander Klibanov, dated November 24, 2018, 45 pages.	

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	18	Declaration of Dr. Bruce Andrien with Exhibits, dated May 23, 2017, 36 pages.	
	19	Declaration of Dr. Bruce Andrien, dated August 15, 2018, 2 pages.	
	20	Declaration of Dr. Miano, dated March 22, 2018, 27 pages.	
	21	Declaration of Joseph P. Balthasar, Ph.D. and Curriculum Vitae, dated February 27, 2019, 129 pages.	
	22	Declaration of Stephen A. Saxe, with Exhibits A, B, C, dated January 12, 2018, 10 pages.	
	23	Eli Lilly & Co., ReoPro 1997 Package Insert, 17 pages.	
	24	Emery, P. et al., "The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIB randomized, double blind, placebo controlled, dose ranging trial," Arthritis & Rheumatism, vol. 54(5): 1390-1400 (2006).	
	25	European Application No. 11001632.6, Patentee's Response to Oppositions, dated March 22, 2018, 24 pages.	
	26	European Application No. 11001632.6, Summons to Attend Oral Proceedings, dated July 5, 2018, 10 pages.	
	27	European Application No. 11001632.6, Urgent Oral Proceedings of the Patentee, dated January 14, 2019, 2 pages.	
	28	European Application No. 11001632.6, Written Submission in Preparation of Oral Proceedings of the Patentee, dated November 24, 2018, 7 pages.	

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	29	European Application No. 16172335.8, Summons to Attend Oral Proceedings, dated March 27, 2019, 13 pages.	
	30	European Application No. 16172335.9, Reply To Written Opinion, dated October 30, 2017, 7 pages.	
	31	European Application No. 16195355.9, Extended European Search Report, dated March 17, 2017, 8 pages.	
	32	European Application No. 16195355.9, Reply to Third Party Communication, dated January 16, 2018, 3 pages.	
	33	European Application No. 16195355.9, Reply To Written Opinion, dated July 10, 2017, 7 pages.	
	34	European Application No. 16195355.9, Summons to Attend Oral Proceeding, dated May 7, 2018, 10 pages.	
	35	European Application No. 16195355.9, Table of Alexion European patents and patent applications, cited in Third Party Observation filed on December 12, 2017, 1 page.	
	36	European Application No. 16195355.9, Written Submission in Preparation of Oral Proceedings, dated August 15, 2018, 13 pages.	
	37	European Patent No. 1720571, Opposition File History, 515 pages.	
	38	European Patent No. 1720571, Pfizer Inc's Opposition statement, dated August 15, 2018, 13 pages.	
	39	European Patent No. 1720571, Third Party Observation filed on December 12, 2017, 1 page.	

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	40	European Patent No. 2359834, Graphical representation of D20 Table 2, cited in Opposition on March 22, 2018, 1 page.	
	41	European Patent No. 2359834, Opposition File History, 2685 pages.	
	42	European Patent No. 2359834, Summary of antibodies listed in D20/D21 Tables, cited in Opposition on March 22, 2018.	
	43	European Patent No. 2359834, Summary of antibody products approved by EMA since filing date EMA Approved Antibodies C411599EP, cited in Opposition on March 22, 2018, 2 pages.	
	44	European Patent No. 3167888, File History, 348 pages.	
	45	Extracts from Kabat et al., Sequences of Proteins of Immunological Interest, US Dept, Health and Human Services, 10 pages (1991).	
	46	FDA Approval Letter dated March 16, 2007, 8 pages.	
	47	FDA Medical Review for Application Number 125166 (eculizumab), March 28, 2017, 122 pages.	
	48	FDA Pharmacometrics Review for Application Number 125166 (eculizumab), dated February 28, 2007, 21 pages.	
	49	Genentech, Inc., Avastin 2004 Package Insert, 27 pages.	
	50	Genentech, Inc., Herceptin 1998 Package Insert, 2 pages.	

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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2019-04-29
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.

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.

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 29, 2019
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

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. 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.

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

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Page 1598

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: April 29, 2019

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, 30th Floor
Boston, Massachusetts 02109-2127
617-217-4630 (Tel)
617-217-4699 (Fax)
Attorney/Agent For Applicant

Electronic Acknowledgement Receipt	
EFS ID:	35848470
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:	29-APR-2019
Filing Date:	05-JUL-2017
Time Stamp:	16:34:15
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	ROUET.pdf	1833361 2e0955e93337eb7447decc63176e98de94679cdd	no	9
Warnings:					

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Page 1600

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Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
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Page 1601

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14	Non Patent Literature	AXJ-114BUSCN5_-_EX1015pt1.pdf	15056680 f7e017d250b12e5fa4a3c5bffb2562c185b5a216	no	202
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Information:					
18	Information Disclosure Statement (IDS) Form (SB08)	SB02.pdf	1036152 2523351528c56ef02e0fa8aa9f4c80b79fe3c049	no	7
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
19	Information Disclosure Statement (IDS) Form (SB08)	SB01.pdf	1037349 835afc2f858102003b1d8df6bb1a286b1ee22f10	no	10
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Information:					

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Page 1603

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Information:					
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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.

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Page 1604

Electronic Acknowledgement Receipt	
EFS ID:	35848765
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:	29-APR-2019
Filing Date:	05-JUL-2017
Time Stamp:	16:35:32
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.)
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Page 1605

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Warnings:					

Samsung Bioepis Exhibit No. 1002
Page 1607

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Information:					
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Samsung Bioepis Exhibit No. 1002
Page 1608

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.

Samsung Bioepis Exhibit No. 1002
Page 1609

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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 05/31/2019

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
05/31/2019	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

Office Action Summary	Application No. 15/642,096	Applicant(s) BELL et al.	
	Examiner JAMES L ROGERS	Art Unit 1644	AIA (FITF) 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 8/24/2017.

☐ 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) 52-59 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) 52-59 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: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

1. Claims 52-59 pending and under consideration in the instant examination.

2. Applicant's IDSs filed on 8/22/2017, 3/28/2018, 4/27/2018, and 4/29/2019 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. 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 52 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 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019).

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patent 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 differs from the claimed invention 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. Instead, Hillmen teaches that patients received infusion of 600 mg of eculizumab (treatment schedule at p. 554).

Evans teaches the antibody 5G1.1, eculizumab, 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 PNH 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.

The combined references still do not precisely teach that the antibody that binds C5 has a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently claimed.

Bowdish teaches construction of a 5G1.1+peptide antibody (see ¶191 which references Figs. 13A and 13B) having a humanized antibody H chain with an amino acid sequence (SEQ ID NO: 67) which has 96% sequence identity to the currently claimed heavy chain SEQ ID NO: 2. (see sequence alignment below)

```
Query Match             96.0%;  Score 2300.5;  DB 1;  Length 472;\par
  Best Local Similarity   95.4%;  \par
  Matches  437;  Conservative    2;  Mismatches    4;  Indels   15;  Gaps    2;\par
\par
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db         20 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 79\par
\par
Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR----------YFFGSSPNWYFD 110\par
              |||||||||||||||||||||||||||||||||||||||          :    :|     \par
Db         80 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAP----- 134\par
\par
Qy        111 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 170\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        135 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 194\par
\par
Qy        171 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 230\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        195 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 254\par
\par
Qy        231 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 290\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        255 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 314\par
\par
Qy        291 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 350\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        315 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 374\par
\par
Qy        351 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 410\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        375 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 434\par
\par
Qy        411 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448\par
              |||||||||||||||||||||||||||||||||||||\par
Db        435 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 472\par
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Bowdish also teaches that the 5G1.1+ peptide has a humanized antibody L chain with an amino acid sequence (SEQ ID NO: 69) which has 100% sequence identity to the currently claimed light chain SEQ ID NO: 4 (see sequence alignment below).

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Query Match             100.0%;  Score 1110;  DB 4;  Length 236;
  Best Local Similarity   100.0%;
  Matches  214;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

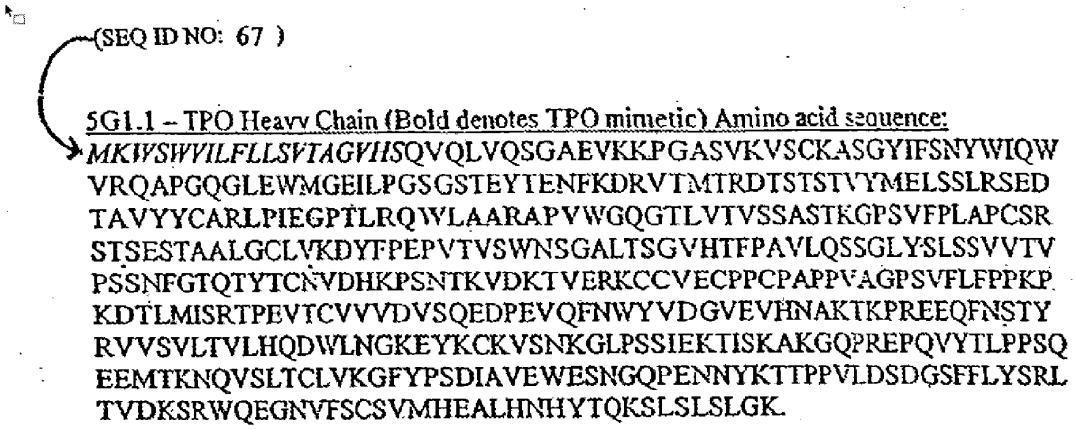
Qy          1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 82

Qy         61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 142

Qy        121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        143 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 202

Qy        181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
              |||||||||||||||||||||||||||||||||
Db        203 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
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Bowdish further teaches that the sequence of the above **humanized antibody H chain** SEQ ID NO: 67, which as noted supra has 96% sequence identity to the currently claimed H chain SEQ ID NO: 2, is based on Evan's eculizumab 5G1.1 antibody framework from U.S. Application Ser. No. 06/487,263, which is the USD 6,355,245 Evans Patent supra, with the exception that the CD3 region was replaced with a TPO mimetic peptide sequence (¶191). (see Fig. 13A of Bowdish which depicts the TPO H chain sequence where the CDR3 region that has been substituted with the TPO mimetic is highlighted in bold).



However, Evan's '245 Patent in Fig. 19 provides the missing CD3 sequence for the5G1.1 eculizumab antibody (see Fig. 19 from Evans, which shows framework 5G1.1

antibody with the CDR3 sequence underlined).

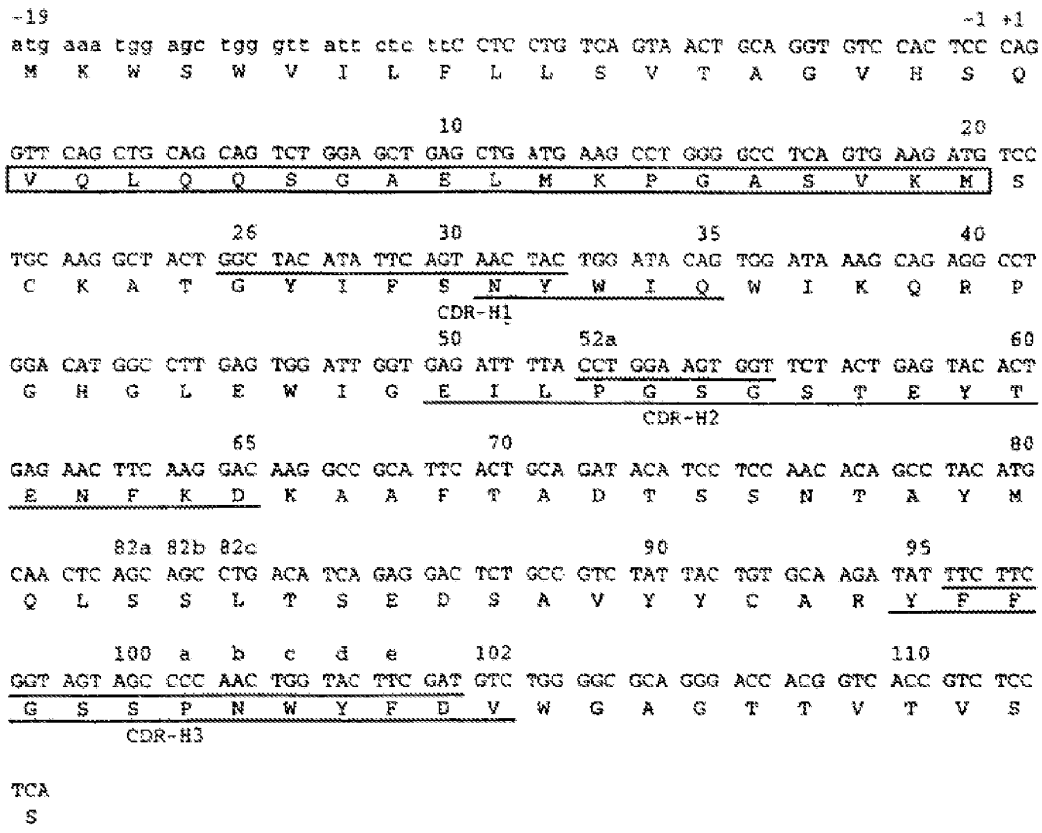


FIG.19

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Bowdish's TPO mimic amino acid sequence in Bowdish's H chain published SEQ ID NO: 67 which is 96% identical with currently claimed H chain SEQ ID NO: 2 with Evan's CDR3 5G1.1 eculizumab amino acid sequence, thereby arriving at a H chain sequence having 100% sequence identity to currently claimed H chain SEQ ID NO: 2 and to have combined that H chain sequence with Bowdish's L chain SEQ ID NO 69 that has 100% sequence identity to currently claimed L chain SEQ ID NO: 4.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Bowdish teaches that the 5G1.1+peptide antibody H chain is based on the 5G1.1 antibody framework taught by Evans, with the exception that the

CDR3 was replaced with a TPO mimic sequence. But the substituted CDR3 was taught by Evans. One of skill in the art would accordingly look to the '245 Evans Patent for the native CDR3. Evans Fig. 19 shows the heavy chain variable region as residues 95-102. Substituting the CDR3 from Evans into the heavy chain 5G1.1+ taught by Bowdish would result in a sequence having 100% sequence identity to currently claimed SEQ ID No: 2. Bowdish also teaches that the light chain of 5G1.1" (published SEQ ID NO: 69), which as shown supra has 100% amino acid sequence identity to currently claimed L chain SEQ ID NO:4.

Thus upon reading Bowdish, one of ordinary skill in the art would have found it obvious to substitute CDRH3 from the 5G1.1 of Evans into the H chain SEQ ID NO: 67 which is only 96% identical in sequence identity due to the missing CDR3 region as taught by Bowdish to arrive at 100% sequence identity for the H chain of currently claimed SEQ ID NO: 2 and to pair it with the L chain SEQ ID NO: 69 from Bowdish, thereby producing an antibody identical to currently claimed SEQ ID NO: 2 and 4. The motivation to do so comes directly form the two references, as Bowdish indicates that the 5G1.1 sequence is that of Evans, albeit with an altered CDR3 in the heavy chain.

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. Claims 52-59 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 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019), as applied to claim 52 above, and further in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

The prior art teachings of Hillmen, Evans, Wang, and Bowdish are discussed supra.

The teachings differs with respect to the characteristics of the patient population. For example, the references differ in the recitation that the patient has received at least four transfusion in the twelve months prior to administration of the antibody (claims 53 and 57), has a platelet count greater than or equal to 100k per microliter prior to administration of the antibody (claims 54 and 58).

The teachings also differ in the recitation that the patient exhibits decreased lactate dehydrogenase levels (claim 56).

The teachings also differ in the recitation that the patient is treated with the antibody for at least 26 weeks as in claims 55 and 59.

However, Hillmen further teaches that the patients in its study had received at least four red-cell transfusions in the preceding 12 months (p. 553, last 2 lines).

Bell also teaches treating PNH using an anti-C5 antibody such as h5G1.1 mAb eculizumab (¶52). Bells teaches that PNH patients were transfusion dependent and hemolytic with a history of four or more transfusion within 12 months (¶81).

Bell further teaches that the patient for treatment has a platelet count preferably in excess of 150k per microliter (¶67).

Bell further teaches that that patients received weekly intravenous infusion of anti-C5 antibody for 64 weeks (¶82).

Bell also teaches that lactate dehydrogenase levels (LDH) are used as an objective indicator of hemolysis and that LDH levels were decreased as a result of the treatment (¶85).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have continued eculizumab treatment for PNH for a period of at least 26 weeks to a patient population having received at least four transfusion in the twelve months prior to administration of eculizumab and having a platelet count in excess of 100k per microliter prior to administration of the antibody as well as to have also used a decreased LDH as a measure of clinical outcome in a method of treating PNH as taught by Hillmen. Those of skill in the art would have had reason to do so because Hillmen itself teaches that patients for treatment of PNH by administration of eculizumab had received at least 4 transfusion in the preceding 12 months, most preferably having a platelet count in excess of 150k, and Bell teaches that in the treatment of PNH with eculizumab, LDH is a known indicator of efficacy and that treatment can continue for 64 weeks, which is a period of greater than 26 weeks. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

From the 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.

Double Patenting

7. 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 time wise 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.

8. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of **US Patent 9,732,149,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 149 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4.

While the ‘149 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the ‘149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the

appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '149 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would have been obvious in view of Bell as is discussed supra.

9. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of **US Patent 9,718,880,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 880 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution..

While the '880 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '880 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would be obvious in view of Bell as is discussed supra.

10. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of **US Patent 9,725,504,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 504 Patent claim the same method of treating PNH using an antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution. See in particular claims 1, and 4-6 of the '504 patent.

The '504 also claims a decreased in mean levels of LDH after administration (claim 9).

11. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of **US Patent 9,409,980,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 980 Patent appear to claim the same anti-C5 antibody (see claim 1 of the '980). In addition, the '980 claim using the antibody to treat PNH (see claim 17).

While the '980 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

12. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of **US Patent 9,415,102,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 102 Patent appear to claim the same anti-C5 antibody (see claims 1-2 of the '102). In addition, the '102 claims using the antibody to treat PNH (see claim 17).

While the '102 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '102 that the intended use for the antibody is PNH (see methods of treatment in the specification) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '102 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

13. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of **US Patent 9,556,263,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 256 Patent appear to claim the same eculizumab antibody (see claim 1 of the '263). In addition, the '263 claim using the antibody to treat PNH (see claim 3).

While the '263 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

14. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-12 of **US Patent 9,352,035,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 035 Patent appear to claim the same eculizumab antibody (see claim 1 of the '035).

While the '035 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '035 that the intended use for the antibody is PNH (see ¶129 of the '35 which lists PNH as one of the complement associated disorders that can be treated by the composition) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '035 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

15. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of **US Patent 9,925,262,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 262 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 4 of the '262 patent.

While the '262 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

16. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-33 of **US Patent 10,239,937,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 937 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 11 of the '937 patent.

While the '937 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

17. No claim is allowed.

18. 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 14, 2019

/JAMES ROGERS/
Art Unit 1644

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/642,096	BELL et al.
	Examiner	Art Unit
	JAMES L ROGERS	1644

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
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Search Notes	Date	Examiner
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EAST: PGPUB, USPAT, JPO, EPO, DRWNT, INVENTOR SEARCH	05/01/2019	JR

Interference Search			
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Attorney Docket Number	AXJ-114BUSCN5

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	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.	☐
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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

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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Privacy Act Statement

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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.

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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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Samsung Bioepis Exhibit No. 1002
Page 1637

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Samsung Bioepis Exhibit No. 1002
Page 1638

	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

/JAMES L ROGERS/ 04/30/2019

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

Samsung Bioepis Exhibit No. 1002
Page 1639

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. 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	1662
Examiner Name	Not Yet Assigned
Attorney Docket Number	AXJ-114BUSCN5

U.S.PATENTS Remove

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
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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
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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 Remove

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]

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	First Named Inventor	Leonard BELL
	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

	1	PCT/US2007/006606 Certified Copy of Priority document US 60/783,070, March 15, 2006, 43 pages.	
	2	PIERANGELI,S. et al., "Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia," Arthritis & Rheumatology, vol. 52, Issue 7: 2120-2124(2005)	
	3	REITER et al., "Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease," Nature Med., vol. 8 (12):1383-1389(2002)	
	4	RICHARDS et al., "Evolution of GPI-Deficient Clones Predicts Clinical Course in Paroxysmal Nocturnal Haemoglobinuria," Blood, vol. 104:Abstract 172 (2004)	
	5	RICKLIN, D. et al., "Complement-targeted therapeutics," Nature Biotechnology, vol. 25(11): 1265-1275 (2007)	
	6	RODARY et al., "Patient preference for either the EORTC QLQ-C30 or the FACIT Quality of Life (QOL) measures: a study performed in patient suffering from carcinoma of an unknown primary site (CUP)," European Journal of Cancer, Vol. 40, pp. 521-528 (2004).	
	7	Rosse et al. "Immune-mediated hemolytic anemia" Hematology Am Soc, 48-62 (2004)	
	8	ROTHER et al., "The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin, " JAMA, vol. 293(13):1653-1662 (2005).	
	9	ROTHER et al., Eculizumab, a C5 complement-blocking antibody, abolishes hemolysis and reduces transfusion dependency in patients with paroxysmal nocturnal hemoglobinuria (PNH)," Molecular Immunology, Vol. 40(2-4): page 197, XP009163498, (2003).	
	10	ROTHER et al., "Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria," Nature Biotechnology, vol. 25 (11): 1256-1264 (2007)	
	11	Safety and Effectiveness of h5G1.1-mAb for dermatomyositis" clinicaltrials.gov identifier NCT00005571, April 25, 2000, pp. 1-4	

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	12	SIERRA, G. et al., "Vaccine against group B Neisseia meningitidis: Protection trial and mass vaccination results in Cuba," NIPH ANNALS 1991, vol. 14(2):195-210, ISSN: 0332-5652 (1991)	
	13	Soliris® (eculizumab) Highlights of prescribing information, 8 pages	
	14	STEBLER et al., "High-dose recombinant human erythropoietin for treatment of anemia in myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria: a pilot study," Exp. Hematol., vol. 18:1204-1208 (1990).	
	15	STRAUSS et al. "Alternative pathway of complement in sickle cell disease," Pediat. Res., vol. 11:285-289 (1977)	
	16	STUART et al., "Sickle-cell disease," Lancet, vol. 364:1343-1360 (2004)	
	17	TANG, et al., "Pikal, Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice," Pharmaceutical Research, Vol. 21 (2):191-200 (2004).	
	18	The MERCK MANUAL of Diagnosis and Therapy, Seventeenth Edition, Chapter 127 Anemias,; pp. 849-883 (1999).;	
	19	THOMAS et al., "Inhibition of complement activity by humanized anti-C5 antibody and single-chain Fv, " Mol. Imm., vol. 33(17-18):1389-1401 (1996)	
	20	US Pharmacopeia (USP29-NF24), p. 2989, retrieved from http://www.pharmacopeia.cn/v29240/usp29nf24s0 c1136.html on May 17, 2017, 4 pages.	
	21	VAKEVA, et al., "Myocardial infarction and apoptosis after myocardial ischemia and reperfusion," Circulation vol. 97:2259-2267 (1998).	
	22	WANG, W. et al., "Antibody Structure, Instability, and Formulation" Journal of Pharmaceuticals, vol. 96(1): 26 pages (2007)	

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	Art Unit	1662
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN5

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	04/30/2019

*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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Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

PTO/SB/08a (03-15)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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(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

U.S.PATENTS Remove

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	4686100		1987-08-11	Raffin et al.	
	2	5135916		1992-08-04	Sims et al.	
	3	5660825		1997-08-26	Sims et al.	
	4	6171586		2001-01-09	Lam et al.	
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Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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Examiner Name	J. L. Rogers
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

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	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

	23	Study Protocol: A redacted version of the representative clinical trial protocol C04-001, June 2, 2004, 9 pages.	
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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2019-04-29
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN5

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	1	Termination of opposition proceedings of European Patent No. 1720571, dated April 13, 2018, 16 pages.	☐

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Page 1672

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L230       1101 S (H5G1.1 OR 5G1.1)
L231          0 FILE DISSABS
L232          0 FILE 1MOBILITY
L233          0 FILE AGRICOLA
L234          0 FILE BIOTECHNO
L235          0 FILE COMPENDEX
L236          0 FILE EMBASE
L237          0 FILE INSPEC
L238          0 FILE PQSCITECH
L239          0 FILE ADISCTI
L240          0 FILE ADISINSIGHT
L241          0 FILE ADISNEWS
L242          0 FILE ANABSTR
L243          0 FILE BIOSIS
L244          0 FILE BIOTECHDS
L245          0 FILE CABA
L246          0 FILE CAPLUS
L247          0 FILE CEABA-VTB
L248          0 FILE CIN
L249          0 FILE CROPB
L250          0 FILE CROPU
L251          0 FILE DDFB
L252          0 FILE DGENE
L253          0 FILE DRUGB
L254          0 FILE DRUGU
L255          0 FILE ESBIOBASE
L256          0 FILE FSTA
L257          0 FILE GENBANK
L258          0 FILE IFIALL
L259          0 FILE IMSRESEARCH
L260          0 FILE KOSMET
L261          0 FILE MEDLINE
L262          0 FILE NTIS
L263          0 FILE PCTGEN
L264          0 FILE PS
L265          0 FILE RDISCLOSURE
L266          0 FILE SCISEARCH
L267          0 FILE TOXCENTER
L268          0 FILE USGENE
L269          1 FILE USPATFULL
L270          0 FILE USPATOLD
L271          0 FILE USPAT2
L272          0 FILE VETB
L273          0 FILE VETU
L274          0 FILE IPA
L275          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L276          1 S L230 AND ((SINGLE (2A) UNIT) (50A) (300 (2A) MG))
L277          0 FILE DISSABS
L278          0 FILE 1MOBILITY
L279          0 FILE AGRICOLA
L280          0 FILE BIOTECHNO
```


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```
L281          0 FILE COMPENDEX
L282          0 FILE EMBASE
L283          0 FILE INSPEC
L284          0 FILE PQSCITECH
L285          0 FILE ADISCTI
L286          0 FILE ADISINSIGHT
L287          0 FILE ADISNEWS
L288          0 FILE ANABSTR
L289          0 FILE BIOSIS
L290          0 FILE BIOTECHDS
L291          0 FILE CABA
L292          0 FILE CAPLUS
L293          0 FILE CEABA-VTB
L294          0 FILE CIN
L295          0 FILE CROPB
L296          0 FILE CROPU
L297          0 FILE DDFB
L298          0 FILE DGENE
L299          0 FILE DRUGB
L300          0 FILE DRUGU
L301          0 FILE ESBIOBASE
L302          0 FILE FSTA
L303          0 FILE GENBANK
L304          4 FILE IFIALL
L305          0 FILE IMSRESEARCH
L306          0 FILE KOSMET
L307          0 FILE MEDLINE
L308          0 FILE NTIS
L309          0 FILE PCTGEN
L310          0 FILE PS
L311          0 FILE RDISCLOSURE
L312          0 FILE SCISEARCH
L313          0 FILE TOXCENTER
L314          0 FILE USGENE
L315          9 FILE USPATFULL
L316          0 FILE USPATOLD
L317          3 FILE USPAT2
L318          0 FILE VETB
L319          0 FILE VETU
L320          0 FILE IPA
L321          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L322         16 S ((SINGLE (2A) UNIT) (50A) (300 (2A) MG)) AND (ECULIZUMAB OR S
L323         12 DUP REM L322 (4 DUPLICATES REMOVED)
L324         94 FILE DISSABS
L325          0 FILE 1MOBILITY
L326        109 FILE AGRICOLA
L327       1690 FILE BIOTECHNO
L328         57 FILE COMPENDEX
L329      29082 FILE EMBASE
L330         23 FILE INSPEC
L331       2229 FILE PQSCITECH
L332        410 FILE ADISCTI
L333         88 FILE ADISINSIGHT
L334        685 FILE ADISNEWS
L335          5 FILE ANABSTR
L336      14004 FILE BIOSIS
L337        513 FILE BIOTECHDS
L338        508 FILE CABA
```


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```
L339       7140 FILE CAPLUS
L340         10 FILE CEABA-VTB
L341         50 FILE CIN
L342          4 FILE CROPB
L343          4 FILE CROPU
L344       1030 FILE DDFB
L345     118208 FILE DGENE
L346       1030 FILE DRUGB
L347       2537 FILE DRUGU
L348       2749 FILE ESBIOBASE
L349         17 FILE FSTA
L350        318 FILE GENBANK
L351       1434 FILE IFIALL
L352         64 FILE IMSRESEARCH
L353          3 FILE KOSMET
L354      18461 FILE MEDLINE
L355         58 FILE NTIS
L356       2981 FILE PCTGEN
L357          0 FILE PS
L358          1 FILE RDISCLOSURE
L359      14044 FILE SCISEARCH
L360       8142 FILE TOXCENTER
L361      28347 FILE USGENE
L362      13906 FILE USPATFULL
L363         14 FILE USPATOLD
L364       5331 FILE USPAT2
L365         24 FILE VETB
L366         51 FILE VETU
L367        357 FILE IPA
L368         10 FILE NAPRALERT
     TOTAL FOR ALL FILES
L369     275822 S (NOCTURNAL (2A) HEMOGLOBINURIA) OR (APLASTIC (2A) ANEMIA) OR
L370          0 FILE DISSABS
L371          0 FILE 1MOBILITY
L372          0 FILE AGRICOLA
L373         25 FILE BIOTECHNO
L374          0 FILE COMPENDEX
L375         81 FILE EMBASE
L376          0 FILE INSPEC
L377         24 FILE PQSCITECH
L378         48 FILE ADISCTI
L379          6 FILE ADISINSIGHT
L380         71 FILE ADISNEWS
L381          0 FILE ANABSTR
L382         54 FILE BIOSIS
L383          1 FILE BIOTECHDS
L384          6 FILE CABA
L385         32 FILE CAPLUS
L386          0 FILE CEABA-VTB
L387          0 FILE CIN
L388          0 FILE CROPB
L389          0 FILE CROPU
L390          0 FILE DDFB
L391        168 FILE DGENE
L392          0 FILE DRUGB
L393         91 FILE DRUGU
L394         37 FILE ESBIOBASE
L395          0 FILE FSTA
L396          0 FILE GENBANK
```


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```
L397          15 FILE IFIALL
L398           1 FILE IMSRESEARCH
L399           0 FILE KOSMET
L400          45 FILE MEDLINE
L401           0 FILE NTIS
L402           0 FILE PCTGEN
L403           0 FILE PS
L404           0 FILE RDISCLOSURE
L405          39 FILE SCISEARCH
L406          22 FILE TOXCENTER
L407           0 FILE USGENE
L408         110 FILE USPATFULL
L409           0 FILE USPATOLD
L410          52 FILE USPAT2
L411           0 FILE VETB
L412           0 FILE VETU
L413           4 FILE IPA
L414           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L415         932 S L369 (50A) (PLATELET (5A) COUNT)
L416           0 FILE DISSABS
L417           0 FILE 1MOBILITY
L418           0 FILE AGRICOLA
L419           3 FILE BIOTECHNO
L420           0 FILE COMPENDEX
L421          10 FILE EMBASE
L422           0 FILE INSPEC
L423           3 FILE PQSCITECH
L424          18 FILE ADISCTI
L425           0 FILE ADISINSIGHT
L426          27 FILE ADISNEWS
L427           0 FILE ANABSTR
L428           2 FILE BIOSIS
L429           1 FILE BIOTECHDS
L430           1 FILE CABA
L431           1 FILE CAPLUS
L432           0 FILE CEABA-VTB
L433           0 FILE CIN
L434           0 FILE CROPB
L435           0 FILE CROPU
L436           0 FILE DDFB
L437          15 FILE DGENE
L438           0 FILE DRUGB
L439          22 FILE DRUGU
L440           6 FILE ESBIOBASE
L441           0 FILE FSTA
L442           0 FILE GENBANK
L443           1 FILE IFIALL
L444           0 FILE IMSRESEARCH
L445           0 FILE KOSMET
L446           3 FILE MEDLINE
L447           0 FILE NTIS
L448           0 FILE PCTGEN
L449           0 FILE PS
L450           0 FILE RDISCLOSURE
L451           1 FILE SCISEARCH
L452           1 FILE TOXCENTER
L453           0 FILE USGENE
L454          47 FILE USPATFULL
```


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```
L455          0 FILE USPATOLD
L456         20 FILE USPAT2
L457          0 FILE VETB
L458          0 FILE VETU
L459          1 FILE IPA
L460          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L461        183 S L415 (50A) TRANSFUSION
L462          0 FILE DISSABS
L463          0 FILE 1MOBILITY
L464          0 FILE AGRICOLA
L465          0 FILE BIOTECHNO
L466          0 FILE COMPENDEX
L467          0 FILE EMBASE
L468          0 FILE INSPEC
L469          0 FILE PQSCITECH
L470          7 FILE ADISCTI
L471          0 FILE ADISINSIGHT
L472          0 FILE ADISNEWS
L473          0 FILE ANABSTR
L474          0 FILE BIOSIS
L475          0 FILE BIOTECHDS
L476          0 FILE CABA
L477          0 FILE CAPLUS
L478          0 FILE CEABA-VTB
L479          0 FILE CIN
L480          0 FILE CROPB
L481          0 FILE CROPU
L482          0 FILE DDFB
L483          0 FILE DGENE
L484          0 FILE DRUGB
L485          0 FILE DRUGU
L486          0 FILE ESBIOBASE
L487          0 FILE FSTA
L488          0 FILE GENBANK
L489          0 FILE IFIALL
L490          0 FILE IMSRESEARCH
L491          0 FILE KOSMET
L492          0 FILE MEDLINE
L493          0 FILE NTIS
L494          0 FILE PCTGEN
L495          0 FILE PS
L496          0 FILE RDISCLOSURE
L497          0 FILE SCISEARCH
L498          0 FILE TOXCENTER
L499          0 FILE USGENE
L500          0 FILE USPATFULL
L501          0 FILE USPATOLD
L502          0 FILE USPAT2
L503          0 FILE VETB
L504          0 FILE VETU
L505          0 FILE IPA
L506          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L507          7 S L461 (50A) (LACTATE (3A) DEHYDROGENASE)
L508          7 DUP REM L507 (0 DUPLICATES REMOVED)
L509          0 FILE DISSABS
L510          0 FILE 1MOBILITY
L511          0 FILE AGRICOLA
```


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```
L512          0 FILE BIOTECHNO
L513          0 FILE COMPENDEX
L514          4 FILE EMBASE
L515          0 FILE INSPEC
L516          1 FILE PQSCITECH
L517         18 FILE ADISCTI
L518          5 FILE ADISINSIGHT
L519          3 FILE ADISNEWS
L520          0 FILE ANABSTR
L521          4 FILE BIOSIS
L522          0 FILE BIOTECHDS
L523          0 FILE CABA
L524         54 FILE CAPLUS
L525          0 FILE CEABA-VTB
L526          0 FILE CIN
L527          0 FILE CROPB
L528          0 FILE CROPU
L529          0 FILE DDFB
L530         20 FILE DGENE
L531          0 FILE DRUGB
L532          3 FILE DRUGU
L533          5 FILE ESBIOBASE
L534          0 FILE FSTA
L535          3 FILE GENBANK
L536          2 FILE IFIALL
L537          5 FILE IMSRESEARCH
L538          0 FILE KOSMET
L539          3 FILE MEDLINE
L540          0 FILE NTIS
L541          0 FILE PCTGEN
L542          0 FILE PS
L543          0 FILE RDISCLOSURE
L544          3 FILE SCISEARCH
L545          1 FILE TOXCENTER
L546          0 FILE USGENE
L547          6 FILE USPATFULL
L548          0 FILE USPATOLD
L549          3 FILE USPAT2
L550          0 FILE VETB
L551          0 FILE VETU
L552          0 FILE IPA
L553          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L554        143 S (NOCTURNAL (2A) HEMOGLOBINURIA) (50A) (LACTATE (3A) DEHYDROGE
L555          0 FILE DISSABS
L556          0 FILE 1MOBILITY
L557          0 FILE AGRICOLA
L558          0 FILE BIOTECHNO
L559          0 FILE COMPENDEX
L560          1 FILE EMBASE
L561          0 FILE INSPEC
L562          0 FILE PQSCITECH
L563         11 FILE ADISCTI
L564          3 FILE ADISINSIGHT
L565          1 FILE ADISNEWS
L566          0 FILE ANABSTR
L567          0 FILE BIOSIS
L568          0 FILE BIOTECHDS
L569          0 FILE CABA
```


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```
L570          2 FILE CAPLUS
L571          0 FILE CEABA-VTB
L572          0 FILE CIN
L573          0 FILE CROPB
L574          0 FILE CROPU
L575          0 FILE DDFB
L576          0 FILE DGENE
L577          0 FILE DRUGB
L578          2 FILE DRUGU
L579          2 FILE ESBIOBASE
L580          0 FILE FSTA
L581          0 FILE GENBANK
L582          0 FILE IFIALL
L583          1 FILE IMSRESEARCH
L584          0 FILE KOSMET
L585          0 FILE MEDLINE
L586          0 FILE NTIS
L587          0 FILE PCTGEN
L588          0 FILE PS
L589          0 FILE RDISCLOSURE
L590          0 FILE SCISEARCH
L591          0 FILE TOXCENTER
L592          0 FILE USGENE
L593          1 FILE USPATFULL
L594          0 FILE USPATOLD
L595          0 FILE USPAT2
L596          0 FILE VETB
L597          0 FILE VETU
L598          0 FILE IPA
L599          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L600         24 S L554 (50A) TRANSFUSION
L601          0 FILE DISSABS
L602          0 FILE 1MOBILITY
L603          0 FILE AGRICOLA
L604          0 FILE BIOTECHNO
L605          0 FILE COMPENDEX
L606          0 FILE EMBASE
L607          0 FILE INSPEC
L608          0 FILE PQSCITECH
L609          7 FILE ADISCTI
L610          0 FILE ADISINSIGHT
L611          0 FILE ADISNEWS
L612          0 FILE ANABSTR
L613          0 FILE BIOSIS
L614          0 FILE BIOTECHDS
L615          0 FILE CABA
L616          0 FILE CAPLUS
L617          0 FILE CEABA-VTB
L618          0 FILE CIN
L619          0 FILE CROPB
L620          0 FILE CROPU
L621          0 FILE DDFB
L622          0 FILE DGENE
L623          0 FILE DRUGB
L624          0 FILE DRUGU
L625          0 FILE ESBIOBASE
L626          0 FILE FSTA
L627          0 FILE GENBANK
```


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```
L628          0 FILE IFIALL
L629          0 FILE IMSRESEARCH
L630          0 FILE KOSMET
L631          0 FILE MEDLINE
L632          0 FILE NTIS
L633          0 FILE PCTGEN
L634          0 FILE PS
L635          0 FILE RDISCLOSURE
L636          0 FILE SCISEARCH
L637          0 FILE TOXCENTER
L638          0 FILE USGENE
L639          0 FILE USPATFULL
L640          0 FILE USPATOLD
L641          0 FILE USPAT2
L642          0 FILE VETB
L643          0 FILE VETU
L644          0 FILE IPA
L645          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L646          7 S L600 (50A) (PLATELET (5A) COUNT)
L647         18 FILE DISSABS
L648          0 FILE 1MOBILITY
L649         21 FILE AGRICOLA
L650        451 FILE BIOTECHNO
L651         11 FILE COMPENDEX
L652       6118 FILE EMBASE
L653          3 FILE INSPEC
L654        447 FILE PQSCITECH
L655        136 FILE ADISCTI
L656         42 FILE ADISINSIGHT
L657         81 FILE ADISNEWS
L658          0 FILE ANABSTR
L659       3067 FILE BIOSIS
L660        100 FILE BIOTECHDS
L661         22 FILE CABA
L662       1906 FILE CAPLUS
L663          0 FILE CEABA-VTB
L664         19 FILE CIN
L665          0 FILE CROPB
L666          0 FILE CROPU
L667        135 FILE DDFB
L668      50579 FILE DGENE
L669        135 FILE DRUGB
L670        345 FILE DRUGU
L671        724 FILE ESBIOBASE
L672          0 FILE FSTA
L673         69 FILE GENBANK
L674        342 FILE IFIALL
L675         33 FILE IMSRESEARCH
L676          1 FILE KOSMET
L677       2909 FILE MEDLINE
L678          5 FILE NTIS
L679       2941 FILE PCTGEN
L680          0 FILE PS
L681          1 FILE RDISCLOSURE
L682       3916 FILE SCISEARCH
L683        893 FILE TOXCENTER
L684      27311 FILE USGENE
L685       3532 FILE USPATFULL
```


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```
L686          1 FILE USPATOLD
L687       1082 FILE USPAT2
L688          0 FILE VETB
L689          0 FILE VETU
L690         42 FILE IPA
L691          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L692     107438 S (NOCTURNAL (2A) HEMOGLOBINURIA) (5A) PAROXYSMAL
L693          0 FILE DISSABS
L694          0 FILE 1MOBILITY
L695          0 FILE AGRICOLA
L696          1 FILE BIOTECHNO
L697          0 FILE COMPENDEX
L698          3 FILE EMBASE
L699          0 FILE INSPEC
L700          2 FILE PQSCITECH
L701         15 FILE ADISCTI
L702          0 FILE ADISINSIGHT
L703          2 FILE ADISNEWS
L704          0 FILE ANABSTR
L705          1 FILE BIOSIS
L706          0 FILE BIOTECHDS
L707          1 FILE CABA
L708          3 FILE CAPLUS
L709          0 FILE CEABA-VTB
L710          0 FILE CIN
L711          0 FILE CROPB
L712          0 FILE CROPU
L713          0 FILE DDFB
L714          0 FILE DGENE
L715          0 FILE DRUGB
L716          9 FILE DRUGU
L717          1 FILE ESBIOBASE
L718          0 FILE FSTA
L719          0 FILE GENBANK
L720          0 FILE IFIALL
L721          0 FILE IMSRESEARCH
L722          0 FILE KOSMET
L723          1 FILE MEDLINE
L724          0 FILE NTIS
L725          0 FILE PCTGEN
L726          0 FILE PS
L727          0 FILE RDISCLOSURE
L728          1 FILE SCISEARCH
L729          1 FILE TOXCENTER
L730          0 FILE USGENE
L731         15 FILE USPATFULL
L732          0 FILE USPATOLD
L733         12 FILE USPAT2
L734          0 FILE VETB
L735          0 FILE VETU
L736          1 FILE IPA
L737          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L738         69 S L692 (50A) (PLATELET (5A) COUNT)
L739          0 FILE DISSABS
L740          0 FILE 1MOBILITY
L741          0 FILE AGRICOLA
L742          0 FILE BIOTECHNO
```


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```
L743           0 FILE COMPENDEX
L744           0 FILE EMBASE
L745           0 FILE INSPEC
L746           0 FILE PQSCITECH
L747           9 FILE ADISCTI
L748           0 FILE ADISINSIGHT
L749           0 FILE ADISNEWS
L750           0 FILE ANABSTR
L751           0 FILE BIOSIS
L752           0 FILE BIOTECHDS
L753           0 FILE CABA
L754           0 FILE CAPLUS
L755           0 FILE CEABA-VTB
L756           0 FILE CIN
L757           0 FILE CROPB
L758           0 FILE CROPU
L759           0 FILE DDFB
L760           0 FILE DGENE
L761           0 FILE DRUGB
L762           2 FILE DRUGU
L763           1 FILE ESBIOBASE
L764           0 FILE FSTA
L765           0 FILE GENBANK
L766           0 FILE IFIALL
L767           0 FILE IMSRESEARCH
L768           0 FILE KOSMET
L769           0 FILE MEDLINE
L770           0 FILE NTIS
L771           0 FILE PCTGEN
L772           0 FILE PS
L773           0 FILE RDISCLOSURE
L774           0 FILE SCISEARCH
L775           0 FILE TOXCENTER
L776           0 FILE USGENE
L777           8 FILE USPATFULL
L778           0 FILE USPATOLD
L779           6 FILE USPAT2
L780           0 FILE VETB
L781           0 FILE VETU
L782           1 FILE IPA
L783           0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L784          27 S L738 (50A) TRANSFUSION
L785          27 DUP REM L784 (0 DUPLICATES REMOVED)
L786           0 S L785
L787           0 FILE DISSABS
L788           0 S L785
L789           0 FILE 1MOBILITY
L790           0 S L785
L791           0 FILE AGRICOLA
L792           0 S L785
L793           0 FILE BIOTECHNO
L794           0 S L785
L795           0 FILE COMPENDEX
L796           0 S L785
L797           0 FILE EMBASE
L798           0 S L785
L799           0 FILE INSPEC
L800           0 S L785
```


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```
L801          0 FILE PQSCITECH
L802          9 S L785
L803          0 FILE ADISCTI
L804          0 S L785
L805          0 FILE ADISINSIGHT
L806          0 S L785
L807          0 FILE ADISNEWS
L808          0 S L785
L809          0 FILE ANABSTR
L810          0 S L785
L811          0 FILE BIOSIS
L812          0 S L785
L813          0 FILE BIOTECHDS
L814          0 S L785
L815          0 FILE CABA
L816          0 S L785
L817          0 FILE CAPLUS
L818          0 S L785
L819          0 FILE CEABA-VTB
L820          0 S L785
L821          0 FILE CIN
L822          0 S L785
L823          0 FILE CROPB
L824          0 S L785
L825          0 FILE CROPU
L826          0 S L785
L827          0 FILE DDFB
L828          0 S L785
L829          0 FILE DGENE
L830          0 S L785
L831          0 FILE DRUGB
L832          2 S L785
L833          1 FILE DRUGU
L834          1 S L785
L835          1 FILE ESBIOBASE
L836          0 S L785
L837          0 FILE FSTA
L838          0 S L785
L839          0 FILE GENBANK
L840          0 S L785
L841          0 FILE IFIALL
L842          0 S L785
L843          0 FILE IMSRESEARCH
L844          0 S L785
L845          0 FILE KOSMET
L846          0 S L785
L847          0 FILE MEDLINE
L848          0 S L785
L849          0 FILE NTIS
L850          0 S L785
L851          0 FILE PCTGEN
L852          0 S L785
L853          0 FILE PS
L854          0 S L785
L855          0 FILE RDISCLOSURE
L856          0 S L785
L857          0 FILE SCISEARCH
L858          0 S L785
L859          0 FILE TOXCENTER
```


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```
L860          0 S L785
L861          0 FILE USGENE
L862          8 S L785
L863          0 FILE USPATFULL
L864          0 S L785
L865          0 FILE USPATOLD
L866          6 S L785
L867          0 FILE USPAT2
L868          0 S L785
L869          0 FILE VETB
L870          0 S L785
L871          0 FILE VETU
L872          1 S L785
L873          1 FILE IPA
L874          0 S L785
L875          0 FILE NAPRALERT
     TOTAL FOR ALL FILES
L876          3 S L785 AND PY<2009

     FILE 'STNGUIDE' ENTERED AT 15:07:32 ON 30 APR 2019

     FILE 'DRUGU, ESBIOBASE, IPA' ENTERED AT 15:10:14 ON 30 APR 2019

     FILE 'STNGUIDE' ENTERED AT 15:10:14 ON 30 APR 2019

     FILE 'DRUGU, ESBIOBASE, IPA' ENTERED AT 15:12:39 ON 30 APR 2019
```


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PTO/SB/08a (02-18)
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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 Remove

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	6407213		2002-06-18	Carter et al.	

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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	20030232972	A1	2003-12-18	Bowdish et al.	
	2	20040146948	A1	2004-07-29	Britton et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	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	1720571	EP	B9	2012-10-24	Alexion Pharmaceuticals, Inc		
	2	1755674	EP	B1	2014-11-19	Alexion Pharmaceuticals, Inc		

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

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

	3	2006122257	WO	A2	2006-11-16	Alexion Pharmaceuticals, Inc		
	4	1988882	EP	B1	2014-12-17	Alexion Pharmaceuticals, Inc		X
	5	2013235	EP	A1	2009-01-14	Alexion Pharmaceuticals, Inc		☐
	6	2061810	EP	B1	2014-11-12	Alexion Pharmaceuticals, Inc		☐
	7	2089058	EP	A2	2009-08-19	Alexion Pharmaceuticals, Inc		☐
	8	2815767	EP	A1	2014-12-24	Alexion Pharmaceuticals, Inc		☐
	9	2910253	EP	A1	2015-08-26	Alexion Pharmaceuticals, Inc		☐
	10	3056218	EP	A1	2016-08-17	Alexion Pharmaceuticals, Inc		☐
	11	2380907	EU	B1	2016-11-30	Alexion Pharmaceuticals, Inc		☐
	12	2004/050017	WO	A2	2004-06-17	Alexion Pharmaceuticals, Inc		☐
	13	2004/071439	WO	A2	2004-08-26	Elan Pharmaceuticals, Inc		☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

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

	14	2004/108158	WO	A1	2004-12-16	Alexion Pharmaceuticals, Inc		☐
	15	2005/092073	WO	A2	2005-10-06	Protein Design Labs, Inc		☐
	16	2006003179	WO	A2	2006-01-12	Novo Nordisk As		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

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.	T5
	1	ADDERSON, E., et al., "Immunoglobulin Light Chain Variable Region Gene Sequences for Human Antibodies to Haemophilus influenza Type b Capsular Polysaccharide Are Dominated by a Limited Number of Vk and VI Segments and V J Combinations," J. Clin. Invest. vol. 89: 729-738 (1992).	
	2	ALBERTS, B. et al., "Intracellular Compartments and Protein Sorting," in Molecular Biology of the Cell, Chapter 12:55 pages (1994).	
	3	Alexion Pharmaceuticals, Inc.: "FDA Approves Alexion's Soliris(TM) for All Patients With PNH Alexion First Therapy Approved for This Rare and Life-Threatening Blood Disease," Press Release, March 16, 2007, 3 pages.	
	4	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,718,880," Case IPR2019-00740, filed February 28, 2019, 84 pages.	
	5	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,725,504," Case IPR2019-00739, filed February 28, 2019, 88 pages.	
	6	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Petition for Inter Partes Review of U.S. Patent No, 9,732,149," Case IPR2019-00741, filed February 28, 2019, 62 pages.	

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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	7	ASHP statement on unit dose drug distribution, Am. J. Hosp. Pharm., vol. 46:2346: 3 pages (1989).	
	8	Australian Government Department of Public Health, Pharmaceutical Benefits Advisory Committee, "Public Summary Document" for Eculizumab, 6 pages (2009).	
	9	Bessler, M., et al., "Paroxysmal nocturnal haemoglobinuria (PNH) is caused by somatic mutations in the PIG-A gene," The EMBO Journal, vol. 13: 110 - 117 (1994).	
	10	Biogen Idec Inc., Tysabri 2004 Package Insert, 11 pages.	
	11	Boehringer Ingelheim Int'l GmbH, Verluma 1996 Package Insert, 25 pages.	
	12	Centocor Ortho Biotech, LP, Orthoclone OKT3 Package Insert, retrieved 1/24/2019, 14 pages.	
	13	Centocor, Inc., Remicade 1998 Package Insert, 12 pages.	
	14	Corixa Corp., Bexxar 2003 Package Insert, 49 pages.	
	15	Cytogen Corp., ProstaScint 1996 Package Insert, 17 pages.	
	16	Declaration by Prof. Ronald Taylor and Curriculum Vitae, November 21, 2018, 9 pages.	
	17	Declaration of Dr. Alexander Klibanov, dated November 24, 2018, 45 pages.	

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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	18	Declaration of Dr. Bruce Andrien with Exhibits, dated May 23, 2017, 36 pages.	
	19	Declaration of Dr. Bruce Andrien, dated August 15, 2018, 2 pages.	
	20	Declaration of Dr. Miano, dated March 22, 2018, 27 pages.	
	21	Declaration of Joseph P. Balthasar, Ph.D. and Curriculum Vitae, dated February 27, 2019, 129 pages.	
	22	Declaration of Stephen A. Saxe, with Exhibits A, B, C, dated January 12, 2018, 10 pages.	
	23	Eli Lilly & Co., ReoPro 1997 Package Insert, 17 pages.	
	24	Emery, P. et al., "The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIB randomized, double blind, placebo controlled, dose ranging trial," Arthritis & Rheumatism, vol. 54(5): 1390-1400 (2006).	
	25	European Application No. 11001632.6, Patentee's Response to Oppositions, dated March 22, 2018, 24 pages.	
	26	European Application No. 11001632.6, Summons to Attend Oral Proceedings, dated July 5, 2018, 10 pages.	
	27	European Application No. 11001632.6, Urgent Oral Proceedings of the Patentee, dated January 14, 2019, 2 pages.	
	28	European Application No. 11001632.6, Written Submission in Preparation of Oral Proceedings of the Patentee, dated November 24, 2018, 7 pages.	

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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	29	European Application No. 16172335.8, Summons to Attend Oral Proceedings, dated March 27, 2019, 13 pages.	
	30	European Application No. 16172335.9, Reply To Written Opinion, dated October 30, 2017, 7 pages.	
	31	European Application No. 16195355.9, Extended European Search Report, dated March 17, 2017, 8 pages.	
	32	European Application No. 16195355.9, Reply to Third Party Communication, dated January 16, 2018, 3 pages.	
	33	European Application No. 16195355.9, Reply To Written Opinion, dated July 10, 2017, 7 pages.	
	34	European Application No. 16195355.9, Summons to Attend Oral Proceeding, dated May 7, 2018, 10 pages.	
	35	European Application No. 16195355.9, Table of Alexion European patents and patent applications, cited in Third Party Observation filed on December 12, 2017, 1 page.	
	36	European Application No. 16195355.9, Written Submission in Preparation of Oral Proceedings, dated August 15, 2018, 13 pages.	
	37	European Patent No. 1720571, Opposition File History, 515 pages.	
	38	European Patent No. 1720571, Pfizer Inc's Opposition statement, dated August 15, 2018, 13 pages.	
	39	European Patent No. 1720571, Third Party Observation filed on December 12, 2017, 1 page.	

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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

	40	European Patent No. 2359834, Graphical representation of D20 Table 2, cited in Opposition on March 22, 2018, 1 page.	
	41	European Patent No. 2359834, Opposition File History, 2685 pages.	
	42	European Patent No. 2359834, Summary of antibodies listed in D20/D21 Tables, cited in Opposition on March 22, 2018.	
	43	European Patent No. 2359834, Summary of antibody products approved by EMA since filing date EMA Approved Antibodies C411599EP, cited in Opposition on March 22, 2018, 2 pages.	
	44	European Patent No. 3167888, File History, 348 pages.	
	45	Extracts from Kabat et al., Sequences of Proteins of Immunological Interest, US Dept, Health and Human Services, 10 pages (1991).	
	46	FDA Approval Letter dated March 16, 2007, 8 pages.	
	47	FDA Medical Review for Application Number 125166 (eculizumab), March 28, 2017, 122 pages.	
	48	FDA Pharmacometrics Review for Application Number 125166 (eculizumab), dated February 28, 2007, 21 pages.	
	49	Genentech, Inc., Avastin 2004 Package Insert, 27 pages.	
	50	Genentech, Inc., Herceptin 1998 Package Insert, 2 pages.	

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	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

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EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	04/30/2019

*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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	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)	2019-04-29
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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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.

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	921	("H5G1.1" or "5G1.1")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:28
L2	107	L1 and (single near3 unit)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:29
L3	47	L2 and ("300" near2 mg)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:30
L4	28	L3 and ("10" near2 ml)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:30
L5	21226	(nocturnal near2 hemoglobinuria) or (aplastic near2 anemia) or (myeladysplastic near2 syndrome)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:34
L6	200	L5 same (platelet near5 count)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:35
L7	48	L6 same transfusion	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:35
L8	0	L7 same Eculizumab	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:36
L9	0	L7 and Eculizumab	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:36
L10	0	L7 same (lactate near3 dehydrogenase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:37
L11	0	L7 and (lactate near3 dehydrogenase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:37
L12	53	L5 same (lactate near3 dehydrogenase)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:37

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L15	525	(mark near3 evans).in.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:41
L16	3	L13 and L4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:41
L17	3	L14 and L4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:42
L18	3	L15 and L4	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/04/30 14:42

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	309	("5g1.1" or eculizumab).clm.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/05/14 14:34
L3	92	L2 and (PNH or paroxysmal)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/05/14 14:35
L4	19	L3 and (alexion near3 pharmaceuticals).as.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2019/05/14 14:36

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	("(5g1.1oreculizumab).clm.").PN.	US-PGPUB; USPAT	OR	OFF	2019/05/14 14:34

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 06/11/2019

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
06/11/2019	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

Office Action Summary	Application No. 15/642,096	Applicant(s) BELL et al.	
	Examiner JAMES L ROGERS	Art Unit 1644	AIA (FITF) 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 8/24/2019.

☐ 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) 52-59 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) 52-59 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: _____.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

This Office Action vacates the Office Action mailed on 5/31/2019 and resets the time to respond. The Office Action is identical to the correspondence mailed on 5/31/2019 except that the Office Action includes a TC Director's signature.

DETAILED ACTION

1. Claims 52-59 pending and under consideration in the instant examination.

2. Applicant's IDSs filed on 8/22/2017, 3/28/2018, 4/27/2018, and 4/29/2019 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. 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

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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 52 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 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019).

Hillmen teaches a method for treating a human patient that suffers from paroxysmal nocturnal hemoglobinuria (PNH) by administering to the patent 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 differs from the claimed invention 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. Instead, Hillmen teaches that patients received infusion of 600 mg of eculizumab (treatment schedule at p. 554).

Evans teaches the antibody 5G1.1, eculizumab, 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 PNH 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.

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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.

The combined references still do not precisely teach that the antibody that binds C5 has a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4 as currently claimed.

Bowdish teaches construction of a 5G1.1+peptide antibody (see ¶191 which references Figs. 13A and 13B) having a humanized antibody H chain with an amino acid sequence (SEQ ID NO: 67) which has 96% sequence identity to the currently claimed heavy chain SEQ ID NO: 2. (see sequence alignment below)

```
Query Match             96.0%;  Score 2300.5;  DB 1;  Length 472;\par
  Best Local Similarity   95.4%;  \par
  Matches  437;  Conservative    2;  Mismatches    4;  Indels   15;  Gaps    2;\par
\par
Qy          1 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 60\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db         20 QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMGEILPGSGSTEY 79\par
\par
Qy         61 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR----------YFFGSSPNWYFD 110\par
              |||||||||||||||||||||||||||||||||||||||          :    :|     \par
Db         80 TENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARLPIEGPTLRQWLAARAP----- 134\par
\par
Qy        111 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 170\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        135 VWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS 194\par
\par
Qy        171 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 230\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        195 GVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPP 254\par
\par
Qy        231 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 290\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        255 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKT 314\par
\par
Qy        291 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 350\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        315 KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY 374\par
\par
Qy        351 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 410\par
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||\par
Db        375 TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSR 434\par
\par
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Qy        411 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 448\par
              ||||||||||||||||||||||||||||||||||||||\par
Db        435 LTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 472\par
```

Bowdish also teaches that the 5G1.1+ peptide has a humanized antibody L chain with an amino acid sequence (SEQ ID NO: 69) which has 100% sequence identity to the currently claimed light chain SEQ ID NO: 4 (see sequence alignment below).

```
Query Match             100.0%;  Score 1110;  DB 4;  Length 236;
  Best Local Similarity   100.0%;
  Matches  214;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         23 DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYGATNLADGVPS 82

Qy         61 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         83 RFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQGTKVEIKRTVAAPSVFIFPP 142

Qy        121 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        143 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT 202

Qy        181 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 214
              |||||||||||||||||||||||||||||||||
Db        203 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC 236
```

Bowdish further teaches that the sequence of the above **humanized antibody H chain** SEQ ID NO: 67, which as noted supra has 96% sequence identity to the currently claimed H chain SEQ ID NO: 2, is based on Evan's eculizumab 5G1.1 antibody framework from U.S. Application Ser. No. 06/487,263, which is the USD 6,355,245 Evans Patent supra, with the exception that the CD3 region was replaced with a TPO mimetic peptide sequence (¶191). (see Fig. 13A of Bowdish which depicts the TPO H chain sequence where the CDR3 region that has been substituted with the TPO mimetic is highlighted in bold).

(SEQ ID NO: 67)

5G1.1 – TPO Heavy Chain (Bold denotes TPO mimetic) Amino acid sequence:

*MKHVSHVILFLLSVTAGVHS*QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQW
VRQAPGQGLEWMGEILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSED
TAVYYCARLPIEGPTLRQWLAARAPVWGQGTLVTVSSASTKGPSVFPLAPCSR
STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
PSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKP
KDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL
TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK.

However, Evan's '245 Patent in Fig. 19 provides the missing CD3 sequence for the5G1.1 eculizumab antibody (see Fig. 19 from Evans, which shows framework 5G1.1

antibody with the CDR3 sequence underlined).

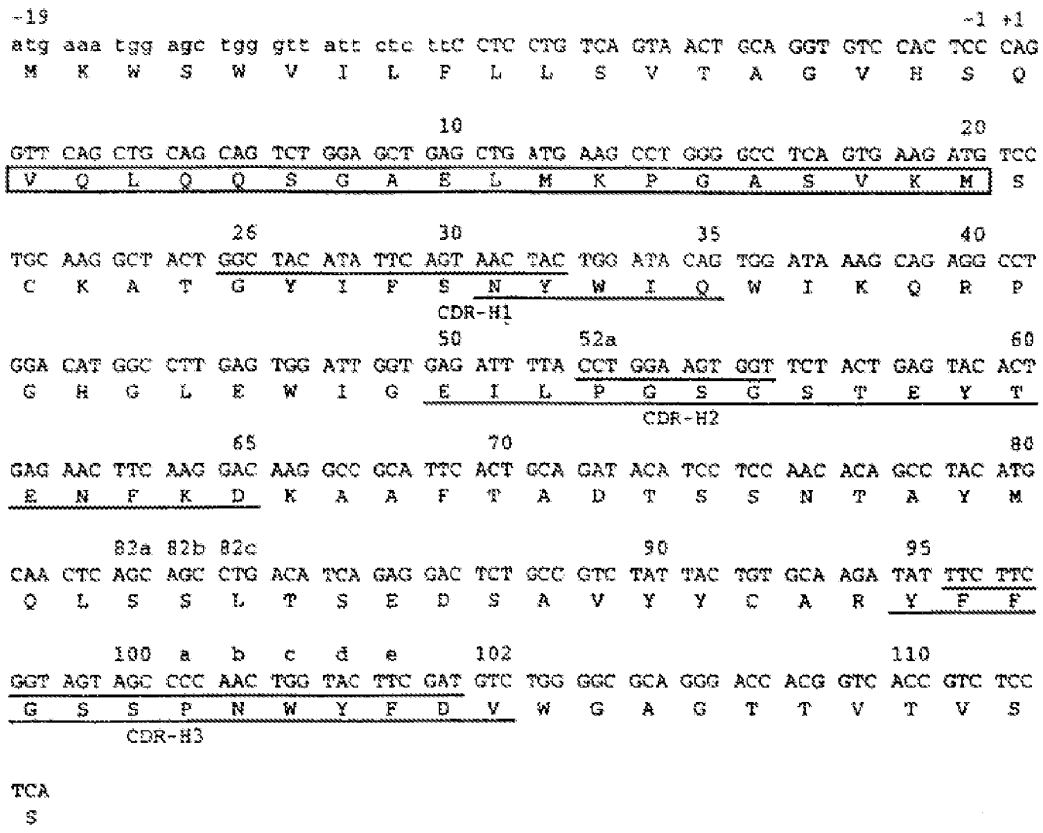


FIG.19

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Bowdish's TPO mimic amino acid sequence in Bowdish's H chain published SEQ ID NO: 67 which is 96% identical with currently claimed H chain SEQ ID NO: 2 with Evan's CDR3 5G1.1 eculizumab amino acid sequence, thereby arriving at a H chain sequence having 100% sequence identity to currently claimed H chain SEQ ID NO: 2 and to have combined that H chain sequence with Bowdish's L chain SEQ ID NO 69 that has 100% sequence identity to currently claimed L chain SEQ ID NO: 4.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because Bowdish teaches that the 5G1.1+peptide antibody H chain is based on the 5G1.1 antibody framework taught by Evans, with the exception that the

CDR3 was replaced with a TPO mimic sequence. But the substituted CDR3 was taught by Evans. One of skill in the art would accordingly look to the '245 Evans Patent for the native CDR3. Evans Fig. 19 shows the heavy chain variable region as residues 95-102. Substituting the CDR3 from Evans into the heavy chain 5G1.1+ taught by Bowdish would result in a sequence having 100% sequence identity to currently claimed SEQ ID No: 2. Bowdish also teaches that the light chain of 5G1.1" (published SEQ ID NO: 69), which as shown supra has 100% amino acid sequence identity to currently claimed L chain SEQ ID NO:4.

Thus upon reading Bowdish, one of ordinary skill in the art would have found it obvious to substitute CDRH3 from the 5G1.1 of Evans into the H chain SEQ ID NO: 67 which is only 96% identical in sequence identity due to the missing CDR3 region as taught by Bowdish to arrive at 100% sequence identity for the H chain of currently claimed SEQ ID NO: 2 and to pair it with the L chain SEQ ID NO: 69 from Bowdish, thereby producing an antibody identical to currently claimed SEQ ID NO: 2 and 4. The motivation to do so comes directly form the two references, as Bowdish indicates that the 5G1.1 sequence is that of Evans, albeit with an altered CDR3 in the heavy chain.

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. Claims 52-59 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 8/22/2017), in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017), and Bowdish et al. (US 2003/232972; IDS 4/29/2019), as applied to claim 52 above, and further in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

The prior art teachings of Hillmen, Evans, Wang, and Bowdish are discussed supra.

The teachings differs with respect to the characteristics of the patient population. For example, the references differ in the recitation that the patient has received at least four transfusion in the twelve months prior to administration of the antibody (claims 53 and 57), has a platelet count greater than or equal to 100k per microliter prior to administration of the antibody (claims 54 and 58).

The teachings also differ in the recitation that the patient exhibits decreased lactate dehydrogenase levels (claim 56).

The teachings also differ in the recitation that the patient is treated with the antibody for at least 26 weeks as in claims 55 and 59.

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However, Hillmen further teaches that the patients in its study had received at least four red-cell transfusions in the preceding 12 months (p. 553, last 2 lines).

Bell also teaches treating PNH using an anti-C5 antibody such as h5G1.1 mAb eculizumab (¶52). Bells teaches that PNH patients were transfusion dependent and hemolytic with a history of four or more transfusion within 12 months (¶81).

Bell further teaches that the patient for treatment has a platelet count preferably in excess of 150k per microliter (¶67).

Bell further teaches that that patients received weekly intravenous infusion of anti-C5 antibody for 64 weeks (¶82).

Bell also teaches that lactate dehydrogenase levels (LDH) are used as an objective indicator of hemolysis and that LDH levels were decreased as a result of the treatment (¶85).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have continued eculizumab treatment for PNH for a period of at least 26 weeks to a patient population having received at least four transfusion in the twelve months prior to administration of eculizumab and having a platelet count in excess of 100k per microliter prior to administration of the antibody as well as to have also used a decreased LDH as a measure of clinical outcome in a method of treating PNH as taught by Hillmen. Those of skill in the art would have had reason to do so because Hillmen itself teaches that patients for treatment of PNH by administration of eculizumab had received at least 4 transfusion in the preceding 12 months, most preferably having a platelet count in excess of 150k, and Bell teaches that in the treatment of PNH with eculizumab, LDH is a known indicator of efficacy and that treatment can continue for 64 weeks, which is a period of greater than 26 weeks. The combination of familiar elements according to known methods is obvious when it does no more than yield predictable results (see KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

From the 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.

Double Patenting

7. 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 time wise 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.

8. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of **US Patent 9,732,149,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 149 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4.

While the ‘149 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the ‘149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the

appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '149 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would have been obvious in view of Bell as is discussed supra.

9. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of **US Patent 9,718,880,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 880 Patent claim the same antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution..

While the '880 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '149 that the intended use for the antibody is PNH (see abstract) and that said antibody is administered as a single unit dosage form at 300 mg in 30 ml of a 10 mg/ml sterile, preservative free solution (¶ before detailed description). See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '880 does not specifically recite some of the limitations contained in the dependent claims such as that the patient exhibits decreased LDH levels, these limitations would be obvious in view of Bell as is discussed supra.

10. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of **US Patent 9,725,504,** in view of Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 504 Patent claim the same method of treating PNH using an antibody having a H chain of SEQ ID NO: 2 and L chain of SEQ ID NO: 4, in a sterile, preservative free 300 mg single-use dosage form comprising 30 ml of a 10 mg/ml solution. See in particular claims 1, and 4-6 of the '504 patent.

The '504 also claims a decreased in mean levels of LDH after administration (claim 9).

11. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of **US Patent 9,409,980,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 980 Patent appear to claim the same anti-C5 antibody (see claim 1 of the '980). In addition, the '980 claim using the antibody to treat PNH (see claim 17).

While the '980 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

12. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of **US Patent 9,415,102,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 102 Patent appear to claim the same anti-C5 antibody (see claims 1-2 of the '102). In addition, the '102 claims using the antibody to treat PNH (see claim 17).

While the '102 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '102 that the intended use for the antibody is PNH (see methods of treatment in the specification) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '102 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

13. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of **US Patent 9,556,263,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 256 Patent appear to claim the same eculizumab antibody (see claim 1 of the '263). In addition, the '263 claim using the antibody to treat PNH (see claim 3).

While the '263 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

14. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-12 of **US Patent 9,352,035,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 035 Patent appear to claim the same eculizumab antibody (see claim 1 of the '035).

While the '035 Patent is drawn to a composition whereas the current application is drawn to administering the antibody to a patient suffering from PNH, it is clear from the specification of the '035 that the intended use for the antibody is PNH (see ¶129 of the '35 which lists PNH as one of the complement associated disorders that can be treated by the composition) See *Sun Pharmaceuticals Industries, Ltd., v. Eli Lilly and Company*, Fed. Cir. 2010 for the appropriateness of making an ODP to a product claim where one of the intended uses of the product is for the method as now claimed).

While the '035 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

15. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of **US Patent 9,925,262,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 262 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 4 of the '262 patent.

While the '262 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

16. Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-33 of **US Patent 10,239,937,** in view of Evans et al. (US 6,355,245 B1, issued 3/12/2002; IDS 8/22/2017), Wang (US 2005/0271660; IDS 8/22/2017) and Bell et al. (US 2005/0191298; IDS 8/22/2017).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the current application and 937 Patent claim the same method of treating PNH using an eculizumab antibody. See in particular claims 1, and 11 of the '937 patent.

While the '937 does not specifically recite that the antibody is a single-unit dosage form of 300 mg in 30 mL of sterile, preservative free solution or the various limitations contained in the dependent claims, those limitation would be obvious in view of Evans, Wang and Bell as is discussed supra.

17. No claim is allowed.

18. 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).

June 6, 2019

/JAMES ROGERS/
Art Unit 1644

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644

/W GARY JONES/
Director, Technology Center 1600

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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 11/18/2019

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
11/18/2019	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

Applicant-Initiated Interview Summary	**Application No.** 15/642,096	**Applicant(s)** BELL et al.	
	Examiner JAMES L ROGERS	**Art Unit** 1644	**AIA (FITF) Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) JAMES L. ROGERS.

(2) DANIEL KOLKER, SPE.

(3) JANE REMILLARD.

(4) JILL SLOPER.

Date of Interview: 12 November 2019.

Type: ☐ Telephonic ☐ Video Conference
☑ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☑103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 52.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

In addition to the above named participants, Tara Rahemba was present for the applicant. The outstanding 35 USC 103 (a) rejection was discussed as well as possible strategies for overcoming the rejection, including indicia of nonobviousness..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JAMES L ROGERS/ Examiner, Art Unit 1644	/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

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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: **December 11, 2019**
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

DECLARATION PURSUANT TO 37 CFR 1.132 BY DR. DEEPAK JAIN

I, Deepak Jain, MD, MBA, declare the following:

1. I have been employed by Alexion Pharmaceuticals ("Alexion") since April 2015. In my first role at Alexion, I was the Senior Director of Global Medical Affairs and directed a team focused on Soliris® for treating paroxysmal nocturnal hemoglobinuria (PNH). From March 2017 to May 2018, I was the Head of Alexion's Canada Medical Affairs Department in Vaughan, Ontario. I am presently the Executive Director of Global Medical Affairs, Leader of the Hematology and Global Program Team Leader of the Ultomiris® PNH Program at Alexion Pharmaceuticals, which is located in Boston, Massachusetts. Alexion Pharmaceuticals is the Assignee of the above-referenced patent application. I received a Medical Degree (MD) from Maharaja Sayajirao University (Baroda, India), a Master of Science (MS) from McGill University (Montreal, Quebec), and a Master of Business Administration (MBA) in Pharmaceutical Management from Drexel University (Philadelphia, USA). My *curriculum vitae* is provided herewith.

Samsung Bioepis Exhibit No. 1002
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2. I have reviewed the Office Action dated June 11, 2019 and provide the following statements.

3. Soliris® (eculizumab) satisfies a long-felt, but previously unmet need, for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH (see Appendix E). Soliris® (eculizumab) is not only the first FDA-approved anti-C5 antibody, but also the first FDA-approved treatment for PNH. In 2006, the FDA granted Soliris® (eculizumab) "Priority Review" status, demonstrating just how groundbreaking and transformative the FDA believed it could be for PNH patients (see Appendix D). Prior to FDA approval of Soliris® (eculizumab), patients with PNH had to suffer from debilitating symptoms, such as anemia, fatigue, thrombosis, hemoglobinuria, dyspnea, dysphagia, erectile dysfunction, hypertension and kidney problems for 10 to 15 years, with extremely limited treatment options (see Appendix D). In the absence of treatment, PNH resulted in a 5-year mortality rate of up to ~35% (see Appendix T). The FDA approval of the orphan drug Soliris® (eculizumab) in March 2007 marked a distinct change in how physicians were able to treat patients with PNH (see Appendices E-F). Importantly, Soliris® (eculizumab) has not only transformed the standard of care for PNH patients, but it has also significantly improved individual patient lives (see Appendices E-J). Specifically, treatment with Soliris® (eculizumab) has dramatically improved their quality of life and eliminated painful and debilitating symptoms that once plagued their lives and made day-to-day life challenging and unbearable (see Appendices G-J). Moreover, the cumulative survival rate increased from 66.8% before Soliris® (eculizumab) to 95.5% with Soliris® (eculizumab) (see Appendices U-W). It is the complete structure (*i.e.*, particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that imparts Soliris® (eculizumab) with the therapeutically advantageous features that made it the "gold" standard of treatment and forever changed the standard of care for PNH patients.

4. There are at least four instances of commercial copying of Soliris® (eculizumab):

A. Amgen is developing a biosimilar eculizumab ("ABP 959") for use in treating paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG) (see Appendix K).

B. Samsung Bioepis is developing a biosimilar eculizumab ("SB12") and is currently recruiting for a clinical trial to compare "SB12 (Proposed Eculizumab Biosimilar) to Soliris in subjects with Paroxysmal Nocturnal Haemoglobinuria" (see Appendices L-M).

C. Generium is developing a biosimilar eculizumab ("Elizaria®"), which launched in April 2019 in Russia (see Appendix N).

D. Biocad is developing a biosimilar of eculizumab ("BCD-148"), which was to be tested in a clinical trial alongside eculizumab in an early healthy volunteer study (see Appendix O).

These companies are copying Soliris® (eculizumab) and developing biosimilars because the antibody as a whole (*i.e.*, the antibody's complete sequence) renders it effective and advantageous in treating PNH, as claimed.

5. In 2008, Soliris® (eculizumab) received the Prix Galien USA Award for Best Biotechnology Product. The Prix Galien Award recognizes the technical, scientific and clinical research skills necessary to develop innovative medicines and is considered the industry's equivalent of the Nobel Prize, the highest accolade for biomedical research and innovation (see Appendix P). Soliris® (eculizumab) received this prestigious award because it is a groundbreaking, first-in-line treatment that is effective in treating PNH patients. It is the complete structure (*i.e.*, the particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that imparts Soliris® (eculizumab) with the features that has made it exceptionally therapeutically effective and worthy of the Prix Galien USA Award.

6. Soliris® (eculizumab) has been one of the twenty top selling biopharmaceutical products in recent history (see Appendix Q). Soliris® (eculizumab) has generated over one billion dollars of annual revenue during each of the last three years, and more than $3.4 billion

since its launch in 2007 has been attributed to sales for PNH treatment (see Appendices R-S). It is the complete structure (*i.e.*, the particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that impart Soliris® (eculizumab) with efficacious and advantageous functional features (*e.g.*, binds to C5 with sufficient affinity and specificity to prevent cleavage of C5, while not activating complement and having no effector function) that have made it a groundbreaking blockbuster product.

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; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or of any patent issued thereon.

Deepak Jain, MD, MBA — Date: Dec 10, 2019

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DEEPAK JAIN, MD, MBA
Boston, MA
==========

EDUCATIONAL QUALIFICATION

- M.D. from Maharaja Sayajirao University of Baroda, India
- Master of Science (MSc.) from McGill University, Montreal, Quebec
- MBA in Pharmaceutical Management from Drexel University, Philadelphia

PROFESSIONAL PROFILE

Excellent track record of leadership and advancement in the pharmaceutical / biotech industry spanning from global medical affairs, clinical development & strategic planning. I have extensive pre-launch, launch, life cycle management experience, and have developed and led high performing teams.

Clinical background covering wide range of therapeutic disciplines including Infectious disease (antiviral/antibacterial), Transplant (Liver, BMT), Medical Countermeasures (Anthrax/Vaccinia), Hematology (PNH, ITP), Immunology (PID), Neurology (Multiple Sclerosis, MG), and other areas in Internal Medicine.

Solid understanding of product launches & Life cycle planning for major brands Soliris, (WinRho (Plasma derived anti-D), HepaGam B (Plasma derived Hep IgG), AVONEX (recombinant IFN), Plegridy (recombinant IFN), Zerbaxa (Ceftolozane/tazobactam, Surotomycin including early asset development, health outcomes & market access challenges (Canada and EU), managed care & prescription benefit management, global regulatory, biomarker, pharmacovigilance & epidemiology, strategic planning & transactions.

Strong background in the development, roll out and implementation of early asset, pre-launch and in-market product integrated strategic summaries and functional plans.

Strong entrepreneurial drive, excelling in diversified, fast-paced, cross-functional teaming business environments, with a focus on building a high performing organization and culture.

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PROFESSIONAL HISTORY

May, 2018- Present — **Executive Director, Global Medical Affairs Leader Hematology and Global Program Team Leader, Ultomiris PNH**
Alexion Pharmaceuticals, Boston, MA

- Lead team of 3 direct reports Global Medical Directors and direct global medical affairs team to support Hematology therapeutic area
- Responsible to develop and implement global medical (TA) strategy and plan for GMA activities (pre-launch and post -launch as applicable) for Hematology by providing medical leadership, insight and strategy to TA global medical affairs team across functions and countries globally.
- Responsible for providing strategic direction and leading the Ultomiris PNH Global Program Team.
- Global Program Team Leader (GPTL), leads and chairs the Global Program Team (GPT), leading the creation of an integrated development plan, maintaining a strategic focus and ensuring the GPT's commitments are met.
- Lead on the situational assessment and the global product strategy development including harmonization of activities involving KOLs.
- Develop in-year global medical strategy, Implementation and budget plan for global initiatives
- Provide medical strategic recommendation for in-line life cycle management (LCM) and late phase pipeline programs
- Develop Phase 3b/4 and ISR evidence generation strategy for late phase pipeline and in-line TA programs
- Develop and oversee clinical study design (non-registration phase IIIb/IV, registries, outcomes research etc.) for late phase pipeline and in-line TA programs in close collaboration with relevant functions
- Provide medical review and ensure alignment with TA strategy of Investigator sponsored research (ISR) proposals
- Provide clear strategic guidance to scientific communication, internal medical training, external medical education (CME, Symposia, medical education), Medical info, PEVT teams in developing functional plans supporting global medical strategy
- Develop medically appropriate commercial strategy/tactic, planning and execution
- Provide global medical guidance to country medical teams in developing country medical plans aligned with global medical strategy
- Collaborate with country medical TA lead to ensure local activities are aligned with global medical strategy and that Global Medical is sufficiently aware of country insights and needs. Alignment among Global and Country Medical Plans, adjust if needed.
- Monitor team performance in terms of goals and delivery of global medical plans

- Responsible for development and execution of major registration LCM program and geographically expansion strategy

Mar, 2017- May, 2018 **Head of Medical Affairs Canada**
Alexion Pharmaceuticals, Vaughan, ON

- Lead Canadian strategic planning, all in-country Medical Affairs activities and manage the performance and development of the local Medical team.
- Led team of 4 direct reports (3 Medical Directors) and manage Canadian medical affairs group of 12

Canada Medical Affairs Management:

- Develop local Medical Plan aligned with Global TA Plan and manage execution
- Develop field-based medical teams objectives and performance metrics
- Assess and maximize the performance of the medical affairs team
- Lead and manage direct reports to ensure achievement of objectives, personal development, and ensuring the team is trained and equipped to achieve established goals
- Define the country Medical resource and budget needs and lead the Medical budget planning, resource allocation and budget management
- Manage country pharmacovigilance activities, in conjunction with Regional and Global pharmacovigilance
- Manage the country patient support program setup and execution
- Manage the country medical information function, ensure timely response to medical information inquiries and collation of requests, utilizing global medical information resources and in line with local regulatory requirements and company policy
- Identify training needs with other functional leaders and ensure implementation of training programs for the commercial teams and other functions, providing medical leadership and education in line with local and global strategy and preparing staff to handle interactions with customers

April, 2015- Feb, 2017 **Sr. Director, Medical Affairs/Global Medical Affairs Lead PNH**
Alexion Pharmaceuticals, Lexigton, MA

Lead and direct global medical affairs team to support Paroxysmal Nocturnal Hemoglobinuria therapeutic area for Soliris and ALXN1210

Global Medical Affairs Management:

- Lead the development and execution of Global Medical Affairs Plans in support of best clinical practices and overall corporate objectives aligned with Global Medical Affairs plans and commercial Brand strategy for Soliris and ALXN1210
- Develop Phase IIIb-IV data generation strategy (observational cohort/ registries. HEOR, Biomarker, label expansion for Soliris and ALXN1210
- Provide medical leadership, insight and strategy to all Alexion activities, collaborating across functions to ensure the highest level of medical support for all Alexion products within a therapeutic area that maximize patient outcomes
- Provide medical input to the development of impactful scientific and medical education
- Lead the implementation of medical affairs practices to assess new indications, the treating community, patient pathways, identifying patients for clinical research and to develop a thorough understanding of the disease area
- Support cross-functional teams to ensure patient-focused activities at all times, including rapid responses to internal and external requests for support to all stakeholders
- Engage thought leader network to support the successful execution of Global Medical Affairs tactics
- Establish and manage scientific/clinical relations with global KOL and identify emerging global KOLs of the therapeutic area
- Leadership in planning and development of Global Scientific Advisory boards/working groups with National Associations/Societies Medical lead in providing input and medical accuracy review for Outcomes Research (OR) teams to develop materials and programs to support (OR) initiatives in the preparation of formulary documents and Global Economic Dossiers

June 2013 – March, 2015 **Medical Director, Clinical Research & Medical Affairs/Global Medical Lead Zerbaxa & Surotomycin Cubist Pharmaceuticals, Lexington, MA**

- Lead the late phase clinical development strategy and execution for anti-infectives and acute care franchise and early access strategy (compassionate use, named patient program and Canadian Special Access Program)- Zerbaxa & Surotomycin
- Led team of 3 direct reports (1 Medical Monitors and 2 Clinical Research Scientist) to manage late phase clinical development program for Zerbaxa & Surotomycin

Clinical Program Management

- Develop Phase IIIb-IV data generation strategy (observational cohort/ registries. HEOR, Biomarker, label expansion, new indication(e.g. Nosocomial Pneumonia, Cystic Fibrosis, Bacteremia) for Ceftolozane/tazobactam

- Oversee the planning, execution and reporting of clinical studies for Surotomycin (Phase III)
- Ensure that studies planned by subsidiaries and affiliates fit into the global product strategy (global ←→regional ←→ local alignment)
- Oversee Clinical Trials Review Committee review process, protocol review and revision, and facilitate the development of an approved clinical trial protocol and the associated contractual documents
- Ensure appropriate documentation, tracking and retrievability of study activities
- Monitor performance of phase IIIb- IV activities (e.g. value creation through publication of clinical study results) and take corrective actions
- Contribute to continuous improvement of phase IV study related processes

KOL Management

- Engage thought leader network to support the successful execution of Global Medical Affairs tactics
- Establish and manage scientific/clinical relations with global KOL and identify emerging global KOLs of the therapeutic area

General Management and Leadership Activities

- Develop and led team to support product lifecycle initiatives
- Manage budget assigned to Phase IIIb & IV activities for life cycle management Oversee and monitor adherence to program timelines
- Member of Clinical Development Leadership Team

December 2011 – June, 2013 **Medical Director**
Biogen Idec, Boston, MA, USA

- Lead the Global Medical Affairs Team activities associated with product life cycle management of Interferon Beta-1a (AVONEX indicated for Multiple Sclerosis) and launch of Plegridy (Pegylated Interferon).

Global Medical Affairs Management:

- Guide cross-functional Medical Affairs teams to develop the Global Medical Affairs tactics in support of global brand plan strategies
- Develop and support short- and long-term goals of Global Medical Affairs with respect to prioritization of research interests and in collaborations local and regional Medical Affairs (global ←→regional ←→ local alignment)
- Develop Phase IIIb-IV data generation strategy (HEOR, Biomarker, label expansion, new indication etc) for Interferon franchise
- Develop and manage a thought leader network to support the successful execution of Global Medical Affairs tactics

General Management and Leadership Activities

- Provide leadership and oversight of the review and approval of scientific communication plans , global medical education as well as medical, marketing and sales training materials for individual markets
- Manage budget GMA budget for Avonex and Plegridy
- Oversee and monitor adherence to timelines of all GMA related activities

March 2008- December 2011 **Manager, Medical Affairs**
Cangene Corporation, Toronto, ON, Canada

Role/Responsibilities

- Lead the MSL Team activities associated with product life cycle management of WinRho SDF – Liquid and launch of HepaGam B
- Led team of 3 direct reports (2 MSLs and 1 Medical Information Scientist) to manage WinRho SDF – Liquid and launch of HepaGam B

Build Medical Affairs strategy and field based MSLs team

- Medical Lead for Hepatology, Infectious Disease and Hematology Portfolios.
- Advisory Board Meetings, investigator meetings and CMEs.
- Successful launch of new products (WinRho SDF – Liquid and HepaGam B)
- Development of Key Opinion Leaders (KOLs) for Canada plus ex-US market : Hepatology, Infectious disease specialist, Hematologist, Immunologist, Transplant surgeons, and Pharmacy Directors
- Interaction with Medical Affairs, Clinical Development and Commercial colleagues for development and implementation of medical strategies for key portfolios.
- Member of the Therapeutic Area Team and the Brand Team.
- Medical training to field force during launch of products as well as training programs at regular intervals.
- Support Market Access Team for successful product launch
- Review of promotional material. Slide decks and all other material related to promotion of the product to HCPs in accordance with Canadian PAAB regulations

Medical Information

- Established Medical information department, facilitated development of medical info process and setting up electronic database to capture medical info
- Ensured rapid and timely generation of ethical and scientific medical responses to questions posted by doctors.
- Sound experience in development of standard response letters, FQA and researching manuscripts/publications online.

Oct 2006- Feb 2008 **Clinical Research Scientist**
Cangene Corporation, Winnipeg, MB, Canada

- Development of the clinical research programs and clinical research protocol for Hepatitis, Anthrax and Vaccinia program
- CRO and site selection and contract negotiation Manage coordination of on-site monitoring, TMF filing, and clinical trial administration
- Writing investigator's brochure, clinical study report, package insert and other marketing documents.
- Presenting clinical study protocols and results to regulatory authorities and investigators
- Training medical affairs and sales team
- Networking with key opinion leaders
- Developing product development plans
- Planning and conducting market survey
- Strategic inputs for regulatory approval

Oct 2005 – Oct 2006 **Operations Manager**
Richardson Center, Winnipeg, MB, Canada

- Managing centre resources
- Financial management
- Management of all clinical and pre-clinical studies
- Purchasing analytical and pilot plant equipment
- Writing, establishing and enforcing SOPs related to GMP, GLP and GCP
- Commissioning and validating research equipment
- Develop operating budgets and strategic plans for the centre
- Networking with opinion leader and business development.

Mar 2002 – Apr 2004 **Medical Officer**
Bhailal Amin Hospital, Baroda, Gujarat, India

EDUCATION

2008- 2010 MBA in Pharmaceutical Management
Drexel University, Philadelphia

2004 – 2005 Master of Science
McGill University, Montreal, Quebec

1996 – 2002 Doctor of Medicine, MD
Maharaja Sayajirao University of Baroda, India.
(University degree recognized by World Health Organization (WHO) included a one year of rotating clinical internship)

CERTIFICATIONS

2007 Certified Clinical Research Professional (C.C.R.P.)
Awarded by Society of Clinical Research Associates (SoCRA).

MEMBERSHIPS

- Society of Clinical Research Associates (SoCRA)
- Canadian Society of Transplant (CST)
- American Association Study of Liver Disease (AASLD)
- American Society of Hematology (ASH)
- Drug Information Association (DIA)
- American Academy of Neurology (AAN)
- Consortium of Multiple Sclerosis Centers (CMSC)
- Infectious Diseases Society of America (IDSA)

CONTINUING EDUCATION

Mar 2015	Leadership and Decision Making, Harvard Professional Programs
Sep 2013	Negotiation & Dispute Resolution Program at Harvard Law School
Feb 2012	Media Training& Executive Speech Coaching
Feb 2010	Off-label Promotion vs. Scientific Exchange
Nov 2009	DIA Conference on Signal Detection and Data Mining
Oct 2009	Risk Management and Drug Safety Summit
May 2008	Public Speaking: Conveying Your Message with Confidence
Sep 2008	Ethics and Code of Conduct – Working on U.S. Gov. Contracts
Feb 2007	Submission Ready, Winnipeg Technical College
Feb 2007	Good Clinical Practice, CFPIE
Jan 2007	Report Writing, HCPAM
Dec 2006	Risk Management Strategy
Nov 2006	FDA Prescription Drug Labeling

REVIEWER

- Canadian Institutes of Health Research (CIHR) - China-Canada Joint Health Research Initiative Grants

PUBLICATIONS

Röth A, Maciejewski J, Nishimura J, **Jain D,** Weitz J. Screening and Diagnostic Clinical Algorithm for Paroxysmal Nocturnal Hemoglobinuria: Expert Consensus. Eur J Haematol. Mar 2018

Harding SV, Zhao HL, Marinangeli CP, Day AG, Dillon HF, **Jain D**, Jones PJ. Red algal cellular biomass lowers circulating cholesterol concentrations in Syrian golden hamsters consuming hypercholesterolaemic diets. Br J Nutr. 2009 Jun 16:1-6. (Cited by 10)

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CONFERENCE PRESENTATION

Röth A, Maciejewski J, Nishimura J, Jain D, Weitz J. Developing a Screening and Diagnostic Consensus-based Clinical Algorithm for Paroxysmal Nocturnal Hemoglobinuria: A Modified Delphi Panel Approach, EHA, 2017

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Jain D, Ebine N, Jia X, Kassis A, Marinangelia C, Hicks K, Moreau R and Jones P. Effects of corn fiber oil and plant stanols on plasma lipids and gene expression of intestinal sterol transporter in hamsters. Proceedings of Second Northern Lights Summer Conference, 48th Annual Meeting of the Canadian Federation of Biological Societies, Guelph Ontario.

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Electronic Patent Application Fee Transmittal	
Application Number:	15642096
Filing Date:	05-Jul-2017
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/Melissa St Germain
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:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
		Total in USD ($)		**1400**

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Electronic Acknowledgement Receipt	
EFS ID:	37993078
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/Melissa St Germain
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN5
Receipt Date:	11-DEC-2019
Filing Date:	05-JUL-2017
Time Stamp:	15:38:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1400
RAM confirmation Number	E2019BAF38553176
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Samsung Bioepis Exhibit No. 1002
Page 1731

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	2019_12_11_Petition_for_Extension_of_Time_--_AXJ-114BUSCN5.pdf	181576 b2dd2960fdd15487360c9832804b99d003134096	no	1
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4	Terminal Disclaimer Filed	AXJ-114BUSCN5_TD_and_373.pdf	2303202 21fb1e478fb9f35fd2fac6942004d0b4ad26e6d4	no	4
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Page 1735

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Information:					
			Total Files Size (in bytes):	17194312	

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.

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PTO/AIA/22 (03-13)
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 displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) AXJ-114BUSCN5
Application Number 15/642,096-Conf. #7606	Filed July 5, 2017
For TREATMENT OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA PATIENTS BY AN INHIBITOR OF COMPLEMENT	
Art Unit 1644	Examiner J. L. Rogers

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐ Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☒ Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 1,400.00
☐ Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐ Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-1196 .

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☒ attorney or agent of record. Registration number 60,760 .

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____ .

/Jill Gorny Sloper, Esq./ — Signature
December 11, 2019 — Date

Jill Gorny Sloper, Esq. — Typed or printed name
617-217-4630 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of 1 forms are submitted.

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

Dated: December 11, 2019 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Electronic Patent Application Fee Transmittal	
Application Number:	15642096
Filing Date:	05-Jul-2017
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/Anita Costa
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:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**240**

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Page 1739

Electronic Acknowledgement Receipt	
EFS ID:	37989115
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:	11-DEC-2019
Filing Date:	05-JUL-2017
Time Stamp:	16:19:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$240
RAM confirmation Number	E2019BAG19464127
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Samsung Bioepis Exhibit No. 1002
Page 1740

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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2	Foreign Reference	WO2004035607A2.pdf	10212581 d6aa52bd1dc8065c37da8155a32a5acd4cc6a74c	no	201
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3	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2045_-_2007_USP_Dictionary_of_USAN_and_Intl_Drug_Names.pdf	1037635 a9bbb815caeca479e3830dc5c7ae84b2998b2ad5	no	85
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Page 1741

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Page 1742

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Page 1744

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35	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2077-_Chain_of_Custody_Log.pdf	1096954 ecec350735ca00feeeea42b411accd56371aa278	no	1
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38	Non Patent Literature	AXJ-114BUSCN5_-_IPR2019-00740_DI_Final.pdf	1386288 3f5949e515c19664b655c18b186b2efc622731a9	no	69
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39	Non Patent Literature	AXJ-114BUSCN5_-_IPR2019-00741_DI_final.pdf	2692581 9da987fd0c3406ccbb5bb198cf812ac247d86097	no	61
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42	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2056_BAZARKO_DECLARATION_880.pdf	258119 9ccd3f08da49cc5752546e98ace5824b435498a8	no	7
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48	Non Patent Literature	AXJ-114BUSCN5_-_Declaration_of_Dr_Laural_Boone.pdf	2975314 fa639b86ed1eb083168ae6adea96c4f429621e3f	no	8
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49	Non Patent Literature	AXJ-114BUSCN5_-_Declaration_of_Dr_Leonard_Bell.pdf	1439250 2883aed2c061bc666d089c8a16eefce3b7721439	no	4
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51	Non Patent Literature	AXJ-114BUSCN5_-_Denosumab_Drug_Bank_accessed_November_04_2019.pdf	326711 f8dba94f3729796bc336af2201646e66a183cd85	no	6
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58	Non Patent Literature	AXJ-114BUSCN5_-_161723358_Alexion_Pharmaceuticals_Inc_Written_Submission_in_Response_to.pdf	1466605 26e3f5ab844c3956dcbcf046e30f4cc26e73c19d	no	23
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59	Non Patent Literature	AXJ-114BUSCN5_-_Bombara_Declaration.pdf	5448766 4ce664ea47b53e96ac8914eb6e11f7fa7e9f5c1a	no	90
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(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

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	1	European Application No. 11001632.6 Hoffmann Eitle's Response to the Statement of Grounds of Appeal filed by the Appellant on June 24, 2019, dated November 8, 2019, 45 pages.	
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	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN5

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.	T5
	1	2007 USP Dictionary of USAN and International Drug Names, 85 pages.	
	2	Alexion Form 10-K for FY 2008 (Excerpts) 3 pages.	
	3	Alexion Form 10-K for FY 2009 (Excerpts) 3 pages.	
	4	Alexion Form 10 K for FY 2011 (Excerpts) 3 pages.	
	5	Alexion Form 10-K for FY 2007 (Excerpts) 3 pages.	
	6	Alexion Form 10-K for FY 2010 (Excerpts) 3 pages.	
	7	Alexion Form 10-K for FY 2016 (Excerpts) 3 pages.	
	8	Alexion Form 10-K for FY 2017 (Excerpts) 3 pages.	
	9	Alexion Form 10-K for FY 2018 (Excerpts) 3 pages.	
	10	Alexion Form 10-Q for Q1 of FY 2019 (Excerpts) 3 pages.	

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	11	Alexion Form 10-Q for Q2 of FY 2019 (Excerpts) 3 pages.	
	12	Alexion Form 10-Q for Q3 of FY 2019 (Excerpts) 3 pages.	
	13	Alexion Form 10-K for FY 2012 (Excerpts) 3 pages.	
	14	Alexion Form 10-K for FY 2013 (Excerpts) 3 pages.	
	15	Alexion Form 10-K for FY 2014 (Excerpts) 3 pages.	
	16	Alexion Form 10-K for FY 2015 (Excerpts) 3 pages.	
	17	Alexion Pharmaceuticals, Inc. Form 10-K for the fiscal year ending December 31, 2018 (excerpts), 3 pages.	
	18	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris(TM) (eculizumab)," 2 pages (Sept. 20, 2006).	
	19	Alexion Press Release, "Alexion Submits Market Authorization Application for Soliris(TM) (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency," 2 pages (Sept. 26, 2006).	
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	22	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen's Inc.'s Objections to Evidence," Case IPR2019-00739, filed December 2, 2019, 9 pages.	
	23	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen's Inc.'s Objections to Evidence," Case IPR2019-00740, filed December 2, 2019, 9 pages.	
	24	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen's Inc.'s Objections to Evidence," Case IPR2019-00741, filed December 2, 2019, 9 pages.	
	25	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Response Pursuant to 37 C.F.R. § 42.120," Case IPR2019-00739, filed November 22, 2019, 80 pages.	
	26	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Response Pursuant to 37 C.F.R. § 42.120," Case IPR2019-00740, filed November 22, 2019, 80 pages.	
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	29	ATCC Packing Slip, 1 page (2019).	
	30	ATCC Product Sheet HB11625, 2 pages (2019).	
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	35	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00739, dated August 30, 2019, 65 pages.	
	36	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00740, dated August 30, 2019, 69 pages.	
	37	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00741, dated August 30, 2019, 61 pages.	
	38	Declaration of Arturo Casadevall and Curriculum Vitae, dated November 22, 2019, 251 pages.	
	39	Declaration of Bernhardt L. Trout, Ph.D. and Curriculum Vitae, dated November 22, 2019, 95 pages.	
	40	Declaration of Daniel Bazarko, dated November 22, 2019, 7 pages.	
	41	Declaration of Michel C. Nussenzweig, M.D., Ph.D. and Curriculum Vitae, dated November 21, 2019, 55 pages.	
	42	Deposition Transcript of Joseph P. Balthasar, Ph.D., Amgen, Inc. v. Alexion Pharmaceuticals, Inc., 342 pages (Oct. 23, 2019).	
	43	Dmytrijuk, A. et al., "FDA Report: Eculizumab (SOLIRIS®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, The Oncologist, vol. 13:993-1000 (2008).	

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	44	European Application No. 11001632.6 Amgen's Response to the Statement of Grounds of Appeal filed by the Appellant on June 24, 2019, dated November 8, 2019, 47 pages.	
	45	European Application No. 11001632.6 Declaration of Dr. Bruce Andrien, dated May 23, 2017, 23 pages, cited in Opposition.	
	46	European Application No. 11001632.6 Declaration of Dr. Laural Boone, dated May 11, 2017, 8 pages, cited in Opposition.	
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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)	2019-12-11
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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Examiner Name	J. L. Rogers
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	12	Alexion Form 8-K for FY 2019 (Excerpts) 3 pages, September 5, 2019.	

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Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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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
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Attorney Docket Number:	AXJ-114BUSCN5
Receipt Date:	11-DEC-2019
Filing Date:	05-JUL-2017
Time Stamp:	16:20:55
Application Type:	Utility under 35 USC 111(a)

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10	Non Patent Literature	EXH_2089_-_Generium_Elizaria.pdf	86132 1e1abc0837d69615c1e79171d93b7d9c13beb5f7	no	2
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11	Non Patent Literature	EXH_2075_-_GenScript_Final_Report.pdf	368377 554917741e9634133e81eb8f56d4da4e6a8e6948	no	4
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12	Non Patent Literature	EXH_2076_-_GenScript_Sequencing_Record.pdf	890395 20c1c2af53ec55c7999834987baf52117b57c1d2	no	4
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13	Non Patent Literature	Project_Proposal_for_Monoclonal_Antibody_Sequencing_Service.pdf	1581380 8468ab2818ea75be10c0212ace828941470 2b746	no	3
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14	Non Patent Literature	AXJ-114BUSCN5_-_GREENSPAN.pdf	947396 2df3172aa35f4ed75e3c8f2bc2e56ab68de1c2ae	no	5
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15	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2046_-_1997_INN_Naming_Guidelines.pdf	2185545 e7f6d5cba47629dc1aa3d150abc66cfcceb8f6ad	no	41
Warnings:					
Information:					

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Page 1774

16	Non Patent Literature	AXJ-114BUSCN5_-_Haller_et_al_Safety_Issues_Specific_to_Clinical_Development.pdf	162987 7f6517c7b40e2cf2320ecd587d559bcfc8986df3	no	4
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17	Non Patent Literature	EXH_2091_-_Harlowe_and_Lane_.pdf	12118447 c56cc368ac440ba327c62e4650c6160ad57648ab	no	7
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18	Non Patent Literature	AXJ-114BUSCN5_-_HAWKINS.pdf	1740772 1ecfb2b9e57d41f23e76c39ab2601d40ad674941	no	7
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The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
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19	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2049__-_HemeOnc_Today.pdf	263796 26efb6cf82e58d8036fdc6b30140158c1acdc382	no	9
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20	Non Patent Literature	EXH_2081_-_Hermeling.pdf	848554 9e3baaa3814948884db2950c34fc62146748bf332	no	7
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21	Non Patent Literature	AXJ-114BUSCN5_-_Hill_et_al_Erythropoietin_treatment_during_complement_inhibition_with.pdf	599642 9736d4e0d44a4513074ce60458b9247ba1aa81c9	no	10
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22	Non Patent Literature	HILLMEN_Long-term_effect_of_the_complement_inhibitor_eculizumab.pdf	130493 2d32ee2748569fe4d9545962636ceb3a684ca2d7	no	7
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23	Non Patent Literature	HILLMEN_Long-term_safety_and_efficacy_of_sustained.pdf	212552 bcd944ee8b3a8394d6c11c50ffa9c2fff1299f60	no	12
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24	Non Patent Literature	HILLMEN-NATURAL_02.pdf	506472 6e620f15ac4518ae24b706c820a01d51e2c4e588	no	6
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25	Non Patent Literature	AXJ-114BUSCN5_-_Hwang_et_al_Immunogenicity_of_engineered_antibodies_SCIENCE.pdf	984680 09ba2ec90c7dc6220b6cd5ff3a74eeeef074aab9	no	8
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26	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2084_-_ICH_Topic_Q5C.pdf	209443 1383c2508c725d8d397286f97d990e3cc7162706	no	9
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27	Non Patent Literature	AXJ-114BUSCN5_-_JANDA.pdf	3052222 eb52c08023ab478ada533be4fd191751aaedf8d8	no	10
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Information:					
28	Non Patent Literature	AXJ-114BUSCN5_-_Janeway_and_Travers_Immunobiology_The_Immune_System_in_Health_.pdf	2110503 fd5201652812ffe1372f0c25efb43210ab2f8898	no	12
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29	Non Patent Literature	AXJ-114BUSCN5_-_JANEWAY_Janeway_et_al_Immunobiology_The_Immune_System_in_Health_and.pdf	4716820 b064af599bbc9295d4c89fbfe39979d7a2afa84d	no	6
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Page 1776

30	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2053_-_Soliris_Current_Label_06-2019_Label.pdf	604553 d2ce79fd38528cb89202a9f36e1e82637805f010	no	35
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31	Non Patent Literature	KELLY.pdf	542857 9fc117f5f10731f4af57878af7917a6ac0550e91	no	7
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33	Non Patent Literature	AXJ-114BUSCN5_-_Lo_Benny_K_Antibody_Engineering_Methods.pdf	12159204 38565b18081deb6aeea0944dbe05846c7f1ebb26	no	28
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34	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2042_-_Mathieu_2004.pdf	2373430 4d010694a92bd02b99a1e81e2e163e95e8219799	no	22
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36	Non Patent Literature	AXJ-114BUSCN5_-_McLean.pdf	4314678 663c5163ccd6e2c560b3fde1491cf6de43e8d602	no	11
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37	Non Patent Literature	AXJ-114BUSCN5_-_Points_to_Consider_in_the_Manufacture_and_Testing_of_Monoclonal.pdf	796249 ed6dd8e2cdfa55a72ff6ffdc87c0952a3db1ddbf	no	50
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40	Non Patent Literature	AXJ-114BUSCN5_-_RADBRUCH.pdf	460676 689d16816f197a391b37b9cb5322f30a28a0c354	no	3
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41	Non Patent Literature	AXJ-114BUSCN5_-_Ricklin__Lambris.pdf	1260702 27c9f421df75f8983961e3372d044a8cedfab684	no	11
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42	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2083_-_Rosenberg.pdf	263133 b3853aed447a79fdbf250b263e3670e65d7209a5	no	7
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43	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2090_-_Samsung_Biosimilar_Pipeline.pdf	95398 9be24710167e8ec8e62961c9dbb1ca9a22f2bf12	no	3
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44	Non Patent Literature	AXJ-114BUSCN5_-_SHEPPARD.pdf	919629 145f6d33b4c2bbee68acd5749098649848e54a41	no	11
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46	Non Patent Literature	TORRES_2007.PDF	1230473 5963c58123014d7d6655787109de8c07c67ce5a4	no	10
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47	Non Patent Literature	AXJ-114BUSCN5_-_Torres.pdf	1383687 b3fda070ca5f567bcc5e48bf8dc0321e159026bd	no	11
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48	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2040_-_Torres_2005.pdf	1246890 cd9e38ce36c6f7c4798db18629b18cf4a938e20a	no	11
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49	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2085_-_Q1AR2_Stability_Testing_Guidance.pdf	302799 1fc7d4ee0a3e14b02fb62c872b47648dbfb5b5ef	no	25
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50	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2080_-_Wang_1999.pdf	1113530 a21d136d8eb73c7c1290459de092139aaeb8f904	no	60
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Information:					

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Page 1779

51	Non Patent Literature	AXJ-114BUSCN5_-_Welt_et_al_Phase_I_Study_of_Anticolon_Cancer.pdf	253276 12cf2444668757 4a4150739d59fb765afdb71351	no	10
Warnings:					
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52	Non Patent Literature	AXJ-114BUSCN5_-_EXH_2052_-_Xiang_1995_1.pdf	217662 5690393f41fafd1e889d2a0c0bc668caa3a61428	no	6
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Information:					
53	Non Patent Literature	SEC_8K_09052019.pdf	35919 aea61846f445dbb7c9b3d84c86bb33362eb73855	no	3
Warnings:					
Information:					
54	Transmittal Letter	AXJ-114BUSCN5_-_IDSTRANS_02.pdf	27004 1d0c7ad1a51dda139d45f471f1afc595b5e886ca	no	2
Warnings:					
Information:					
55	Information Disclosure Statement (IDS) Form (SB08)	SB02.pdf	1037615 5abd178a60357c453bc7818472605537cdb30757	no	8
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56	Information Disclosure Statement (IDS) Form (SB08)	SB01.pdf	1036390 d0c26f175aceee84e3f8fe67fe124561142287 83d	no	8
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Information:					
57	Non Patent Literature	McClean_2005.pdf	936640 c5ed73830da82f66a0c043170d8ab82ceca15842	no	9

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58	Information Disclosure Statement (IDS) Form (SB08)	SB03.pdf	1035493 90ac5c762c0310f801906dcbb110c799a77dc546	no	5
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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

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

New International Application Filed with the USPTO as a Receiving Office

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Page 1781

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Dated: December 11, 2019
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

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. 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/or U.S. patent applications.

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

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Page 1782

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 after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

Please charge our Deposit Account No. 50-1196 in the amount of $240.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed to our Deposit Account No. 50-1196, under Order No. AXJ-114BUSCN5.

Dated: December 11, 2019

Respectfully submitted,

Electronic signature: /Jill Gorny Sloper, Esq./
Jill Gorny Sloper, Esq.
Registration No.: 60,760
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One Post Office Square, 30th Floor
Boston, Massachusetts 02109-2127
617-217-4630 (Tel)
617-217-4699 (Fax)
Attorney/Agent For Applicant

PTO/SB/06 (09-11)
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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

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ 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 $80 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $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).				
☐ 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	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	12/11/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	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

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ 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.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/DORIS M BURNS/
*** 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.	

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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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AXJ-114BUSCN5

In re Application of: Leonard BELL *et al.*

Application No.: 15/642,096-Conf. #7606

Filed: July 5, 2017

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

The applicant, Alexion Pharmaceuticals, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. (see attached) as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

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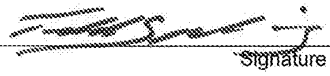
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is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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2. [ ] The undersigned is an attorney or agent of record. Reg. No. _____



Signature — 12/13/19 Date

Todd Spalding
Typed or printed name

Vice President, Head of Intellectual Property
Title — Telephone Number

[X] Terminal disclaimer fee under 37 CFR 1.20(d) included.

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Dated: December 11, 2019 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

SUPPLEMENTAL SHEET FOR TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) AXJ-114BUSCN5

Prior patent Nos. applicable to this terminal disclaimer (referenced on first page):

9,732,149
9,718,880
9,725,504
9,409,980
9,415,102
9,556,263
9,352,035
9,925,262
10,239,937

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Alexion Pharmaceuticals, Inc.

Application No./Patent No.: 15/642,096 Filed/Issue Date: July 5, 2017

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

Alexion Pharmaceuticals, Inc. , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):
   - [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
   - [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

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   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Mark J. Evans To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 042921, Frame 0158, or for which a copy thereof is attached.

2. From: Leonard Bell To: Alexion Pharmaceuticals, Inc.
   The document was recorded in the United States Patent and Trademark Office at Reel 042921, Frame 0063, or for which a copy thereof is attached.

[Page 1 of 2]

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: Russell P. Rother To: Alexion Pharmaceuticals, Inc.
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The document was recorded in the United States Patent and Trademark Office at
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☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	Date: 12/13/19
Todd Spalding	Vice President, Head of Intellectual Property
Printed or Typed Name	Title or Registration Number

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

Dated: December 11, 2019 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

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

Dated: December 11, 2019
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

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: James L. Rogers

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

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

Dear Sir:

In response to the Office Action dated June 11, 2019, please amend the above-identified U.S. patent application as follows:

Listing of Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

Samsung Bioepis Exhibit No. 1002
Page 1789

LISTING OF CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-51. (Canceled)

52. **(Previously presented)** 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. **(Previously presented)** 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. **(Previously presented)** 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. **(Previously presented)** The method of claim 54, wherein the patient is treated with the antibody for at least 26 weeks.

56. **(Previously presented)** 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. **(Previously presented)** 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. **(Previously presented)** 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. **(Previously presented)** The method of claim 58, wherein the patient is treated with the antibody for at least 26 weeks.

REMARKS

Applicants acknowledges with appreciation the in-person interview with the Examiner and his supervisor on November 12, 2019, during which the following rejections were discussed.

Claims 52-59 are pending. *No new matter has been added.*

Information Disclosure Statement

Applicants acknowledge with appreciation the Examiner's indication that the Information Disclosure Statements submitted on August 22, 2017, March 28, 2018, April 27, 2018, and April 29, 2019 have been considered. Applicants submit herewith a Supplemental Information Disclosure Statement to make of record additional information for the Examiner's consideration.

Rejection of Claim 52-59 under 35 U.S.C. § 103(a)

Claim 52 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), Wang (US 2005/0271660), and Bowdish *et al.* (US 2003/0232972).

In addition, claims 52-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen *et al.*, in view of Evans *et al.*, Wang, and Bowdish *et al.*, as applied to claim 52, and further in view of Bell *et al.* (US 2005/0191298).

A. Rejection of Claim 52

Claim 52 is directed to 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.

The Examiner relies on Hillmen *et al.* for teaching a method of treating a paroxysmal nocturnal hemoglobinuria (PNH) patient by administering an effective amount of eculizumab. The Examiner relies on Evans *et al.* for teaching effective doses of eculizumab and that it is

within the skill of the art to determine the optimal dose. While the Examiner acknowledges that neither Hillmen *et al.* nor Evans *et al.* teach "a 300 mg single unit dosage as recited in the claims", the Examiner asserts that it would have been obvious to modify the teachings of Hillmen *et al.* and Evans *et al.* to arrive at a 300 mg dosage.

Moreover, the Examiner alleges that one of ordinary skill in the art would have had a reasonable expectation of success in making a 10 mg /ml solution of the antibody in a sterile, preservative free solution in view of Wang, which the Examiner alleges teaches that eculizumab is highly soluble, including up to 30 mg per ml and can be formulated in a sterile, preservative free solution. While the Examiner acknowledges that neither Hillmen *et al.*, Evans *et al.*, nor Wang teach an antibody having the presently claimed heavy chain consisting of SEQ ID NO:2 and light chain consisting of SEQ ID NO:4, the Examiner nonetheless concludes that:

> [i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Bowdish's TPO mimic amino acid sequence in Bowdish's H chain published SEQ ID NO:67 which is 96% identical with currently claimed H chain SEQ ID NO:2 with Evan's CDR3 5G1.1 eculizumab amino acid sequence, thereby arriving at a H chain sequence having 100% sequence identity to currently claimed H chain SEQ ID NO:2 and to have combined that H chain sequence with Bowdish's L chain SEQ ID NO: 68 that has 100% sequence identity to currently claimed L chain SEQ ID NO:4.

Applicant respectfully traverses the rejection. To establish a *prima facie case of obviousness*, it must be demonstrated that the presently claimed invention constitutes nothing more than a combination of known elements ***yielding a predictable result***, and that one of ordinary skill in the art would have had a ***clear reason to combine the elements***, as well as the technical ability to do so, based on the teachings and motivation provided by the prior art (see *KSR International Co. v. Teleflex Inc. et al*.127 S. Ct. 1727 (2007) ("*KSR International Co.*") and *Ecolab, Inc. v. FMC Corp.*, 569 F. 3d 1335 (Fed. Cir. 2009) ("*Ecolab, Inc.*")). The cited references fail to render the presently claimed invention obvious, at least because ***they provide no motivation, let alone a reasonable expectation of success***, in arriving at the claimed invention. Moreover, the secondary indicia of non-obviousness presented by Applicant herein (discussed below) provide clear, factually supported evidence, that the invention was non-obvious prior to the relevant filing date (see, *e.g.*, *Transocean Offshore Deepwater Drilling, Inc.*

v. Maersk Drilling USA, Inc., 699 F.3d 1340, 1349 (Fed. Cir. 2012)), noting objective evidence of non-obviousness "may often be the most probative and cogent evidence in the record" and "may often establish that an invention appearing to have been obvious in light of the prior art was not").

1. **The Relevant Literature Prior to March 15, 2007 Repeatedly and Consistently Described "Eculizumab" as Having an IgG4 Heavy Chain Constant Region**

Prior to March 15, 2007, the priority date of the present application, the unique amino acid sequence of the antibody in Soliris® (eculizumab) recited in the pending claims was not publicly known or disclosed in the prior art. In particular, while a person of ordinary skill in the art as of that date would have known that Alexion had designed and clinically tested an antibody named "eculizumab," the person of ordinary skill in the art would not have known that "eculizumab" had the uniquely-engineered amino acid sequence claimed in the present application. That is because the literature as of March 15, 2007 – shown by at least eight publications listed in Table 1 below – consistently identified "eculizumab" as the antibody described in the "Thomas" publication (Thomas TC, *et al.*, Mol. Immunol., 1996;33:1389-1401), which has a naturally-occurring "IgG4" heavy chain constant region. Accordingly, a person of ordinary skill in the art as of March 15, 2007 would have had no doubt that "eculizumab" was Thomas's IgG4-isotype humanized antibody, because the pertinent literature consistently and unambiguously said so:

Table 1: References to "Eculizumab" as Thomas's Humanized IgG4 Antibody

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hillmen 2004 (Hillmen, P., *et al.*, "Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria," *N. Engl. J. Med.* 350:552-559 (2004)) at 553 – Phase II clinical trial for treatment of PNH	"***Eculizumab is*** a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components." (Citing ***Thomas***, Ref. No. 15)

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Hill 2005 (Hill, A., *et al.,* "Sustained response and long-term safety of eculizumab in paroxysmal nocturnal Hemoglobinuria," Blood 106: 2559-2565 (2005)) at 2559 – 52-week extension of Hillmen 2004 Phase II clinical trial	"***Eculizumab is*** a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage." (Citing ***Thomas***, Ref. No. 9)
Hillmen 2006 (Hillmen, P., *et al*., "The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria," *N. Engl. J. Med.* 355:1233-1243 (2006)) at 1234 – pivotal Phase III clinical trial for treatment of PNH,	"***Eculizumab (Soliris, Alexion Pharmaceuticals) is*** a humanized monoclonal antibody directed against the terminal complement protein C5." (Citing ***Thomas***, Ref. No. 13)
Hill 2007 (Hill, *et al*., Erythropoietin treatment during complement inhibition with eculizumab in a patient with paroxysmal nocturnal hemoglobinuria, THE HEMATOLOGY JOURNAL, 31-33, 2007**)** – post-Phase III case report for PNH patient	"***Eculizumab is*** a novel humanized monoclonal antibody directed against the complement protein C5." (Citing ***Thomas***, Ref. No. 6)
Bell (Bell, L. and Rother, R., "Method of Treating Hemolytic Disease," U.S. Patent Application Publication No. 2005/0191298 Al (filed February 3,2005; published September 1, 2005)) at [0052] –Phase II clinical studies described in Hillmen 2004 and Hill 2005	States that "[m]ethods for the preparation of h5G1.1-mAb" are described in ***Thomas***, and that "[t]he antibody h5G1.1-mAb is currently undergoing clinical trials under the name ***eculizumab***."
Kaplan (Kaplan, M., "Eculizumab (Alexion)," Curr. Opin. Investig. Drugs 3: 1017-1023 (2002)) at 1018	States that "***Eculizumab*** (5G1.1), under development by Alexion Pharmaceuticals Inc. is a humanized C5 inhibitory monoclonal antibody (mAb)," and cites ***Thomas*** for the synthesis and complement-blocking activity of "intact humanized 5G1.1 antibody" or "humanized 5G1.1"

Exhibit	Statement Identifying "Eculizumab" as the IgG4 Humanized Antibody of Thomas
Brekke (Brekke, 0. and Sandlie, I., "Therapeutic antibodies for human diseases at the dawn of the twenty-first century," Nature Reviews Drug Discovery 2: 52-62 (2003)) at 56	"***Eculizumab*** (5G1.1; Alexion Pharmaceuticals) ***is*** a humanized monoclonal antibody that prevents the cleavage of human complement component C5 . . . ." (citing ***Kaplan***, Ref. No. 31, which in turn cites to ***Thomas***)
Pierangeli (Pierangeli, S., *et al.*, "Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia," Arthritis & Rheumatism 52: 2120-2124 (2005)) at 2123	Stating that "***eculizumab*** has been shown to prevent C5 activation in humans and to have beneficial effects in patients with [PNH] . . . ." (citing to ***Hillmen 2004***, Ref No. 18, which in turn cites to ***Thomas***)

Looking at this literature, a person of ordinary skill in the art as of March 15, 2007 would have believed that Thomas's IgG4 antibody was the ***only*** full-length humanized antibody shown to bind C5 and prevent its cleavage, that had been tested for safety and efficacy in treating PNH, and that had been submitted to the FDA for marketing approval.[1] In Thomas, a person of ordinary skill in the art would have seen the extensive work in rationally designing an "intact," full-length anti-C5 humanized monoclonal antibody using an IgG4 isotype. In the published literature that followed Thomas, a person of ordinary skill in the art as of March 15, 2007 would have seen how researchers had fully established "eculizumab" – consistently identified as Thomas's IgG4 antibody – to be safe and effective in treating PNH, applying for FDA and European approval for that antibody under the trade name Soliris®.

Contrary to the Examiner's assertion, while Hillmen *et al.* discusses administering "eculizumab" for treating PNH, ***nowhere*** does this reference teach the structure of the antibody, let alone the uniquely-engineered heavy chain constant region amino acid sequence of SOLIRIS® (eculizumab) reflected in SEQ ID NO: 2. Instead, as noted above in Table 1, Hillmen *et al.* references Thomas to further describe "eculizumab," which in turn taught an antibody with an

[1] Thomas also does not disclose the specific light chain amino acid sequence recited in SEQ ID NO: 4 of the present claims. In particular, the light chain variable region sequence provided by Thomas differs from SEQ ID NO: 4 at amino acid position 38, flanking light chain CDR1.

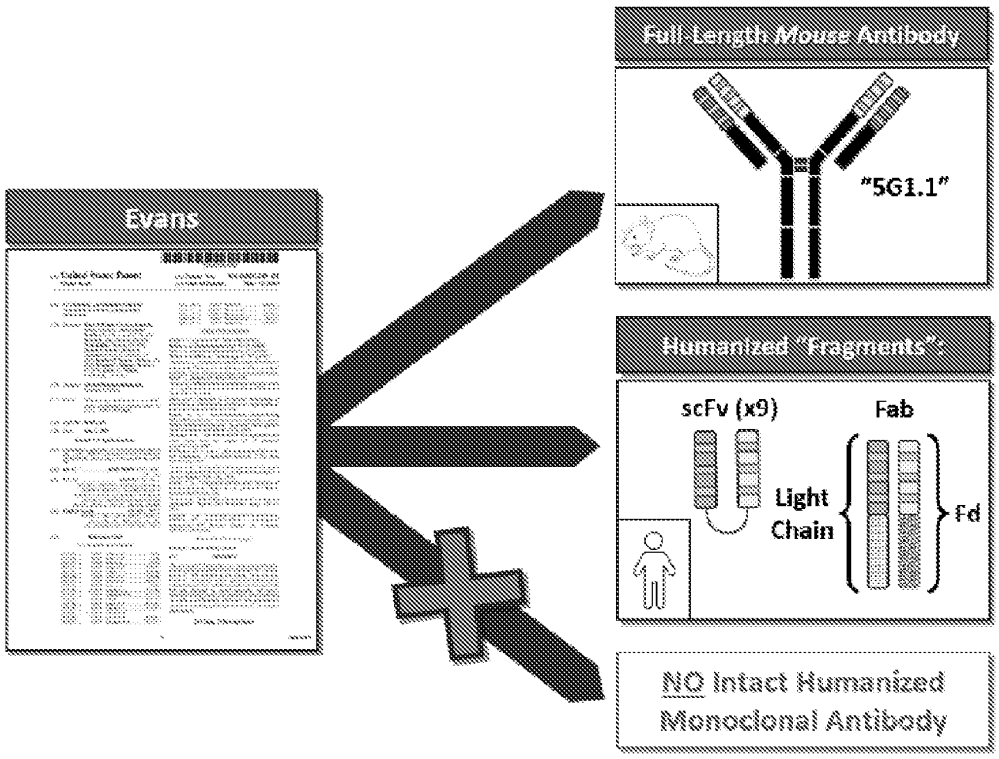
IgG4 heavy chain constant region having a very different amino acid sequence from the heavy chain constant region reflected in SEQ ID NO: 2. Accordingly, a person of ordinary skill in the art as of March 15, 2007 reading Hillmen *et al.* would have envisioned that the "eculizumab" antibody shown in that study to be safe and effective for treating PNH was the ***IgG4*** isotype antibody described in Thomas. Hillmen *et al.* clearly would have led a person of ordinary skill in the art in a direction divergent from the path that was taken by the present invention *i.e.*, towards the IgG4 antibody of Thomas, as opposed to the very different, uniquely-engineered antibody encompassed by the pending claims (see *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017)).

2. Evans *et al.* Does Not Disclose Any Full-Length Humanized Antibodies

Evans *et al.* fails to make up for the deficiencies of Hillmen. In contrast to Thomas and the literature regarding "eculizumab" that followed, a person of ordinary skill in the art would have understood that Evans *et al.* did ***not*** disclose "eculizumab." Rather, a person of ordinary skill in the art would have understood that Evans *et al.* describes an earlier stage of research that predated the design of the intact, full-length humanized antibody "eculizumab" – because Evans *et al.* does not disclose any full-length humanized antibodies. At most, a person of ordinary skill in the art would have read Evans *et al.* as a precursor to the research that resulted in "eculizumab." In fact, the only full-length antibody described in Evans *et al.* is the "5G1.1" mouse antibody, which Evans *et al.* obtained from the "5G1.1" hybridoma (Evans *et al.*, 19:47-49 and Figs. 18-19). Evans *et al.* further describes the researchers' characterization of the "5G1.1" mouse antibody, including its binding affinity, in vitro activity blocking complement in hemolytic assays, and the sequencing and cloning of the variable regions of the "5G1.1 mouse antibody" (Evans *et al.*, Examples 7-10). But Evans *et al.* provides no such information for a full-length humanized antibody derived from the "5G1.1" mouse antibody – which a person of ordinary skill in the art would have understood would have a different amino acid sequence and different clinical properties from the mouse antibody, as attested to by Arturo Casadevall, an independent expert consultant, a Bloomberg Distinguished Professor of Molecular Microbiology & Immunology and Infectious Diseases at the Johns Hopkins Bloomberg School of Public

Health, and the Alfred and Jill Sommer Professor and Chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health (see ¶126 of the Declaration of Arturo Casadevall; Appendix A).

To the extent Evans *et al.* describes "humanization" work based on the "5G1.1" mouse antibody, it was the development of recombinant "fragments" – scFv or Fab – that did not contain an intact heavy chain constant region, let alone the uniquely-engineered heavy chain constant region reflected in SEQ ID NO: 2 of the present application (see Example 11 of Evans *et al*. and ¶126 of the Declaration of Arturo Casadevall; Appendix A). For example, Evans *et al.* describes nine different humanized "scFv" fragments, which are recombinantly-produced molecules containing two variable regions connected by a linker, with no constant region (Evans *et al.*, 43:6-14 and 43:62-45:4), and humanized "Fab" fragments that also lack the "Fc" portion (regions CH2 and CH3) of an intact antibody (Evans *et al.* 43:21-61 and ¶126 of the Declaration of Arturo Casadevall; Appendix A). Notably, the humanized Fab fragments of Evans *et al.* have different heavy chain sequences ("Fd," Evans SEQ ID NOs: 11 and 12) from the non-prior art SEQ ID NO: 2 of the present application, including in the "CH1" constant region (¶12 of the Declaration of Arturo Casadevall; Appendix A). The following figure illustrates how a POSA would have understood what Evans *et al*. did disclose – a mouse antibody and humanized "fragments" – and what Evans *et al*. did <u>not</u> disclose, *i.e*., an intact humanized monoclonal antibody:



In sum, nothing in Evans *et al.*, suggests or discloses constructing the uniquely-engineered heavy chain constant region set forth in SEQ ID NO: 2, and one of ordinary skill in the art as of March 15, 2007 would not have been motivated to make the heavy chain constant region set forth in SEQ ID NO:2, since they would have understood from the literature that the IgG4 isotype antibody of Thomas was clinically successful. Accordingly, like Hillmen *et al.*, Evans *et al.* would not have led one of ordinary skill in the art to make an antibody with the specific sequence encompassed by the pending claims.

3. <u>A Person Skilled in the Art Would Have Had No Reason to Look to Bowdish *et al.*, and, Even Looking to Bowdish, a Person Skilled in the Art Would Not Have Combined Various Portions of Various Sequences to Arrive at the Claimed Sequence</u>

Bowdish *et al.* concerns using an antibody – ***any*** antibody – as a "scaffold" to house a peptide (*e.g.*, the hormone thrombopoietin ("TPO")), thereby providing greater stability and longer half-life for the peptide *in vivo*. The assays reported in Bowdish *et al.* have nothing to do with C5 binding or blocking complement-mediated lysis. Rather, Bowdish *et al.* assessed the binding of TPO-mimetic peptide (presented on an antibody scaffold) with a TPO receptor (the "cMpl receptor") – a biological interaction that is not part of the complement pathway and has nothing to do with cleavage of C5. Accordingly, one of ordinary skill in the art seeking a safe and effective anti-C5 antibody composition for the treatment PNH would <u>not</u> have looked to art, *e.g.*, Bowdish *et al.*, that teaches about something entirely different (see, *e.g.*, *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013)).

Importantly, like Evans *et al.*, Bowdish *et al.* fails to even mention "eculizumab." There is no reason why a person of ordinary skill in the art as of March 15, 2007 would have set aside the literature's clear teaching regarding the structure of the therapeutically successful "eculizumab" antibody and would have instead looked to Bowdish *et al.*, which addresses unrelated problems. None of the prior art references – including Hillmen *et al.*, Evans *et al.*, and Bell *et al.* – cited or pointed to Bowdish *et al.* in any manner.

Indeed, the term "5G1.1" in Bowdish *et al.*, would <u>not</u> have supplied any definitive information about the structure or sequence of "eculizumab." As discussed above, the term "5G1.1" had been used in the literature to broadly refer to many different constructs such as, *e.g.*, the original mouse ("murine") antibody identified by Alexion, and a wide variety of "humanized" constructs (also termed "h5G1.1"), including at least nine different variable region fragments ("scFv") described in Evans *et al.*, as well as Thomas's humanized IgG4 construct that the literature as of March 15, 2007 described as "eculizumab". Thus, neither Bowdish *et al.*'s reference to using "5G1.1" as a scaffold for a TPO-mimetic peptide, nor Bowdish *et al.*'s citation to Evans *et al.*, would have explained to a person of ordinary skill in the art how Bowdish *et al.*'s

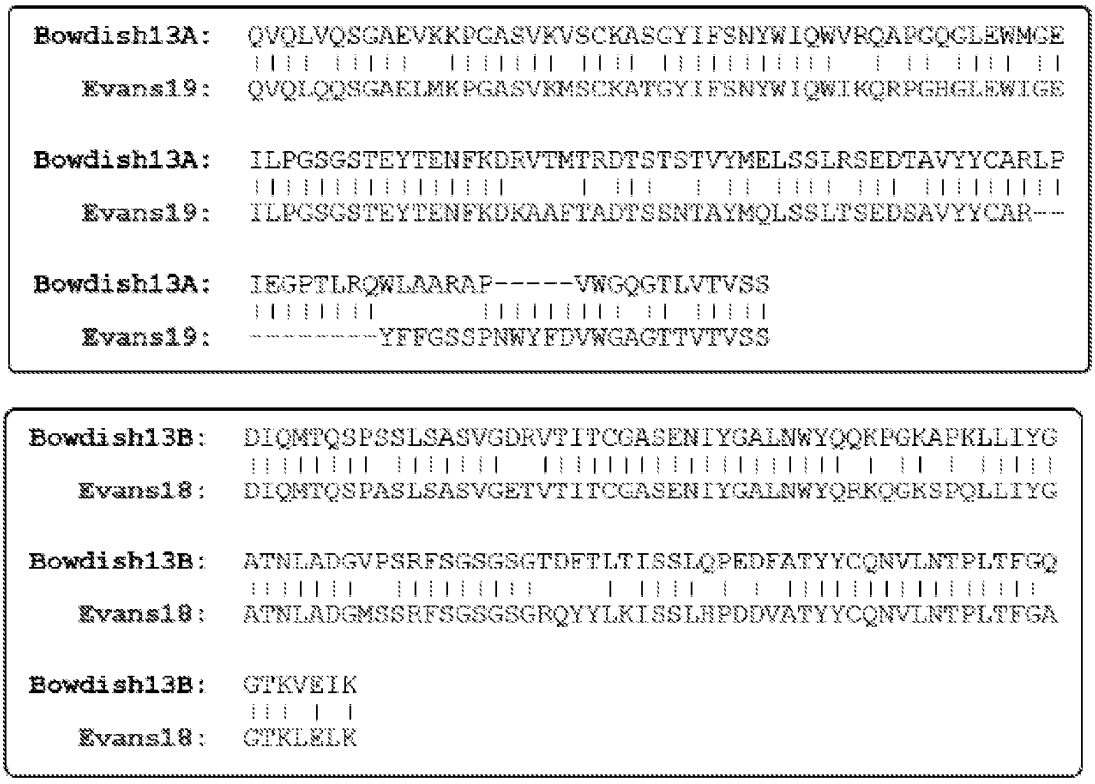
TPO-mimetic construct relates to the structure of "eculizumab," let alone the complete unique sequence recited in the present claims.

Moreover, the only reference in Bowdish *et al.* to Evans *et al.* states: "Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283, incorporated by reference herein." However, Bowdish's vague statement referencing the '283 application for "[c]onstruction of 5G1.1," without further explanation, is not effective to incorporate any specific material from Evans into Bowdish *et al*., because it fails the requirement that "the host document . . . identify with ***detailed particularity*** what specific material it incorporates and ***clearly indicate*** where that material is found in various documents." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Even if a person of ordinary skill in the art had attempted to make sense of Bowdish e*t al.*'s reference to "[c]onstruction of 5G1.1 as described in [the '283 application]," it would not have led them to a clear and unequivocal disclosure of the presently claimed invention. A person of ordinary skill in the art reading Bowdish *et al.*, would have understood that its incorporation was ***limited*** to the portion of the Evans *et al.* describing the "[c]onstruction of 5G.1."

In turn, a person of ordinary skill in the art looking to Evans *et al.* for "[c]onstruction of 5G1.1" would have been directed to Evans's description of a ***mouse*** antibody – "the 5G1.1 antibody" or "the 5G1.1 mAb", obtained from the original "5G1.1" hybridoma (see Evans *et al.* Example 7-10 and Figs. 18-19). For example, Evans *et al.* explains that "[a] particularly preferred antibody of the invention is ***the 5G1.1 antibody*** (5G1.1, ***produced by the 5G.1.1 hybridoma***, ATCC designation HB-11625)," and identifies Figs. 18 and 19 as disclosing the light chain and heavy chain variable regions of "***the antibody 5G1.1***." In particular, nothing in Bowdish *et al.*'s reference to the "5G1.1" mouse antibody of Evans *et al.* would have indicated to a person of ordinary skill in the art that the "scaffold" antibody (whose sequence was not disclosed in Bowdish *et al.*) that was used to generate Bowdish *et al.*'s TPO-mimetic compound was the specific antibody consisting of SEQ ID NOs: 2 and 4, as recited in the pending claims.

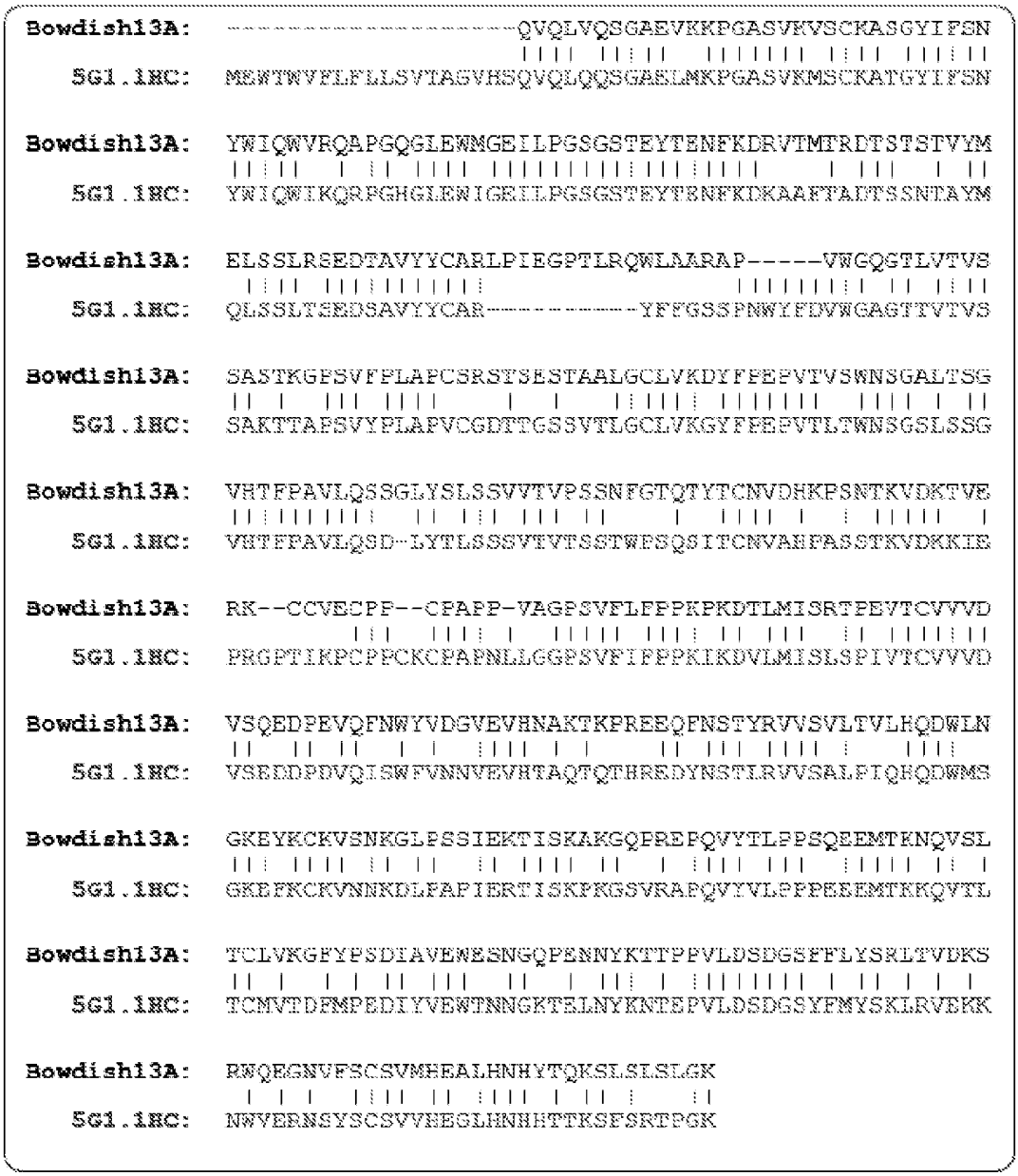
Moreover, as the following figures illustrate, a comparison of the sequences for Evans's "5G1.1" mouse antibody variable regions (Figs. 18-19) or the whole "5G1.1" mouse antibody with the sequences for Bowdish's TPO-mimetic compound (Figs. 13A and 13B) would have

revealed a mismatch in amino acids beyond those that Bowdish *et al.* identified as the TPO-mimetic peptide insert (see ¶¶214-215 of the Declaration of Arturo Casadevall; Appendix A):



Top: Bowdish Figure 13A (SEQ ID NO: 67) compared to Evans Fig. 19

Bottom: Bowdish Fig. 13B compared to Evans Fig. 18



Bowdish Figure 13A (SEQ ID NO: 67) compared to heavy chain of 5G1.1 antibody from HB-11625

In view of the mismatch between the sequences of Bowdish *et al.* and the incorporated sequences of Evans *et al.*, a person of ordinary skill in the art as of March 15, 2007 would have found Bowdish *et al.*'s reference to Evans *et al.*, to be at most, ambiguous, and certainly would not have understood Bowdish *et al.* to clearly and unequivocally disclose an antibody consisting of SEQ ID NOS: 2 and 4 recited in the pending claims. In particular, nothing in Bowdish *et al.*'s reference to the "5G1.1" mouse antibody of Evans *et al.* would have indicated to a person of ordinary skill in the art that the "scaffold" antibody (whose sequence was not disclosed in Bowdish *et al.*) used to generate Bowdish *et al.*'s TPO-mimetic compound was the specific antibody consisting of SEQ ID NOs: 2 and 4 of the present application (see ¶¶162-163, 190 of the Declaration of Arturo Casadevall, Appendix A).

In sum, prior to March 15, 2007, no single document disclosed the entire amino acid sequence in eculizumab. Nor was eculizumab available to the public for testing or analysis prior to that date. If a person of ordinary skill in the art were searching for the sequence of "eculizumab" as described in the art, the literature as of March 15, 2007 identified an amino acid sequence and corresponding structure that is very different from what the present application claims. In particular, publications describing the safety, efficacy, and clinically relevant biological activity of "eculizumab" consistently directed one of ordinary skill in the art to the 1996 Thomas publication for the structure and design of the antibody, which in turn described a humanized antibody constructed with a naturally-occurring ***IgG4*** heavy chain constant region. The antibody encompassed by the pending claims has a very different, uniquely-engineered, non-naturally occurring constant region that was nowhere described in Thomas or the prior art literature showing the safety and efficacy of "eculizumab."

4. <u>The Rejection Improperly Uses Hindsight Knowledge to Piece Together the Claimed Invention</u>

Moreover, the Examiner's reliance on Bowdish *et al.* uses hindsight knowledge to reconstruct the sequences claimed in the present applications from bits and pieces of unrelated, prior art that teaches in an entirely different direction (*e.g.*, TPO-mimetics). Such hindsight-

driven analysis is always an improper basis for alleging obviousness. *See, e.g.*, *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (warning against "slipping into use of hindsight" and "the temptation to read into the prior art the teachings of the invention in issue"); *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2017) (warning against "the distortion caused by hindsight bias" and "arguments reliant upon *ex post* reasoning").

In particular, the Examiner uses hindsight to cobble together the sequence recited in the pending claims from Bowdish *et al.* (for portions of the claimed sequence, including its non-natural heavy chain constant region) and Evans *et al.* (for the variable region of the claimed sequence). However, the Examiner fails to show why one of ordinary skill in the art ***without*** hindsight would have selected Bowdish *et al.* and combined it with Evans *et al.* to obtain the antibody encompassed by the pending claims, or how they could have reasonably expected success in doing so. Specifically, the Examiner improperly uses the present application as a ***reference point*** for reconstructing the amino acid sequence of the claimed antibody ***in hindsight***, from sequences selectively combined from Bowdish *et al.* and Evans. *et al.* However, a person of ordinary skill in the art could not have made any of these comparisons, because a person of ordinary skill in the art would not have had access to the sequence of the present application. But "working backwards from [a] compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019).

For example, in addition to the disclosure of a humanized scFv compounds, Evans *et al.*, also discloses many other sequences, including:

- Figures 18 and 19 (i.e., the variable regions of the mouse antibody that Bowdish *et al.*, references (with respect to the '283 application) for "[c]onstruction of 5G1.1" (see ¶¶214-15 of the Declaration of Arturo Casadevall; Appendix A);
- The "Fd" molecules of Evans et al., SEQ ID NOs: 11, and 12, which a person of ordinary skill in the art would have understood were more "complete" fragments of a humanized antibody than an scFv, and provide sequences in the constant region (and for SEQ ID NO: 11, the variable region) that do not align with the presently

claimed sequences (see ¶¶ 129 and 158 of the Declaration of Arturo Casadevall; Appendix A); and

- The eight other humanized "scFv" molecules of Evans *et al.* (*see* ¶157 of the Declaration of Arturo Casadevall; Appendix A).

Even assuming the disclosures of Bowdish *et al.* and Evans *et al.* were fully combined, a person of ordinary skill in the art without hindsight would not have been directed to the complete amino acid sequence recited in the pending claims. Among other things, a person of ordinary skill in the art would not have reasonably assumed that "heavy chain CDR3" referenced in Bowdish *et al.* was the same as the heavy chain CDR3 described in Evans *et al.* for humanized scFv compounds, which are *not* full-length structures like the TPO-mimetic compound of Bowdish *et al.* (see ¶¶216-220 of the Declaration of Arturo Casadevall, enclosed herewith as Appendix A). Even if a person of ordinary skill in the art reading Bowdish *et al.* were to consider Evans *et al.* for its disclosure of heavy chain CDR3 sequences, Evans *et al.* allows for multiple options, and nothing in Bowdish *et al.* or Evans *et al.* indicates which, if any, were used in the "scaffold" antibody used to produce Bowdish *et al.*'s TPO- mimetic peptide (see ¶¶216-220 of the Declaration of Arturo Casadevall, enclosed herewith as Appendix A).

Critically, ***nowhere*** did Bowdish *et al.* even reference the word "eculizumab." Nor did Bowdish *et al.* address the problem of the instant application – development of a monoclonal antibody that prevents C5 cleavage and is safe and effective for treating PNH. In fact, the Examiner disregards the art's ***actual*** teachings about the structure and sequence of "eculizumab" in favor of a theory that improperly picks and chooses from unrelated art in hindsight.

5. <u>Wang Does Not Disclose or Teach the Remaining Claim Limitations, and a Person Skilled in the Art Would Not Have Reasonably Expected the Claimed Composition to be Successful in Treating PNH</u>

Finally, the Examiner relies on Wang for teaching that eculizumab is highly soluble, including at up to 30 mg per ml. Simply because an antibody may be soluble at a given concentration in a particular medium does not mean that it would be suitable in a pharmaceutical composition at that concentration. As explained in the enclosed Declaration by Dr. Trout (Appendix B), who is a Professor of Chemical Engineering at the Massachusetts Institute of

Technology (MIT) and the Director of the Society, Engineering and Ethics (SEE) Program at MIT, antibody formulation was an unpredictable field prior to March 15, 2007 and one of ordinary skill in the art could not have reasonably expected that any particular uncharacterized antibody would be capable of development into *any* pharmaceutical composition suitable for human therapeutic use, or treatment of PNH in particular, as required by the pending clams (see ¶39-54, 69 of the Declaration by Dr. Trout; Appendix B). Specifically, as attested to be Dr. Trout, "a person of ordinary skill in the art as of March 15, 2007 would have known that, even '[a]mong all the commercial antibody products," only "about half are stable enough to be formulated in a liquid form' (which a solution is)" (¶71 of the Declaration by Dr. Trout; Appendix B).

Moreover, contrary to the Examiner's suggestion, Wang does not disclose "a single-unit dosage form comprising 300 mg of the antibody in 30 mL of a sterile, preservative-free solution", as presently claimed (see ¶80 of the Declaration by Dr. Trout; Appendix B). Specifically, Wang does not specifically teach eculizumab formulations of between 1 and 30 mg/ml, but rather discloses wide ranges, including 1-30 mg/ml, 40-200 mg/ml and 1-200 mg/ml that hypothetically might be used for nebulization of various unrelated "anti-C5" antibodies and derivative compounds (see Wang ¶¶[0067], [0130], [0170]-[0172], Fig. 10; and ¶¶82-83 of the Declaration by Dr. Trout; Appendix B). Regarding stability that a person skilled in the art would understand is needed for a pharmaceutical composition, Wang only contains a highly general, hypothetical statement that compositions of undefined anti-C5 antibodies "may be stable" over a wide concentration range of 1-200 mg/ml (Wang ¶ [0067]). A person skilled in the art would ***not*** have taken this vague, general statement from Wang as fact with respect to every specific antibody and concentration point, as attested in ¶84 of the Declaration by Dr. Trout (Appendix B). Accordingly, one or ordinary skill in the art, without the benefit of hindsight, would not have arrived at the dosage unit, concentration and volume recited in the pending claims (see, *e.g.*, *KSR Int'l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007), wherein the Supreme Court emphasized that "[a] factfinder should be aware of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning").

B. Rejection of Claims 52-59

Claims 52-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hillmen *et al.*, in view of Evans *et al.*, Wang, and Bowdish *et al.*, as applied to claim 52, and further in view of Bell *et al.* The Examiner relies on Hillmen *et al.*, in view of Evans *et al.*, Wang, and Bowdish *et al.* for the reasons discussed above. The Examiner relies on Bell *et al.* for teaching treatment of PNH "using an anti-C5 antibody such as h5G1.1 mAb eculizumab", that LDH is a known indicator of efficacy, and that treatment can continue for 64 weeks.

As discussed above, none of Hillmen *et al.*, in view of Evans *et al.*, Wang, and Bowdish *et al.*, either alone or in combination, render the present claims obvious. Bell *et al.* fails to cure the deficiencies of these references. Bell, like Hillmen *et al.*, would have reinforced one of ordinary skill in the art's understanding as of March 15, 2007 that "eculizumab" was the IgG4 isotype antibody of Thomas, because Bell cited Thomas as describing "[m]ethods for the preparation of h5G1.1-mAb . . . under the tradename eculizumab"[2], and described positive Phase II clinical results for "eculizumab" in PNH patients. Bell thus would have further taught away from other antibody constructs that lacked such published reports of clinical safety and efficacy, such as the uniquely-engineered antibody defined by the claimed full length heavy and light chain sequences (*i.e.*, SEQ ID NOs: 2 and 4). Accordingly, given the consistent teaching as of March 15, 2007 that "eculizumab" was the IgG4 antibody of Thomas, one of ordinary skill in the art would not have found it obvious to use the very different, uniquely-engineered antibody encompassed by the pending claims, without the benefit of hindsight (see, *e.g.*, *KSR Int'l Co. V. Teleflex, Inc.*, 550 U.S. 398 (2007).

Moreover, one of ordinary skill in the art without hindsight also would not have reasonably expected success in combining the Hillmen *et al.*, Evans *et al.*, Wang, Bowdish *et al.*, and Bell *et al.* references. Bell, like Hillmen, taught one of ordinary skill in the art as of March 15, 2007 that "eculizumab" had the ***IgG4*** constant region of Thomas; and nothing in Evans *et al.*, Wang, or Bowdish *et al.* would have given one of ordinary skill in the art a reasonable

[2] While paragraph [0052] of Bell also cited Evans for the disclosure of antibody fragments, one of ordinary skill in the art would have understood that Bell's statements regarding the complete antibody "eculizumab" must refer to Thomas, not Evans, because Evans provided only antibody fragment sequences and no full-length humanized antibody sequence.

expectation that an antibody with a different, non-naturally occurring constant region – with no published reports indicating that such a constant region had even been tested in humans – would be safe and effective to block C5 cleavage and treat conditions such as PNH. One of ordinary skill in the art also would not have reasonably expected that substituting such a uniquely-engineered constant region would allow the antibody to retain the anti-C5 activity and therapeutic efficacy of "eculizumab" as reported in the literature. To the contrary, it was well-known as of 2007 that changes to the amino acid sequence of a monoclonal antibody (including in the heavy chain constant region) could significantly alter antibody properties including affinity, specificity, and immunogenicity, which could translate into unwanted clinical differences *in vivo*.

In sum, the cited references, alone or in combination, fail to render the presently claimed invention obvious, at least because they provide no motivation in arriving at the claimed method, let alone a reasonable expectation of success (see "*KSR International Co.*").

C. Secondary Considerations

It is well-established that objective indicia of non-obviousness (*e.g.*, evidence of copying, long-felt but unsolved needs, industry accolades, and commercial success) play a ***critical role*** in the analysis, and are "not just a cumulative or confirmatory part of the obvious calculus but constitute independent evidence" (see *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1365 (Fed Cir. 2008)). In fact, objective evidence of non-obviousness "may often be the most probative and cogent evidence in the record" and "may often establish that an invention appearing to have been obvious in light of the prior art was not" (see *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012)). Indeed, the Federal Circuit has clearly emphasized that "consideration of the objective indicia is part of the whole obviousness analysis, not just an afterthought," and "are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known elements" (see *Leo Pharmaceutical Products, Ltd. v. Rea,* 726 F.3d 1346, 1357,1358 (Fed. Cir. 2013)).

There are two requirements for evidence of non-obviousness to be relevant. First, the evidence of non-obviousness must be commensurate in scope with the claimed invention (see *In*

re Kao, 639 F.3d 1057, 1068 (Fed. Cir. 2011) citing *In re Tiffin*, 58 CCPA 1420, 448 F.2d 791, 792 (1971) and *In re Hiniker*, 150 F.3d 1362, 1369 (Fed. Cir. 1998)). Second, to be accorded substantial weight, there is fundamental requirement that there be a nexus between the merits of the claimed invention and the evidence of secondary considerations (see M.P.E.P. § 716.01(b), *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995), and *In re Kao* citing *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Moreover, there is a "presumption of a nexus" when a product is "coextensive" with a patent claim (see *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 723 F.3d 1363, 1372 (Fed. Cir. 2013). Specifically, the Federal Circuit has held that "if the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." (see *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000).

In the present case, the strong evidence of secondary considerations (*e.g.*, copying, long-felt unresolved need, industry accolades, and commercial success) weigh significantly in favor of non-obviousness, as discussed in further detail below and in the enclosed Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Deepak Jain. Importantly, the factually supported evidence of non-obviousness presented herein is both commensurate with the scope of the claims *and* results from what is both claimed and novel. As discussed below, the presently claimed complete, full length, uniquely-engineered heavy chain sequence (which was <u>not</u> known in the prior art before the March 15, 2007 priority date of the present application), imparts significant therapeutic advantages which, in turn, directly relate to the merits of the invention (*i.e.*, the commercial success of the marketed product, Soliris® (eculizumab). Therefore, the marketed product embodies the claimed features and is co-extensive with them, such that the required nexus between the merits of the claimed invention and the evidence of secondary indicia has been firmly established.

i. <u>Long-Felt Need</u>

Soliris® (eculizumab) has satisfied a long-felt, but previously unmet need, for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH, which

has been referred to as the "most vicious acquired thrombophilic state known to medicine" (see, Fatimah Al-Ani *et al*., *Ther. Clin. Risk Manag*. 2016; 12: 1161–1170; copy enclosed herewith as Appendix C). The unique anti-C5 therapeutic antibody, Soliris® (eculizumab), defined by the complete structure recited in the present claims (*i.e.,* SEQ ID NOs: 2 and 4) is not only the first FDA-approved anti-C5 antibody, but also the first FDA-approved treatment for PNH. In fact, in 2006, the FDA granted Soliris® (eculizumab) "Priority Review"[3] status (*i.e*., an FDA program to expedite the review process for drugs that are expected to have a particularly great impact on the treatment of a disease), demonstrating just how groundbreaking and transformative the FDA believed it could be for PNH patients.

Prior to FDA approval of Soliris® (eculizumab), patients with PNH had to suffer from debilitating symptoms, such as anemia, fatigue, thrombosis, hemoglobinuria, dyspnea, dysphagia, erectile dysfunction, hypertension and kidney problems for 10 to 15 years, with extremely limited treatment options (see https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh; enclosed herewith as Appendix E). In the absence of treatment, PNH resulted in a 5-year mortality rate of up to ~35% (see Appendix T). The "FDA approval of the orphan drug eculizumab in March 2007 marked a distinct change in how physicians were able to treat patients with paroxysmal nocturnal hemoglobinuria" (see Appendix I). Specifically, as attested by Dr. Peter Hillmen, "[e]culizumab has dramatically changed PNH…[u]ntil eculizumab arrived there was no specific treatment for PNH apart from transfusion and occasionally bone marrow transplant" (see Appendix E).

Dr. Robert A. Brodsky similarly praised Soliris® (eculizumab) as a groundbreaking first-in-class treatment:

> "We had very little to offer patients," Robert A. Brodsky, MD, director of the division of hematology and Clara Lucas Lynn Chair in Medicine at The John Hopkins University, said in an interview. "I recently had a patient with PNH

[3] "A *Priority Review* designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications." (FDA website, https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review; enclosed herewith as Appendix D).

> present in absolute crisis. Several years ago the only thing we would have had to offer him was narcotics and maybe fluids. Now that eculizumab is approved, all I have to do is call down to the pharmacy and tell them that we need to start the patient on this drug." (see Appendix F).

In his own publication, Brodsky touts Soliris® (eculizumab) as being "highly effective in treating PNH" and states that "it has changed the natural history of the disease" (see Brodsky, *Blood*. 2014 Oct 30; 124(18): 2804–2811; enclosed herewith as Appendix F). Brodsky further states:

> [t]he efficacy and safety of eculizumab has been demonstrated in 2 multinational phase 3 trials and a multinational extension study. The drug is highly effective in stopping intravascular hemolysis, eliminating or decreasing the need for red [blood] cell transfusions, improving quality of life, and reducing the risk of thrombosis, the leading cause of mortality from PNH. It has also been shown to improve renal function and to reduce prothrombotic and proinflammatory markers in PNH patients.

The literature is replete with similar testimonials and accolades (see, *e.g.*, Fatimah Al-Ani *et al.*, stating that "[t]he advent of eculizumab has resulted in a dramatic improvement of the natural history of PNH patients with improvement in virtually every aspect of these patients' lives").

Importantly, Soliris® (eculizumab) has not only transformed the standard of care for PNH patients, but also significantly improved individual patient lives. Specifically, the cumulative survival rate increased from 66.8% before Soliris® (eculizumab) to 95.5% with Soliris® (eculizumab) (see Appendices U-W). Moreover, as evidenced by the enclosed testimonials from PNH patients (available at https://alexion.com/patients/patient-stories), treatment with Soliris® (eculizumab) has dramatically improved their quality of life and eliminated painful and debilitating symptoms that once plagued their lives and made day-to-day life challenging and unbearable (see Appendices G-J).

For example, prior to treatment with eculizumab, "Bill", who was diagnosed with PNH in 1985, required hospitalizations and blood transfusions:

> In addition to severe fatigue, Bill experienced stomach pain, kidney pain, dark urine, and dysphagia (difficulty swallowing). His symptoms made it difficult to eat and sleep. Soon, Bill became dependent on regular blood transfusions, which made day-to-day life all the more challenging…After years of managing his

> symptoms as best he could with blood transfusions—and periodic hospitalizations—Bill learned about Soliris® (eculizumab), a then investigational therapy that was undergoing clinical trials. He successfully enrolled in one of the trials in 2005, and soon began to see improvements in his symptoms. Specifically, ***Bill was able to stop receiving blood transfusions*** (emphasis added; see Appendix G)

Similarly, when "Joe" was diagnosed with PNH, "he felt like his dreams were nearly shattered[,]…was worried that he would not have a future with his fiancée and was told he would never be able to compete in contact sports again." Post-treatment with eculizumab, however, Joe "married his college sweetheart, welcomed the birth of two daughters, and is back in his routine" (see Appendix H).

"Victor" was equally devastated when he was diagnosed with PNH and "felt as if he had crawled into a cave":

> He was getting blood transfusions monthly, had little energy and was told he might only have 10 more years to live. The most difficult thing about having PNH was missing out on activities with friends and family, and the toll it took on him mentally. He became depressed. 'People were doing things without me and I felt like I wasn't a part of normal society,' he says. 'I didn't want to talk to people.'

However, after being treated with eculizumab and receiving appropriate support, Victor's life and outlook "radically changed" (see Appendix I).

When "Ruthie" was diagnosed with PNH in 1999, "she and her husband were scared to learn that PNH was a life-threatening illness that at the time had no approved treatments":

> Ruthie first learned about Soliris® (eculizumab) while it was in clinical trials, and began treatment shortly after it was approved by the U.S. FDA in 2007. Today, Ruthie continues to receive treatment, and has the energy to be an engaged and involved mother to three active kids. As her husband David notes, 'In the beginning, we didn't know how long Ruthie would be around, but today I'm excited for our children and for our future' (see Appendix J).

Pursuant to M.P.E.P. § 716.04, the relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors.

> First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967)…Second, the long-felt need must not have been satisfied by

> another before the invention by applicant. *Newell Companies v. Kenney Mfg.* Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988)…Third, the invention must in fact satisfy the long-felt need. *In re Cavanagh*, 436 F.2d 491, 168 USPQ 466 (CCPA 1971).

In the present case, it is clear that all three prongs have been met. Specifically, prior to eculizumab, there was a persistent need in the art for an effective treatment option, as physicians "had very little to offer patients" aside from palliative care (see Appendix E). This long-felt need was not satisfied until Soliris® (eculizumab) was introduced. The introduction of Soliris® (eculizumab) dramatically improved patient lives and satisfied a long-felt need for a safe and effective means for treating the rare, debilitating, and potentially fatal blood disease, PNH, where prior existing treatment options had been limited and ineffective (see Appendices E-J). Importantly, it is the complete structure (*i.e.,* particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that imparts Soliris® (eculizumab) with the therapeutically advantageous features that have made it the "gold" standard treatment and forever changed the standard of care for PNH patients. Accordingly, there is a direct nexus between the claimed invention and its ability to satisfy a long-felt, but previously unmet need.

ii. Copying

There are at least four instances of commercial copying (*i.e.*, biosimilar development) of Soliris® (eculizumab):

1. Amgen is developing a biosimilar eculizumab ("ABP 959") for use in treating paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and generalized myasthenia gravis (gMG) (see https://www.amgenbiosimilars.com/products/our-pipeline/; enclosed herewith as Appendix K).
2. Samsung Bioepis is developing a biosimilar eculizumab ("SB12") and is currently recruiting for a clinical trial to compare "SB12 (Proposed Eculizumab Biosimilar) to Soliris in subjects with Paroxysmal Nocturnal Haemoglobinuria" (see

https://www.samsungbioepis.com/en/product/product02.do; enclosed herewith as Appendix L) and https://www.clinicaltrials.gov/ct2/show/NCT04058158?cond=sb12&rank=1; enclosed herewith as Appendix M).

3. Generium is developing a biosimilar eculizumab ("Elizaria®"), which launched in April 2019 in Russia (see http://www.generium.ru/en/products/elizaria/; enclosed herewith as Appendix N).
4. Biocad is developing a biosimilar of eculizumab ("BCD-148"), which was to be tested in a clinical trial alongside eculizumab in healthy volunteer study (see https://clinicaltrials.gov/ProvidedDocs/03/NCT04027803/Prot_000.pdf; enclosed herewith as Appendix O).

These companies are copying Soliris® (eculizumab) and developing biosimilars because the antibody as a whole (*i.e.*, the antibody's complete sequence) renders it effective and advantageous in treating PNH, as claimed. Accordingly, there is a direct nexus between the claimed invention and copying by others.

iii. Industry Accolades

In 2008, Soliris® (eculizumab) received the Prix Galien USA Award for Best Biotechnology Product. The Prix Galien Award recognizes the technical, scientific and clinical research skills necessary to develop innovative medicines and "is considered the industry's equivalent of the Nobel Prize, the highest accolade for biomedical research and innovation" (see http://register.prix-galien-usa.com/registration/index; Appendix P). The Prix Galien awards committee is made up of 11 individuals, including seven Nobel Laureates, founders of major biotechnology companies and editors of world-renowned biology journals. The candidates for the 2008 awards were selected from drugs approved during the past five years.

Soliris® received this prestigious award because it is a groundbreaking, first-in-line treatment that is effective in treating PNH patients. Again, it is the complete structure (*i.e.*, particular full length heavy and light chain sequences - SEQ ID NOs: 2 and 4) recited in the present claims that imparts Soliris® (eculizumab) with the features that has made it so exceptionally therapeutically effective and worthy of the Prix Galien USA Award. Accordingly,

there is a direct nexus between the claimed invention and its award-winning recognition.

iv. Commercial Success

Soliris® (eculizumab) is unquestionably a commercial success, having generated substantial sales in the relevant market. Soliris® (eculizumab) has been one of the twenty top selling biopharmaceutical products in recent history (see Table 3 of Gary Walsh, *Nature Biotechnology*, volume 36, pages 1136–1145 (2018); enclosed herewith as Appendix Q). As attested in the enclosed Declaration by Daniel Bazarko, the Senior Vice President and Chief Accounting Officer at Alexion (Appendix R), and as evidenced by the enclosed excerpts from Alexion's Forms 10-K for FY 2007-2019 (Appendix S), the annual net product sales for Soliris® have grown consistently since launch, including total U.S. sales of $1 billion over each of the past three years, continuing to grow to over $1.588 billion in 2018 (a 28.6% increase from 2017). Moreover, as also shown in Mr. Bazarko's Declaration, more than $3.4 billion of Soliris' net product sales since its launch in 2007 is attributed to sales for PNH treatment. This astounding commercial success has a direct nexus to the methods of treating patients with Soliris® (eculizumab) (including PNH patients) by administering a unique anti-C5 antibody defined by a novel full-length sequence, which was not known or disclosed prior to the March 15, 2007 priority date of the present application. Specifically, the claimed complete sequence imparts Soliris® (eculizumab) with (*i.e.*, is coextensive with) efficacious and advantageous functional features (*e.g.*, binds to C5 with sufficient affinity and specificity to prevent cleavage of C5, while not activating complement and having no effector function) that have made it a groundbreaking blockbuster product. Accordingly, there is a direct nexus between the claimed invention and its commercial desirability.

D. Conclusion

In sum, the cited references, alone or in combination, fail to render the presently claimed invention obvious because they provide no motivation to arrive at the claimed invention, let alone a reasonable expectation of success (see "*KSR International Co.*"). Moreover, the factually supported evidence of secondary considerations weighs *significantly* in favor of non-obviousness

(see *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Importantly, the evidence of copying, long-felt unresolved need, industry accolades, and commercial success, associated with the use of eculizumab for treatment of PNH has a direct nexus to the novel features of the claimed invention (see *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995)). Therefore, the provided evidence of secondary indicia must be considered in evaluating non-obviousness of the invention.

In view of the above, the presently claimed methods are patentable and Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Non-Statutory Double Patenting

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claim 1 of US Patent 9,732,149, in view of Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-3 of US Patent 9,718,880, in view of Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-10 of US Patent 9,725,504, in view of Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-17 of US Patent 9,409,980, in view of Evans *et al.* (US 6,355,245 B1), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-15 of US Patent 9,415,102, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-14 of US Patent 9,556,263, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

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Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-12 of US Patent 9,352,035, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-13 of US Patent 9,925,262, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

Finally, claims 52-59 are rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-33 of US Patent 10,239,937, in view of Evans *et al.* (US 6,355,245), Wang (US 2005/0271660) and Bell *et al.* (US 2005/0191298).

While in no way acquiescing to the rejection, Applicants respectfully submit herewith a terminal disclaimer over US Patent 9,732,149, US Patent 9,718,880, US Patent 9,725,504, US Patent No: 9,409,980, US Patent No: 9,415,102, US Patent No: 9,556,263, US Patent No: 9,352,035, US Patent 9,925,262, and US Patent 10,239,937.

SUMMARY OF APPENDICES

A	Declaration by Arturo Casadevall
B	Declaration by Dr. Trout
C	Fatimah Al-Ani *et al*., *Ther. Clin. Risk Manag*. 2016; 12: 1161–1170
D	FDA Priority Review (https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review)
E	https://www.healio.com/hematology-oncology/news/print/hemonc-today/%7B01f97d7b-36b4-4462-aab4-02918370caa1%7D/eculizumabs-triumph-over-pnh
F	Brodsky, *Blood*. 2014 Oct 30; 124(18): 2804–2811
G	Patient "Bill" (https://alexion.com/patients/patient-stories)
H	Patient "Joe" (https://alexion.com/patients/patient-stories)
I	Patient "Victor" (https://alexion.com/patients/patient-stories)
J	Patient "Ruthie" (https://alexion.com/patients/patient-stories)
K	Amgen (https://www.amgenbiosimilars.com/products/our-pipeline/)
L	Samsung Bioepis (https://www.samsungbioepis.com/en/product/product02.do)
M	Samsung Bioepis (https://www.clinicaltrials.gov/ct2/show/NCT04058158?cond=sb12&rank=1)
N	Generium (http://www.generium.ru/en/products/elizaria/)
O	Biocad (https://clinicaltrials.gov/ProvidedDocs/03/NCT04027803/Prot_000.pdf)
P	Prix Galien (http://register.prix-galien-usa.com/registration/index)
Q	Gary Walsh, *Nature Biotechnology*, volume 36, pages 1136–1145 (2018)
R	Declaration by Daniel Bazarko
S	Alexion's Forms 10-K for FY 2007-2019
T	Hillmen, P., *et al*., Natural history of paroxysmal nocturnal hemoglobinuria. N. Engl. J. Med., 1995. 333(19): p. 1253-8.
U	Hillmen P, *et al. Br J Haematol.* 2013;162(1):62-73.
V	Hillmen P, *et al. Am J Hematol.* 2010;85(8):553-559.
W	Kelly RJ, *et al*. *Blood.* 2011;117(25):6786-6792.

CONCLUSION

Claims 52-59 are pending. *No new matter has been added.*

If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's attorney at (617) 217-4630. Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 50-1196, under Order No. AXJ-114BUSCN5 from which the undersigned is authorized to draw.

Dated: December 11, 2019

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
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(617) 217-4630
(617) 217-4699 (Fax)
Attorney/Agent For Applicant



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :64734

Sale Accounting Date:01/06/2020

Sale Item Reference Number	Effective Date
15642096	12/11/2019

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I202016957594618	1814	STATUTORY OR TERMINAL DISCLAIMER	$160.00	Deposit Account

Application Number * 15/642,096 *	Application/Control No. 15/642,096	Applicant(s)/Patent under Reexamination BELL et al.	
	Examiner ROGERS, JAMES L	Art Unit 1644	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: 11 December 2019	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

/JEAN PROCTOR/

Technology Center: OPLC

Telephone: (571)272-1040

UNITED STATES PATENT AND TRADEMARK OFFICE

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NOTICE OF ALLOWANCE AND FEE(S) DUE

133485 7590 01/22/2020

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: 01/22/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

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	$1000	$0.00	$0.00	$1000	04/22/2020

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: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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 01/22/2020
Nelson Mullins Riley & Scarborough LLP/Alexion
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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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

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	$1000	$0.00	$0.00	$1000	04/22/2020

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 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

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.
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.
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. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 01/22/2020

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: 01/22/2020

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 30 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.

Samsung Bioepis Exhibit No. 1002
Page 1826

Notice of Allowability	Application No. 15/642,096	Applicant(s) BELL et al.	
	Examiner JAMES L ROGERS	Art Unit 1644	AIA (FITF) 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 12/11/2019.
   ☐ 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 52-59 . 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 L ROGERS/ Examiner, Art Unit 1644	/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

1. Claims 52-59 are pending.

2. Applicant's IDSs, submitted on 12/11/2019 are acknowledged and have been considered.

REASONS FOR ALLOWANCE

3. The following is an Examiner's Statement of Reasons for Allowance:

Applicant's arguments/Response filed 12/11/2019, was considered persuasive and has overcome the obviousness rejections or the prior OA.

The closest prior art was considered to be Evans (US 6,355,245) which was discussed in the prior OA. Evans teaches the antibody 5G1.1, eculizumab. However and as previously noted, Evans does not teach an antibody that binds C5 which have a H and L chain with SEQ ID Nos: 2 and 4, respectively. One of ordinary skill in the art would according need to search for secondary references which provide the missing parts of the currently claimed sequences.

The secondary reference Bowdish (US 2003/232972) which was also discussed in the prior OA teaches an antibody that includes a region where amino acid residues corresponding to at least a portion of two CDRs are replaced with a TPO mimec (see for example claim 1). As was also discussed previously at p. 4 of the prior OA, Bowdish at ¶191 exemplifies this scheme by using an antibody framework, 5G1.1 and refers back to Evans above for this framework. The TPO mimetic peptide was cloned into 5G1.1 so as to replace the native CDR3.

However, and as noted by applicant at p. 12 of applicant's Response, Bowdish is directed to increasing the biological activity of antibody scaffolds rather than to using antibodies against C5 such as the one currently claimed in a method to treating PNH. (see ¶5 of Bowdish).

Even assuming that one of skill in the art would find Bowdish, the fact remains that one of skill in the art would still not end up with the currently claimed antibody. As noted by applicant at pp. 13-14 of the Response, Evan's scaffold 5G1.1 mouse antibody variable regions or the whole 5G1.1 mouse antibody with the sequences for Bowdish's TPO

Samsung Bioepis Exhibit No. 1002
Page 1828

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

It is noted that at least some of the secondary considerations are evidence of non-obviousness, particularly that the invention as claimed satisfies a long felt need and that there is objective evidence of copying. The argument as to commercial success as no evidence has been presented that the commercial success is due to the claimed invention as opposed to other efforts undertaken by the seller, such as marketing; see MPEP 716.03, in particular subsection (b).

Accordingly, claims 52-59 are deemed allowable.

4. 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."

5. 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).

December 27, 2019

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/642,096	BELL et al.
	Examiner	Art Unit
	JAMES L ROGERS	1644

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	05/01/2019	JR
EAST: PGPUB, USPAT, JPO, EPO, DRWNT, INVENTOR SEARCH	05/01/2019	JR
updated	12/27/2019	JR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	USPAT, USPAD	12/27/2019	JR

/JAMES L ROGERS/ Examiner, Art Unit 1644	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/642,096	BELL et al.
	Examiner	Art Unit
	JAMES L ROGERS	1644

CPC						
Symbol					Type	Version
C07K	/	16	/	18	F	2013-01-01
A61K	/	31	/	7105	I	2013-01-01
A61K	/	9	/	0019	I	2013-01-01
A61K	/	38	/	00	A	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
C07K	/	2317	/	24	A	2013-01-01
C07K	/	2317	/	565	A	2013-01-01
C07K	/	2317	/	51	A	2013-01-01
C07K	/	2317	/	515	A	2013-01-01

CPC Combination Sets							
Symbol					Type	Set	Ranking	Version
	/		/					

/JAMES L ROGERS/ Examiner, Art Unit 1644	27 December 2019	Total Claims Allowed:	
(Assistant Examiner)	(Date)	8	
/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644	07 January 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20191227

Samsung Bioepis Exhibit No. 1002
Page 1831

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/642,096	BELL et al.
	Examiner	**Art Unit**
	JAMES L ROGERS	1644

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	9	/	00
A61K	/	39	/	00
C07K	/	16	/	18

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/JAMES L ROGERS/ Examiner, Art Unit 1644	27 December 2019	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	8	
/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644	07 January 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20191227

Samsung Bioepis Exhibit No. 1002
Page 1832

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	15/642,096	BELL et al.
	Examiner	Art Unit
	JAMES L ROGERS	1644

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JAMES L ROGERS/ Examiner, Art Unit 1644	27 December 2019	Total Claims Allowed:	
(Assistant Examiner)	(Date)	8	
/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644	07 January 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20191227

Bibliographic Data

Application No: 15/642,096

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /JAMES L ROGERS/ (Examiner's Signature) | (Initials)

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

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/05/2017	424	1644	AXJ-114BUSCN5
RULE			

APPLICANTS

Alexion Pharmaceuticals, Inc., New Haven, CT,

INVENTORS

Leonard BELL Woodbridge, CT, UNITED STATES

Russell P. ROTHER Oklahoma City, OK, UNITED STATES

Mark J. EVANS Radnor, PA, UNITED STATES

CONTINUING DATA

This application is a CON of 15284015 10/03/2016 PAT 9732149

15284015 is a CON of 15260888 09/09/2016 PAT 9725504

15260888 is a CON of 15148839 05/06/2016 PAT 9718880

15148839 is a CON of 13426973 03/22/2012ABN

13426973 is a CON of 12225040 05/13/2009ABN

12225040 is a 371 of PCT/US2007/006606 03/15/2007

FOREIGN APPLICATIONS

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07/19/2017

STATE OR COUNTRY

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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

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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	6329509		2001-12-11	Jardieu et al.	

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	1	20050027166	A1	2005-02-03	Matsumoto et al.	

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	1	2581113	EP	A1	2013-04-17	Kyowa Hakko Kirin Co., Ltd		
	2	2004/035607	WO	A2	2004-04-29	Genmab As		

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	Attorney Docket Number	AXJ-114BUSCN5

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.	T5
	1	2007 USP Dictionary of USAN and International Drug Names, 85 pages.	
	2	Alexion Form 10-K for FY 2008 (Excerpts) 3 pages.	
	3	Alexion Form 10-K for FY 2009 (Excerpts) 3 pages.	
	4	Alexion Form 10 K for FY 2011 (Excerpts) 3 pages.	
	5	Alexion Form 10-K for FY 2007 (Excerpts) 3 pages.	
	6	Alexion Form 10-K for FY 2010 (Excerpts) 3 pages.	
	7	Alexion Form 10-K for FY 2016 (Excerpts) 3 pages.	
	8	Alexion Form 10-K for FY 2017 (Excerpts) 3 pages.	
	9	Alexion Form 10-K for FY 2018 (Excerpts) 3 pages.	
	10	Alexion Form 10-Q for Q1 of FY 2019 (Excerpts) 3 pages.	

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	Attorney Docket Number	AXJ-114BUSCN5

	11	Alexion Form 10-Q for Q2 of FY 2019 (Excerpts) 3 pages.	
	12	Alexion Form 10-Q for Q3 of FY 2019 (Excerpts) 3 pages.	
	13	Alexion Form 10-K for FY 2012 (Excerpts) 3 pages.	
	14	Alexion Form 10-K for FY 2013 (Excerpts) 3 pages.	
	15	Alexion Form 10-K for FY 2014 (Excerpts) 3 pages.	
	16	Alexion Form 10-K for FY 2015 (Excerpts) 3 pages.	
	17	Alexion Pharmaceuticals, Inc. Form 10-K for the fiscal year ending December 31, 2018 (excerpts), 3 pages.	
	18	Alexion Press Release, "Alexion Pharmaceuticals Submits Biologics License Application for Soliris(TM) (eculizumab)," 2 pages (Sept. 20, 2006).	
	19	Alexion Press Release, "Alexion Submits Market Authorization Application for Soliris(TM) (eculizumab) in the Treatment of Paroxysmal Nocturnal Hemoglobinuria to the European Medicines Agency," 2 pages (Sept. 26, 2006).	
	20	Alexion Press Release, Alexion's Soliris® Receives 2008 Prix Galien USA Award for Best Biotechnology Product, September 25, 2008, 2 pages.	
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	Attorney Docket Number	AXJ-114BUSCN5

	22	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen's Inc.'s Objections to Evidence," Case IPR2019-00739, filed December 2, 2019, 9 pages.	
	23	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen's Inc.'s Objections to Evidence," Case IPR2019-00740, filed December 2, 2019, 9 pages.	
	24	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen's Inc.'s Objections to Evidence," Case IPR2019-00741, filed December 2, 2019, 9 pages.	
	25	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Response Pursuant to 37 C.F.R. § 42.120," Case IPR2019-00739, filed November 22, 2019, 80 pages.	
	26	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Response Pursuant to 37 C.F.R. § 42.120," Case IPR2019-00740, filed November 22, 2019, 80 pages.	
	27	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Response Pursuant to 37 C.F.R. § 42.120," Case IPR2019-00741, filed November 22, 2019, 83 pages.	
	28	Andersen, D. et al., "Production technologies for monoclonal antibodies and their fragments," Current Opinion in Biology, vol. 15:456-462 (2004).	
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	Attorney Docket Number	AXJ-114BUSCN5

	33	Chain of Custody Log, 1 page (2019).	
	34	Chang, B. et al., "Practical Approaches to Protein Formulation Development," Pharmaceutical Biotechnology, vol. 13:1-25 (2002).	
	35	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00739, dated August 30, 2019, 65 pages.	
	36	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00740, dated August 30, 2019, 69 pages.	
	37	DECISION Institution of Inter Partes Review 35 U.S.C. § 314(a), IPR2019-00741, dated August 30, 2019, 61 pages.	
	38	Declaration of Arturo Casadevall and Curriculum Vitae, dated November 22, 2019, 251 pages.	
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	40	Declaration of Daniel Bazarko, dated November 22, 2019, 7 pages.	
	41	Declaration of Michel C. Nussenzweig, M.D., Ph.D. and Curriculum Vitae, dated November 21, 2019, 55 pages.	
	42	Deposition Transcript of Joseph P. Balthasar, Ph.D., Amgen, Inc. v. Alexion Pharmaceuticals, Inc., 342 pages (Oct. 23, 2019).	
	43	Dmytrijuk, A. et al., "FDA Report: Eculizumab (SOLIRIS®) for the Treatment of Patients with Paroxysmal Nocturnal Hemoglobinuria, The Oncologist, vol. 13:993-1000 (2008).	

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	Attorney Docket Number	AXJ-114BUSCN5

	44	European Application No. 11001632.6 Amgen's Response to the Statement of Grounds of Appeal filed by the Appellant on June 24, 2019, dated November 8, 2019, 47 pages.	
	45	European Application No. 11001632.6 Declaration of Dr. Bruce Andrien, dated May 23, 2017, 23 pages, cited in Opposition.	
	46	European Application No. 11001632.6 Declaration of Dr. Laural Boone, dated May 11, 2017, 8 pages, cited in Opposition.	
	47	European Application No. 11001632.6 Declaration of Dr. Leonard Bell, dated January 12, 2012, 4 pages, cited in Opposition.	
	48	European Application No. 11001632.6 Declaration of Tom Vink, dated August 6, 2009, 17 pages, cited in Opposition.	
	49	European Application No. 11001632.6 Denosumab, Drug Bank, accessed November 04, 2019, 6 pages, cited in Opposition.	
	50	European Application No. 11001632.6 European Board of Appeals Decision, File number T 386/89, dated March 24, 1992, 16 pages, cited in Opposition.	

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EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	12/27/2019

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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.

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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)	2019-12-11
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN5

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	1	Rosenberg, A. "Effects of Protein Aggregates: An Immunologic Perspective," AAPS Journal 8, Article 59: E501-E507 (Aug. 4, 2006).	
	2	Samsung Bioepis - Biosimilar candidates and Novel biologic, 3 pages (2019).	
	3	Shepherd, P. et al., Monoclonal Antibodies, Oxford University Press, pages 58-65 (Appendix) (2000).	
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	12	Alexion Form 8-K for FY 2019 (Excerpts) 3 pages, September 5, 2019.	

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A certification statement is not submitted herewith.

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Signature	/Jill Gorny Sloper, Esq./	Date (YYYY-MM-DD)	2019-12-11
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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L2	410	(nocturnal near2 hemoglobinuria).clm.	US-PGPUB; USPAT	OR	OFF	2019/12/27 08:02
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L4	0	L2 and (SEQ near3 (2 and "4")).clm.	US-PGPUB; USPAT	OR	OFF	2019/12/27 08:04
L5	59	L2 and (SEQ near3 (2 or "4")).clm.	US-PGPUB; USPAT	OR	OFF	2019/12/27 08:04

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(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

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	1	European Application No. 11001632.6 Hoffmann Eitle's Response to the Statement of Grounds of Appeal filed by the Appellant on June 24, 2019, dated November 8, 2019, 45 pages.	
	2	European Application No. 11001632.6 Ranibizumab, Drug Bank, accessed November 05, 2019, 6 pages, cited in Opposition.	
	3	European Application No. 11001632.6 Salbutamol Drug Guidelines, 5 pages, cited in Opposition.	
	4	European Application No. 11001632.6 Statement of Grounds of Appeal on Behalf of Alexion Pharmaceuticals, Inc., dated June 24, 2019.	
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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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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)	2019-12-11
Name/Print	Jill Gorny Sloper, Esq.	Registration Number	60,760

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

133485 7590 02/03/2020

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
02/03/2020	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

Applicant-Initiated Interview Summary	**Application No.** 15/642,096	**Applicant(s)** BELL et al.	
	Examiner JAMES L ROGERS	**Art Unit** 1644	**AIA (FITF) Status** No

All participants (applicant, applicants representative, PTO personnel):

(1) JAMES L. ROGERS.

(2) DANIEL KOLKER, SPE.

(3) JANE REMILLARD.

(4) JILL SLOPER.

Date of Interview: 29 January 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Upon further consideration and reading of the references cited, it is noted that the second sentence of the paragraph beginning "The closest prior art" from the office action mailed 22 January 2020 is incorrect. That sentence states that Evans teaches the antibody 5G1.1, eculizumab. However the Evans reference does not identify this antibody as eculizumab. The 5G1.1 antibody taught by Evans is a mouse antibody (see at least column 37 line 34 through column 38 line 45 of US Patent 6355245) and the Evans reference does not teach any additional full-length antibodies that have the same CDRs as 5G1.1 (note Evans does mention N19/8 at column 39 but there is no indication this is pertinent to the now-claimed invention). Evans does teach scFVs which comprise the CDRs of 5G1.1 (Example 11) but these lack at least the constant region of the antibodies in the claimed methods..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JAMES L ROGERS/ Examiner, Art Unit 1644	/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Samsung Bioepis Exhibit No. 1002
Page 1862

Doc Code: MFEE.C.AD
Document Description: Maintenance Fee Address Change

PTO/AIA/47 (11-18)
Approved for use through 09/30/2021. OMB 0651-0016
U.S. Patent and Trademark Office; U. S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person is required to respond to a collection of information unless it displays a valid OMB control number.

"FEE ADDRESS" INDICATION FORM

Address to:
Mail Stop M Correspondence
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

- OR -

Fax to:
571-273-6500

INSTRUCTIONS: The issue fee must have been paid for the application(s) listed on this form. In addition, only an address represented by a Customer Number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application.

When to check the first box below: If you have a Customer Number to represent the fee address.

When to check the second box below: If you have no Customer Number representing the desired fee address, in which case a completed Request for Customer Number (PTO/SB/125) must be attached to this form. For more information on Customer Numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

For the following listed application(s), please recognize as the "Fee Address" under the provisions of 37 CFR 1.363 the address associated with:

[X] Customer Number: 127532

OR

[ ] The attached Request for Customer Number form (PTO/SB/125)

PATENT NUMBER (if known)	APPLICATION NUMBER
	15/642,096

Completed by (check one):

[ ] Applicant/Inventor

[X] Attorney or Agent of record 60,760 (Reg. No.)

[ ] Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) is enclosed or was filed on _____ (Date)

/Jill Gorny Sloper, Esq./
Signature

Jill Gorny Sloper, Esq.
Typed or printed name

617-217-4630
Requester's telephone number

February 3, 2020
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. If the assignee is a juristic entity, this form must be signed by a patent practitioner (attorney or agent) of record. Submit multiple forms if more than one signature is required, see below*.

[ ] * Total of 1 forms are submitted.

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

Dated: February 3, 2020 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Electronic Patent Application Fee Transmittal	
Application Number:	15642096
Filing Date:	05-Jul-2017
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/Melissa St Germain
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:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Samsung Bioepis Exhibit No. 1002
Page 1864

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
PRINTED COPY OF PATENT - NO COLOR	8001	1	3	3
		Total in USD ($)		**1003**

Samsung Bioepis Exhibit No. 1002
Page 1865

Electronic Acknowledgement Receipt	
EFS ID:	38474107
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/Melissa St Germain
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN5
Receipt Date:	03-FEB-2020
Filing Date:	05-JUL-2017
Time Stamp:	15:56:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1003
RAM confirmation Number	E202023F57127155
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	Issue Fee Payment (PTO-85B)	2020_02_03_Issue_Fee_Transmittal_--_AXJ-114BUSCN5.pdf	241424 670b9494036390844 3be8a81e6b868c7fdac2964	no	1
Warnings:					
Information:					
2	Change of Address	2020_02_03_Fee_Address_Indication_Form_--_AXJ-114BUSCN5.pdf	172466 1dd9e98e006da3c769094bf711a3991b27a1be53	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32143 ecea64e102cd3d9fba9bd93f1d40f5fb035e99b8	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	446033		

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.

Samsung Bioepis Exhibit No. 1002
Page 1867

PART B–FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By fax, send to: (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 01/22/2020

NELSON MULLINS RILEY & SCARBOROUGH LLP
One Post Office Square, 30th Floor
Boston, Massachusetts 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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Jill Gorny Sloper, Esq.	(Typed or printed name)
/Jill Gorny Sloper, Esq./	(Signature)
February 3, 2020	(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
15/642,096	07/05/2017	Leonard BELL	AXJ-114BUSCN5	7606

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	$1,000.00	$0	$0	$1,003.00	04/22/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
J. L. Rogers	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 03-09 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. Nelson Mullins Riley & Scarborough LLP
2. Jane E. Remillard, Esq.
3. Jill Gorny Sloper, Esq.

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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Alexion Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE or COUNTRY): Boston, Massachusetts

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☒ Advance Order - # of Copies 1

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-1196

5. Change of 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 as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as 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 /Jill Gorny Sloper, Esq./ Date February 3, 2020

Typed or printed name Jill Gorny Sloper, Esq. Registration No. 60,760

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 NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/642,096	03/17/2020	10590189	AXJ-114BUSCN5	7606

133485 7590 02/26/2020

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 177 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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 Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Leonard BELL, Woodbridge, CT;
Alexion Pharmaceuticals, Inc., New Haven, CT;
Russell P. ROTHER, Oklahoma City, OK;
Mark J. EVANS, Radnor, PA;

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 USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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: May 13, 2020
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN7
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Application No.: 16/804,567

Confirmation No.: 7508

Filed: February 28, 2020

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

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. 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 after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

Please charge our Deposit Account No. 50-1196 in the amount of $240.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50-1196, under Order No. AXJ-114BUSCN7.

Dated: May 13, 2020

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, 30th Floor
Boston, Massachusetts 02109-2127
617-217-4630 (Tel)
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
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

133485 7590 05/28/2020

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: 05/28/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7	7508

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	$1000	$0.00	$0.00	$1000	08/28/2020

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: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

Samsung Bioepis Exhibit No. 1002
Page 1872

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (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 05/28/2020

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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7	7508

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	$1000	$0.00	$0.00	$1000	08/28/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
ROGERS, JAMES L	1644	530-387300

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 03-09 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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). 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. Fees submitted: ❑Issue Fee ❑Publication Fee (if required) ❑Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

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.
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.
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 (08-18) Approved for use through 01/31/2020 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Page 1873

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 NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7	7508

133485 7590 05/28/2020

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: 05/28/2020

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 30 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. 16/804,567	Applicant(s) BELL et al.	
	Examiner JAMES L ROGERS	Art Unit 1644	AIA (FITF) 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 4/27/2020.
   ☐ 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 1-27 and 29-30 . 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 L ROGERS/ Examiner, Art Unit 1644	/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

1. Applicant's amendment, filed 4/27/2020, is acknowledged.

2. Applicant's IDS, submitted on 5/13/2020, is acknowledged and has been considered.

EXAMINER'S AMENDMENT

3. An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the Issue Fee.

4. Authorization for this Examiner's Amendment was given in a telephone interview with Jill Sloper on 5/18/2020.

In the Claims:

5. Claim 28 has been cancelled.

REASONS FOR ALLOWANCE

6. The following is an Examiner's Statement of Reasons for Allowance:

Applicant's approved Terminal Disclaimers of 5/4/2020 and 5/6/2020 have overcome the outstanding ODP rejection.

The examiner confirms that the cited US Patent Application "16/941,080" should have been "14/941,080" in the prior non-final OA of 4/20/2020.

The closest prior art was considered to be Evans (US 6,355,245) which was discussed in the prior OA. The examiner confirms applicant's characterization of Evans at pp.8-9 of applicant's Response that Evans does not disclose or mention "eculizumab". The 5G1.1 antibody taught by Evans is a mouse antibody (see at least column 37 line 34 through column 38 line 45 of US Patent 6355245) and the Evans reference does not teach any additional full-length antibodies that have the same CDRs as 5G1.1 (note Evans does mention N19/8 at column 39 but there is no indication this is pertinent to the

now-claimed invention). Evans does teach scFVs which comprise the CDRs of 5G1.1 (example 11) but these lack at least the constant region of the antibodies in the claimed methods.

Accordingly, claims 1-27 and 29-30 are deemed allowable.

7. 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."

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 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, 2020

/JAMES ROGERS/
Examiner, Art Unit 1644

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644

Examiner-Initiated Interview Summary	**Application No.** 16/804,567	**Applicant(s)** BELL et al.	
	Examiner JAMES L ROGERS	**Art Unit** 1644	**AIA (FITF) Status** No

All participants (applicant, applicant's representative, PTO personnel):

(1) JAMES L. ROGERS.

(2) DANIEL KOLKER, SPE.

(3) JANE REMILLARD.

(4) JILL SLOPER.

Date of Interview: 15 May 2020.

Type: ☑ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☑ No.
If Yes, brief description: _____.

Issues Discussed ☐ 101 ☐ 112 ☐ 102 ☐ 103 ☑ Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

The terminal disclaimers (TDs) filed on 5/4/2020 and 5/6/202, particularly with respect to the TDs over the pending applications, were discussed..

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JAMES L ROGERS/ Examiner, Art Unit 1644	/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/804,567	BELL et al.
	Examiner	**Art Unit**
	JAMES L ROGERS	1644

CPC						
Symbol					**Type**	**Version**
C07K	/	16	/	18	F	2013-01-01
A61K	/	9	/	0019	I	2013-01-01
A61K	/	31	/	7105	I	2013-01-01
A61K	/	38	/	00	A	2013-01-01
A61K	/	2039	/	505	A	2013-01-01
C07K	/	2317	/	24	A	2013-01-01
C07K	/	2317	/	51	A	2013-01-01
C07K	/	2317	/	515	A	2013-01-01
C07K	/	2317	/	565	A	2013-01-01

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

/JAMES L ROGERS/ Examiner, Art Unit 1644	18 May 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	29	
/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644	19 May 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20200518

Samsung Bioepis Exhibit No. 1002
Page 1880

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/804,567	BELL et al.
	Examiner	**Art Unit**
	JAMES L ROGERS	1644

INTERNATIONAL CLASSIFICATION				
CLAIMED				
C07K	/	16	/	18
A61K	/	31	/	7105
A61K	/	9	/	00
A61K	/	38	/	00

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

/JAMES L ROGERS/ Examiner, Art Unit 1644	18 May 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	29	
/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644	19 May 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20200518

Samsung Bioepis Exhibit No. 1002
Page 1881

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/804,567	BELL et al.
	Examiner	Art Unit
	JAMES L ROGERS	1644

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JAMES L ROGERS/ Examiner, Art Unit 1644	18 May 2020	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	29	
/DANIEL E KOLKER/ Supervisory Patent Examiner, Art Unit 1644	19 May 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

U.S. Patent and Trademark Office — Part of Paper No.: 20200518

Samsung Bioepis Exhibit No. 1002
Page 1882

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/804,567	BELL et al.
	Examiner	Art Unit
	JAMES L ROGERS	1644

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STN: DISSABS MEETINGS BIOSCI CAPLUS MEDICINE	03/31/2020	JR
EAST: PGPUB, USPAT, JPO, EPO, DRWNT, INVENTOR SEARCH	03/31/2020	JR
updated	05/18/2020	JR

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	USPAT, USPAD	05/18/2020	JR

/JAMES L ROGERS/ Examiner, Art Unit 1644	

Bibliographic Data

Application No: 16/804,567

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /James Rogers/ (Examiner's Signature) | (Initials)

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

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
02/28/2020	530	1644	AXJ-114BUSCN7
RULE			

APPLICANTS

Alexion Pharmaceuticals, Inc., Boston, MA,

INVENTORS

Leonard BELL Woodbridge, CT, UNITED STATES

Russell P. ROTHER Oklahoma City, OK, UNITED STATES

Mark J. EVANS Radnor, PA, UNITED STATES

CONTINUING DATA

This application is a CON of 16750978 01/23/2020

16750978 is a CON of 15642096 07/05/2017 PAT 10590189

15642096 is a CON of 15284015 10/03/2016 PAT 9732149

15284015 is a CON of 15260888 09/09/2016 PAT 9725504

15260888 is a CON of 15148839 05/06/2016 PAT 9718880

15148839 is a CON of 13426973 03/22/2012ABN

13426973 is a CON of 12225040 05/13/2009ABN

12225040 is a 371 of PCT/US2007/006606 03/15/2007

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

03/12/2020

STATE OR COUNTRY

UNITED STATES

ADDRESS

Nelson Mullins Riley & Scarborough LLP/Alexion

One Post Office Square

30th Floor
Boston, MA 02109-2127
UNITED STATES

FILING FEE RECEIVED

$6,860

EAST Search History

EAST Search History (Prior Art)

<This search history is empty>

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	281	(C5 near10 antibody).clm.	US-PGPUB; USPAT	OR	OFF	2020/05/18 12:21
L2	366	(eculizumab).clm.	US-PGPUB; USPAT	OR	OFF	2020/05/18 12:21
L3	513	(PNH or (paroxysmal near2 nocturnal)).clm.	US-PGPUB; USPAT	OR	OFF	2020/05/18 12:22
L4	58	L3 and L1	US-PGPUB; USPAT	OR	OFF	2020/05/18 12:22
L5	41	L3 and L2	US-PGPUB; USPAT	OR	OFF	2020/05/18 12:22

5/18/2020 12:23:06 PM

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

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
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	16804567
Filing Date	2020-02-28
First Named Inventor	Leonard BELL
Art Unit	1644
Examiner Name	J. L. Rogers
Attorney Docket Number	AXJ-114BUSCN7

U.S.PATENTS Remove

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
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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
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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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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]

EFS Web 2.1.18

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN7

	1	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen Inc.'s Motion to Exclude Evidence Under C.F.R. § 42.64 (c)," Case IPR2019-00741, filed May 8, 2020, 10 pages.	
	2	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen Inc.'s Objections to Evidence," Case IPR2019-00739, filed May 4, 2020, 4 pages.	
	3	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen Inc.'s Objections to Evidence," Case IPR2019-00740, filed May 4, 2020, 4 pages.	
	4	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Amgen Inc.'s Objections to Evidence," Case IPR2019-00741, filed May 4, 2020, 4 pages.	
	5	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Surreply to Petitioner's Reply," Case IPR2019-00739, filed April 27, 2020, 40 pages.	
	6	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Surreply to Petitioner's Reply," Case IPR2019-00740, filed April 27, 2020, 40 pages.	
	7	Amgen Inc., Petitioner v. Alexion Pharmaceuticals, "Patent Owner's Surreply to Petitioner's Reply," Case IPR2019-00741, filed April 27, 2020, 40 pages.	
	8	ClinicalTrials.Gov, Study No. NCT03818607, "A Study Evaluating the Efficacy and Safety of ABP 959 Compared with Eculizumab in Adult Participants with PNH (DAHLIA)," available at https://clinicaltrials.gov/ct2/show/NCT03818607 (last accessed Apr. 21, 2020) 10 pages.	
	9	Deposition Transcript of Ivan T. Hofmann, Amgen, Inc. v. Alexion Pharmaceuticals, Inc., March 12, 2020, 220 pages. Case IPR2019-00739, IPR2019-00740 and IPR2019-00741	
	10	Deposition Transcript of Joseph P. Balthasar, Ph.D., Amgen, Inc. v. Alexion Pharmaceuticals, Inc., April 22, 2020, 81 pages. Case IPR2019-00739, IPR2019-00740 and IPR2019-00741	
	11	European Application No. 11001632.6, Patentee's Comments on the Arguments Raised in the Response to Grounds of Appeal, dated April 6, 2020, 14 pages.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN7

	12	European Application No. 16172335.8, Notice of Appeal against the Examining Division's Decision of January 28, 2020 to refuse this application, filed March 24, 2020, 4 pages.	
	13	European Application No. 16195355.9, Notice of appeal against the Examining Division's decision of February 11, 2020 to refuse this application, dated July 5, 2019, filed March 24, 2020, 4 pages.	
	14	File History for U.S. Patent No. 10,590,189, 594 pages. Case IPR2019-00739, IPR2019-00740 and IPR2019-00741	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/JAMES L ROGERS/	Date Considered	05/18/2020

*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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	1644
	Examiner Name	J. L. Rogers
	Attorney Docket Number	AXJ-114BUSCN7

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)	2020-05-13
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.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

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.

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Doc Code: MFEE.C.AD
Document Description: Maintenance Fee Address Change

PTO/AIA/47 (11-18)
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P.O. Box 1450
Alexandria, VA 22313-1450

- OR -

Fax to:
571-273-6500

INSTRUCTIONS: The issue fee must have been paid for the application(s) listed on this form. In addition, only an address represented by a Customer Number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application.

When to check the first box below: If you have a Customer Number to represent the fee address.

When to check the second box below: If you have no Customer Number representing the desired fee address, in which case a completed Request for Customer Number (PTO/SB/125) must be attached to this form. For more information on Customer Numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

For the following listed application(s), please recognize as the "Fee Address" under the provisions of 37 CFR 1.363 the address associated with:

[X] Customer Number: 127532

OR

[ ] The attached Request for Customer Number form (PTO/SB/125)

PATENT NUMBER (if known)	APPLICATION NUMBER
	16/804,567

Completed by (check one):

[ ] Applicant/Inventor

[X] Attorney or Agent of record 60,760 (Reg. No.)

[ ] Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) is enclosed or was filed on _____ (Date)

/Jill Gorny Sloper, Esq./
Signature

Jill Gorny Sloper, Esq.
Typed or printed name

617-217-4630
Requester's telephone number

May 28, 2020
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. If the assignee is a juristic entity, this form must be signed by a patent practitioner (attorney or agent) of record. Submit multiple forms if more than one signature is required, see below*.

[ ] *** Total of** 1 **forms are submitted.**

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

Dated: May 28, 2020 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Samsung Bioepis Exhibit No. 1002
Page 1892

Electronic Patent Application Fee Transmittal

Application Number:	16804567
Filing Date:	28-Feb-2020
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/Melissa St Germain
Attorney Docket Number:	AXJ-114BUSCN7

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
PRINTED COPY OF PATENT - NO COLOR	8001	1	3	3
		Total in USD ($)		**1003**

Electronic Acknowledgement Receipt	
EFS ID:	39558787
Application Number:	16804567
International Application Number:	
Confirmation Number:	7508
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/Melissa St Germain
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN7
Receipt Date:	28-MAY-2020
Filing Date:	28-FEB-2020
Time Stamp:	13:15:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1003
RAM confirmation Number	E20205RD15253516
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	AXJ-114BUSCN7_Issue_Fee_Transmittal.pdf	36736 c3edd635d753f9eb3459f022afbe46ac95b6be35	no	1
Warnings:					
Information:					
2	Change of Address	AXJ-114BUSCN7_Fee_Address_Form.pdf	23579 1421fd9851f97756733a0392ad982e9324136570	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32058 595d386e102ba3ad757b59912ae53692c1cad711	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	92373		

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.

PART B–FEE(S) TRANSMITTAL

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Alexandria, VA 22313-1450

By fax, send to: (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.

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133485 7590 05/28/2020

Nelson Mullins Riley & Scarborough LLP/Alexion
One Post Office Square, 30th Floor
Boston, Massachusetts 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.

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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 transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

Jill Gorny Sloper, Esq.	(Typed or printed name)
/Jill Gorny Sloper, Esq./	(Signature)
May 28, 2020	(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7	7508

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	$1,000.00	$0	$0	$1,003.00	08/28/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
J. L. Rogers	1644	530-387300

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 03-09 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. Nelson Mullins Riley & Scarborough LLP
2. Jane E. Remillard, Esq.
3. Jill Gorny Sloper, Esq.

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 must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Alexion Pharmaceuticals, Inc.

(B) RESIDENCE: (CITY and STATE or COUNTRY): Boston, Massachusetts

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☒ Issue Fee ☐ Publication Fee (if required) ☒ Advance Order - # of Copies 1

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☒ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 50-1196

5. Change of 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 as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as 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 /Jill Gorny Sloper, Esq./ Date May 28, 2020

Typed or printed name Jill Gorny Sloper, Esq. Registration No. 60,760

Samsung Bioepis Exhibit No. 1002
Page 1897

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Subject: Private PAIR Correspondence Notification for Customer Number 133485

May 28, 2020 03:41:41 AM

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Boston, MA 02109-2127
UNITED STATES

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Disclaimer:
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Application	Document	Mailroom Date	Attorney Docket No.
16804567	NOA	05/28/2020	AXJ-114BUSCN7
	INTV.SUM.EX	05/28/2020	AXJ-114BUSCN7
	1449	05/28/2020	AXJ-114BUSCN7

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16804567
	Filing Date	2020-02-28
	First Named Inventor	Leonard BELL
	Art Unit	N/A
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	AXJ-114BUSCN7

	6	2013235	EP	A1	2009-01-14	Alexion Pharmaceuticals, Inc			☐
	7	2061810	EP	B1	2014-11-12	Alexion Pharmaceuticals, Inc			☐
	8	2089058	EP	A2	2009-08-19	Alexion Pharmaceuticals, Inc			☐
	9	2581113	EP	A1	2013-04-17	Kyowa Hakko Kirin Co., Ltd			☐
	10	2815767	EP	A1	2014-12-24	Alexion Pharmaceuticals, Inc			☐
	11	2910253	EP	A1	2015-08-26	Alexion Pharmaceuticals, Inc			☐
	12	3056218	EP	A1	2016-08-17	Alexion Pharmaceuticals, Inc			☐
Change(s) applied to document, /B.P./ 6/5/2020	13	2380907	~~EU~~ EP	B1	2016-11-30	Alexion Pharmaceuticals, Inc			☐
	14	05/007809	WO	A2	2005-01-27	Alexion Pharmaceuticals, Inc			☐
	15	2004/029207	WO	A2	2004-04-08	Xencor Inc			☐
	16	2004/035607	WO	A2	2004-04-29	Genmab A/S			☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L.R/

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/804,567	07/07/2020	10703809	AXJ-114BUSCN7	7508

133485 7590 06/17/2020

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

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 Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Leonard BELL, Woodbridge, CT;
Alexion Pharmaceuticals, Inc., Boston, MA;
Russell P. ROTHER, Oklahoma City, OK;
Mark J. EVANS, Radnor, PA;

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 USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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Cc: PAIR_eOfficeAction@uspto.gov
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UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
16804567	ISSUE.NTF	06/17/2020	AXJ-114BUSCN7

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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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
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7

CONFIRMATION NO. 7508

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

PUBLICATION NOTICE

OC00000018012446

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

Publication No.US-2020-0199211-A1
Publication Date:06/25/2020

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/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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Application	Document	Mailroom Date	Attorney Docket No.
16804567	NTC.PUB	06/25/2020	AXJ-114BUSCN7

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Monday - Friday 6:00 a.m. to 12:00 a.m.

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PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

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Dated: August 20, 2020
Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

Docket No.: AXJ-114BUSCN7
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Patent No.: 10,703,809

Issued: July 7, 2020

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

Attention: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION PURSUANT TO 37 C.F.R. § 1.323

Dear Sir:

Upon reviewing the above-identified patent, Patentee noted typographical errors which should be corrected.

In the List of References Cited by Applicant and Considered by Examiner:

On Page 2, column 2, under "Other Publications", line 23, delete "EMAIHMPC" and insert - - EMA/HMPC - -, therefor.

On Page 4, column 1, under "Other Publications", line 5, delete "Hemoglobinuira" and insert - - Hemoglobinuria - -, therefor.

On Page 4, column 1, under "Other Publications", line 8, delete "view newsitem.aspx" and insert - - viewnewsitem.aspx - -, therefor.

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On Page 5, column 1, under “Other Publications”, line 17, delete “/mi mOYUG/is 1 14/ai” and insert - - /mimOYUG/is114/ai - -, therefor.

On Page 5, column 1, under “Other Publications”, line 22, delete “/sub press.cfm?” and insert - - /subpress.cfm? - -, therefor.

On Page 6, column 1, under “Other Publications”, line 49, delete “noctumal” and insert - - nocturnal - -, therefor.

On Page 6, column 2, under “Other Publications”, line 31, delete “noctumal” and insert - - nocturnal - -, therefor.

On Page 6, column 2, under “Other Publications”, line 52, delete “noctumal” and insert - - nocturnal - -, therefor.

On Page 7, column 2, under “Other Publications”, line 9, delete “Neisseia” and insert - - Neisseria - -, therefor.

On Page 8, column 1, under “Other Publications”, line 37, delete “et et” and insert - - et - -, therefor.

On Page 8, column 1, under “Other Publications”, line 43, delete “hemoqlobinuria,"” and insert - - hemoglobinuria," - -, therefor.

On Page 8, column 1, under “Other Publications”, line 63, delete “huan” and insert - - human - -, therefor.

On Page 8, column 2, under "Other Publications", line 17, delete "neisserial" and insert - - neisseria - -, therefor.

On Page 8, column 2, under "Other Publications", line 22, delete "Neisserial" and insert - - Neisseria - -, therefor.

On Page 8, column 2, under "Other Publications", line 63, delete "Medelian" and insert - - Mendelian - -, therefor.

In the Specification:

In column 1, line 42, delete "(typeIII)" and insert - - (type III) - -, therefor.

In column 6, line 42, delete ".htm-1)" and insert - -.html) - -, therefor.

In column 8, line 7, delete "M)." and insert - - μM). - -, therefor.

In column 9, line 12, delete "3):57," and insert - - 3):S7, - -, therefor.

In column 11, line 48, delete "2d" and insert - - 2nd - -, therefor.

In column 14, line 22, delete "NSO" and insert - - NS0 - -, therefor.

In column 16, line 27, delete "perkg" and insert - - per kg - -, therefor.

In column 19, line 12, delete "(mg/mL)]" and insert - - (mg/mL)]. - -, therefor.

In column 20, line 34, delete "PBRC" and insert - - PRBC - -, therefor.

In column 22, line 26, delete "Hemolvtic" and insert - - Hemolytic - -, therefor.

In column 28, line 60, after "11" insert - - . - -.

In column 29, line 22, delete “infravascular” and insert - - intravascular - -, therefor.

In column 29, line 25, delete “hemoglobiruria.” and insert - - hemoglobinuria. - -, therefor.

In column 29, line 61, delete “Hypeension” and insert - - Hypertension - -, therefor.

In column 29, line 64, below “2005.” delete “Ref Type: Abstract”.

In column 30, line 23, delete “Patients.” and insert - - Patients - -, therefor.

Some of the errors were found in the application as filed by applicant.

The errors now sought to be corrected are inadvertent typographical errors the correction of which does not involve new matter or require reexamination.

Transmitted herewith is a proposed Certificate of Correction effecting such amendment. Patentee respectfully solicits the granting of the requested Certificate of Correction.

Please charge our Deposit Account No. 50-1196 in the amount of $150.00 covering the fee set forth in 37 C.F.R. § 1.20(a). 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. 50-1196, under Order No. AXJ-114BUSCN7.

Dated: August 20, 2020

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, 30th Floor
Boston, Massachusetts 02109-2127
617-217-4630 (Tel)
617-217-4699 (Fax)
Attorney/Agent For Applicant

PTO/SB/44 (09-07)
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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	10,703,809
APPLICATION NO.	:	16/804,567
ISSUE DATE	:	July 7, 2020
INVENTOR(S)	:	Leonard BELL *et al.*

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the List of References Cited by Applicant and Considered by Examiner:

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On Page 4, column 2, under "Other Publications", line 16, delete "Pharmaceuitcals" and insert - - Pharmaceuticals - -, therefor.

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In column 29, line 64, below "2005." delete "Ref Type: Abstract".

In column 30, line 23, delete "Patients." and insert - - Patients - -, therefor.

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Dated: August 20, 2020 Electronic Signature for Jill Gorny Sloper, Esq.: /Jill Gorny Sloper, Esq./

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Jill Gorny Sloper, Esq.
NELSON MULLINS RILEY & SCARBOROUGH LLP 4
One Post Office Square, 30th Floor
Boston, Massachusetts 02109-2127

Electronic Patent Application Fee Transmittal

Application Number:	16804567
Filing Date:	28-Feb-2020
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/Melissa St Germain
Attorney Docket Number:	AXJ-114BUSCN7

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
CERTIFICATE OF CORRECTION	1811	1	150	150

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**150**

Electronic Acknowledgement Receipt	
EFS ID:	40335980
Application Number:	16804567
International Application Number:	
Confirmation Number:	7508
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/Melissa St Germain
Filer Authorized By:	Jill R. Gorny Sloper
Attorney Docket Number:	AXJ-114BUSCN7
Receipt Date:	20-AUG-2020
Filing Date:	28-FEB-2020
Time Stamp:	16:14:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$150
RAM confirmation Number	E20208JG14518183
Deposit Account	
Authorized User	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	AXJ-114BUSCN7_Request_for_Certificate_of_Correction.pdf	29505 b69976e988172389df6d653d85d61fa8a5f9eaa1	no	5
Warnings:					
Information:					
2	Request for Certificate of Correction	AXJ-114BUSCN7_Proposed_Certificate_of_Correction.pdf	35221 e5ac0055974508e4cf4db69bf0c12c08bd668560	no	4
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30266 22d89ab5536092c6f7e868693200cd0b06972633	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	94992		

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/804,567	02/28/2020	Leonard BELL	AXJ-114BUSCN7	7508

133485 7590 09/02/2020

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
09/02/2020	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

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Patent No.: 10703809
Issue Date: 07/07/2020
Appl. No.: 16/804,567
Filed: 02/28/2020

PART (A) RESPONSE FOR CERTIFICATES OF CORRECTION

This is a decision on the Certificate of Correction request filed 20 August 2020.

The request for issuance of Certificate of Correction for the above-identified correction(s) under the provisions of 37 CFR 1.322 and/or 1.323 is hereby:

(Check one)
☑ Approved ☐ Approved in Part ☐ Denied

Comments: ____

PART (B) PETITION UNDER 37 CFR 1.324 OR 37 CFR 1.48

☐ This is a decision on the petition filed ____ to correct inventorship under 37 CFR 1.324.

☐ This is a decision on the request under 37 CFR 1.48, petition filed ____. In view of the fact that the patent has already issued, the request under 37 CFR 1.48 has been treated as a petition to correct inventorship under 37 CFR 1.324.

The petition is hereby: ☐ Granted ☐ Dismissed

Comment: ____

The patented filed is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

/DANIEL E KOLKER/
Supervisory Patent Examiner, Art Unit 1644
Technology Center 1600
Phone: (571)272-3181

Certificates of Correction Branch email: CustomerServiceCoC@uspto.gov CoC Central Phone Number: (703) 756-1814

To: ipboston.docketing@nelsonmullins.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 133485

Sep 03, 2020 04:10:00 AM

Dear PAIR Customer:

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

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Application	Document	Mailroom Date	Attorney Docket No.
16804567	COCX	09/02/2020	AXJ-114BUSCN7

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Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 10,703,809 B1
APPLICATION NO. : 16/804567
DATED : July 7, 2020
INVENTOR(S) : Leonard Bell et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

Item (56) In the List of References Cited:

On Page 2, Column 2, under "Other Publications", Line 23, delete "EMAIHMPC" and insert -- EMA/HMPC --, therefor.

On Page 4, Column 1, under "Other Publications", Line 5, delete "Hemoglobinuira" and insert -- Hemoglobinuria --, therefor.

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On Page 6, Column 2, under "Other Publications", Line 31, delete "noctumal" and insert -- nocturnal --, therefor.

Signed and Sealed this
Twenty-second Day of September, 2020

Andrei Iancu
Director of the United States Patent and Trademark Office

On Page 6, Column 2, under "Other Publications", Line 52, delete "noctumal" and insert -- nocturnal --, therefor.

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On Page 8, Column 1, under "Other Publications", Line 43, delete "hemoqlobinuria,"" and insert -- hemoglobinuria," --, therefor.

On Page 8, Column 1, under "Other Publications", Line 63, delete "huan" and insert -- human --, therefor.

On Page 8, Column 2, under "Other Publications", Line 17, delete "neisserial" and insert -- neisseria --, therefor.

On Page 8, Column 2, under "Other Publications", Line 22, delete "Neisserial" and insert -- Neisseria --, therefor.

On Page 8, Column 2, under "Other Publications", Line 63, delete "Medelian" and insert -- Mendelian --, therefor.

In the Specification

In Column 1, Line 42, delete "(typeIII)" and insert -- (type III) --, therefor.

In Column 6, Line 42, delete ".htm-1)" and insert -- .html) --, therefor.

In Column 8, Line 7, delete "M)." and insert -- μM). --, therefor.

In Column 9, Line 12, delete "3):57," and insert -- 3):S7, --, therefor.

In Column 11, Line 48, delete "2d" and insert -- 2nd --, therefor.

In Column 14, Line 22, delete "NSO" and insert -- NS0 --, therefor.

In Column 16, Line 27, delete "perkg" and insert -- per kg --, therefor.

In Column 19, Line 12, delete "(mg/mL)]" and insert -- (mg/mL)]. --, therefor.

In Column 20, Line 34, delete "PBRC" and insert -- PRBC --, therefor.

In Column 22, Line 26, delete "Hemolvtic" and insert -- Hemolytic --, therefor.

In Column 28, Line 60, after "11" insert -- . --.

In Column 29, Line 22, delete "infravascular" and insert -- intravascular --, therefor.

In Column 29, Line 25, delete "hemoglobiruria." and insert -- hemoglobinuria. --, therefor.

In Column 29, Line 61, delete "Hypeension" and insert -- Hypertension --, therefor.

In Column 29, Line 64, below "2005." delete "Ref Type: Abstract".

In Column 30, Line 23, delete "Patients." and insert -- Patients --, therefor.